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ORIGINAL INVESTIGATION

Altered BDNF is correlated to cognition impairment in schizophrenia patients with tardive dyskinesia

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Abstract
Background Long-term antipsychotic treatment for schizophrenia is often associated with the emergence of tardive dyskinesia (TD), which is linked to greater cognitive impairment. Brain-derived neurotrophic factor (BDNF) plays a critical role in cognitive function, and schizophrenia patients with TD have lower BDNF levels than those without TD.
Objective This study examines the BDNF levels, the cognitive function, and the association of BDNF with cognitive function in schizophrenia patients with or without TD.
Methods We recruited 83 male chronic patients with (n=35) and without TD (n=48) meeting DSM-IV criteria for schizophrenia and 52 male control subjects. We examined the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and BDNF levels for all subjects. Positive and Negative Symptom Scale (PANSS) and the Abnormal Involuntary Movement Scale (AIMS) were assessed in patients.
Results BDNF levels were lower in patients with than those without TD (p<0.05). RBANS total score (p<0.01) and subscales of immediate memory, visuospatial/constructional performance, and attention were lower in patients with than those without TD (all p<0.05). BDNF levels were positively associated with immediate memory in patients without TD, but negatively in TD patients (both p<0.05). Multiple regression analysis confirmed that in either TD or non-TD group, BDNF was an independent contributor to immediate memory (both p<0.05).
Conclusions BDNF may be involved in the pathophysiology of TD. While the associations between BDNF and cognition in both TD and non-TD patients suggest a close relationship between BDNF and cognition, the different directions may implicate distinct mechanisms between TD and non-TD patients.

Keywords Schizophrenia · Movement · Cognition · Antipsychotic

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Introduction

Long-term antipsychotic medication for schizophrenia is associated with the emergence of tardive dyskinesia (TD), a motor syndrome consisting of involuntary and hyperkinetic movements (Correll and Schenk 2008; Lohr et al. 2003; Remington 2007). Although the exact mechanisms of TD remain largely unknown, a number of risk factors of TD have been identified, including age, sex, antipsychotic medication (type, dose, and duration), extrapyramidal side effects, organic brain injuries, diabetes mellitus, genetics, and cognitive impairment (Sachdev 2000). Among these factors, cognitive impairment was found to be greater in schizophrenia patients with TD than those without TD by both our recent study (Wu et al. 2013a) and previous studies (Byne et al. 1998;

Waddington and Youssef 1986; Waddington et al. 1987; Wegner et al. 1985b). Longitudinal perspective studies suggested that cognitive deficits preceded the onset of TD and may be a risk factor (Struve and Willner 1983; Wegner et al. 1985a), whereas others found that TD was predictive of impaired cognitive function (Waddington and Youssef 1996). Regarding the etiology and pathophysiology of TD, a leading hypothesis suggests that long-term antipsychotic treatments, by blocking dopamine receptors, could cause compensatory increases in the metabolism of dopamine or the synaptic release of aspartate and glutamate (Bardgett et al. 1993), resulting in increased production of neurotoxic free radicals which cause neuronal degeneration (Lohr 1991; Lohr and Browning 1995; Lohr et al. 2003). Consistently, our recent study has postulated that oxidative stress might serve as a functionally linking node between TD development and cognition dysfunction in schizophrenia (Wu et al. 2013b). On the other hand, it has also been noted that except for antipsychotic drugs, antiemetics such as metoclopramide and promethazine are also in association with TD (Karimi Khaledi et al. 2012; Matson et al. 2002). In untreated schizophrenia patients, involuntary movements similar to TD have been reported for a long time (Whitty et al. 2009). Thus, it is also argued that antipsychotic drugs may interact with the underlying disease process to precipitate and accentuate the intrinsic motor phenomena of schizophrenia (Whitty et al. 2009).

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family of growth factors, plays a crucial role in neuronal survival, synaptic plasticity, and cognitive functions (Altar et al. 1997; Poo 2001). In animal models, it has been shown that inhibition of BDNF signaling by gene knockout or infusion of antisense BDNF impairs spatial learning and memory (Minichiello et al. 1999; Mizuno et al. 2000). Moreover, BDNF appears to participate in both the early and late phase of long-term potentiation (LTP) (Lu and Gottschalk 2000; Poo 2001). Recent studies have reported that BDNF serum levels are significantly decreased in individuals with cognitive decline-related diseases, such as mild cognitive impairment (Yu et al. 2008), Alzheimer disease (Gunstad et al. 2008), and Huntington's disease (Ciammola et al. 2007). In contrast, higher BDNF levels are associated with better neuropsychological test performance in these diseases (Peng et al. 2005; Yu et al. 2008). More recent studies also support the notion that circulating BDNF is a biomarker of memory and general cognitive function in healthy adults (Gunstad et al. 2008; Komulainen et al. 2008). In schizophrenia, our previous study also showed that decreased BDNF levels were positively associated with immediate memory in schizophrenia (Zhang et al. 2012b), suggesting that BDNF may be involved in cognitive impairment in schizophrenia. While a few studies report higher serum BDNF levels in schizophrenia patients, the majority of studies show decreased BDNF levels in treated and first-episode patients (da Chen et al. 2009; Green et al. 2011; Grillo et al. 2007; Ikeda et al. 2008; Palomino et al. 2006; Pirildar et al. 2004; Rizos et al. 2008; Tan et al. 2005a; Toyooka et al. 2002; Xiu et al. 2009; Zhang et al. 2007). Similarly, in schizophrenia patients with TD, it has been shown that serum BDNF levels were lower than those without TD (Tan et al. 2005b; Yang et al. 2011). Furthermore, BDNF was found to protect against the neuronal damages in the nigrostriatal dopaminergic and the glutamatergic systems, which were implicated in the pathogenesis of TD (Cheng and Mattson 1994; Nishio et al. 1998; Tsai et al. 1998).

In view of the cognitive deficits and lower BDNF levels that existed in TD patients, and the important implication of BDNF in cognition and TD pathogenesis, it would be of interest to explore the association between cognitive impairments and BDNF in TD. However, to our best knowledge, none of the previous studies has examined this association in TD. In the present study, we compared the cognitive performance assessed by RBANS and serum BDNF levels in schizophrenia patients with TD to those without TD as well as healthy controls in a Chinese population. Given the fact that gender differences in cognitive domains exist in both schizophrenia patients and controls (Halari et al. 2006; Han et al. 2012; Wisner et al. 2011; Zhang et al. 2012a), we only included male subjects in this study.

Materials and methods

Ethics statement

The research protocol was approved by the Institutional Review Board, Beijing Hui-Long-Guan Hospital. A psychiatrist explained the research protocol and procedures to the potential subject. The description of the study was tailored to maximize the understanding of the subject using language appropriate to the subject's level of comprehension and emotional readiness. If the subject was willing to consent to participate in the study, the researcher provided an in-depth description to the subject and, in certain instances, to their parents or guardians. In cases where the parents or guardians were entrusted with assessing the subject's participation, they gave their written consent on behalf of the subject.

Subjects

Eighty-three inpatients with schizophrenia were recruited from Beijing Hui-Long-Guan Hospital, a Beijing City-owned psychiatric hospital. All patients met the following inclusion criteria: (1) age 40–70 years, Han Chinese; (2) confirmed DSM-IV diagnosis of schizophrenia; (3) with at least 5 years of illness; and (4) had been receiving stable doses of oral antipsychotic drugs for at least 12 months before entry

into the study. All patients were of the chronic type and had been ill for an average 30.3±7.7 years, with current antipsychotic treatment for an average of 4.4±4.4 years. Since admission, all patients received dietetically balanced hospital meals, which were occasionally supplemented by gifts (usually fruit). Patients had the opportunity to exercise for about an hour per day. Antipsychotic drug treatment was mainly monotherapy with clozapine (n=34), risperidone (n=19), and typical drugs (perphenazine, pipotiazine, chlorpromazine, sulpiride, and haloperidol; n=30). Among them, eight patients (six TD and two non-TD; 9.6 % of total patients) received two different antipsychotic drugs, including clozapine and sulpiride, clozapine and risperidone, pipotiazine and risperidone, and perphenazine and pipotiazine (only for non-TD). In addition, 11 patients (six TD and five non-TD; 13.3 % of total patients) received antiparkinsonian drugs. No patient had taken any other central nervous system (CNS)-penetrant medications besides antipsychotics and antiparkinsonian drugs. A mean daily dose of antipsychotics (Table 1), including both the first- and second-generation antipsychotics, was converted to approximate daily mean chlorpromazine milligram equivalents for each subject using standard guidelines (Lehman et al. 2004; Woods 2003).

Fifty-two healthy control subjects (n=52) were recruited from the local community in Beijing. Current mental status and personal or family history of any mental disorder were assessed by unstructured interviews. None of the healthy control subjects presented a personal or family history of psychiatric disorder. All subjects are Han Chinese recruited at the same period from the Beijing area. Demographic data for patients and normal controls are summarized in Table 1.

There were no restrictions on caffeine, nicotine, and other substances/drugs prior to the study. Complete medical history, physical examination, and laboratory tests were obtained from patients and control subjects. Any subjects with major medical illness were excluded. None of the subjects met the criteria for drug or alcohol abuse or dependence. None of the subjects had any disorder of platelet function or platelet number.

Clinical measures

Each subject filled out a detailed questionnaire that recorded general information, sociodemographic characteristics, and medical and psychological conditions. Additional information was collected from available medical records and collateral data (from family and/or treating clinician). Four experienced psychiatrists who were blinded to the clinical status of the patients assessed the severity of tardive dyskinesia using the abnormal involuntary movement scale (AIMS) (Guy 1976).

Diagnosis of TD was based on the Research Diagnostic Criteria in DSM-IV, in combination with the criteria of Schooler and Kane (1982). Dyskinesia was classified as present in a particular subject with an AIMS score of at least 3 (moderate degree) in any body part or with at least 2 (mild degree) in two or more body parts. Each item on the AIMS ranges from 0 to 4, and the total AIMS score was calculated by adding items 1–7. The

Table 1 Characteristics of controls and schizophrenic patients with and without TD

Characteristic	Normal controls (n=52)	Patients without TD (n=48)	Patients with TD (n=35)	F or χ^2	P value
Age (years)	56.2±7	54.6±5.3	56.7±6.6	1.31	0.273
Education (years)	9.4±3.7	8.9±2	9.2±2.2	0.319	0.727
BMI (kg/m^2)	26±3.3	25.1±3.2	25.8±6.7	0.396	0.674
Smoker/nonsmoker	31/21	40/8	30/5	10.431	0.005**
Age of onset (years)		25.8±6.3	24.5±6.6	0.809	0.371
Duration of illness (years)		28.9±8.1	32.2±6.9	3.748	0.056
Number of hospitalizations		4.5±4.8	4.4±2.9	0.037	0.848
Drugs (clozapine/risperidone/typical drugs)		21/12/15	13/7/15	1.19	0.551
Daily AP dose (mg/day) (CPZ equivalent)		494.7±730	449.9±376.1	0.11	0.741
Duration of treatment (ms)		50.2±51.9	56.3±55.8	0.244	0.623
PANSS total score		58±13.2	65.7±11.4	7.766	0.007**
P subscore		11±4.8	14.1±5.2	7.748	0.007**
N subscore		21.9±6.4	24.1±6	2.642	0.108
G subscore		25.2±4.5	27.5±4.6	5.526	0.021*
AIMS total score		1.3±1.5	6.8±2.9	129.952	<0.001**
BDNF (ng/ml)	11.6±2.5	10.2±1.8	9.1±2.5	13.402	<0.001**

TD tardive dyskinesia, *BMI* body mass index, *AP* antipsychotic, *CPZ* chlorpromazine, *PANSS* Positive and Negative Symptom Scale, *P* PANSS positive symptom subscale, *N* PANSS negative symptom subscale, *G* PANSS general psychopathology subscale, *AIMS* Abnormal Involuntary Movement Scale

*p<0.05; **p<0.01

patients with TD were re-evaluated at least 1 month later for TD using the AIMS and diagnosed with TD only if both evaluations consistently revealed the presence of TD.

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) on the same day as the TD evaluation. All raters for the AIMS and PANSS had simultaneously attended a training session in their use before this study started. After training, repeated assessments showed that a correlation coefficient between raters of greater than 0.84 was maintained for the PANSS and 0.88 for the AIMS total scores.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) (Randolph et al. 1998) was individually administered to measure cognitive functioning. The RBANS is comprised of 12 subtests that are used to calculate five age-adjusted index scores and a total score. Test indices are Immediate Memory (comprised of List Learning and Story Memory tasks), Visuospatial/Constructional (comprised of Figure Copy and Line Orientation tasks), Language (comprised of Picture Naming and Semantic Fluency tasks), Attention (comprised of Digit Span and Coding tasks), and Delayed Memory (comprised of List Recall, Story Recall, Figure Recall, and List Recognition tasks). Our group previously translated RBANS into Chinese, and the clinical validity and its test–retest reliability were established among controls and schizophrenia patients (Zhang et al. 2009). Each subject came in the testing room on a separate day to be introduced to our research center by a research member, and a proper training session had been performed for individuals to become acclimated to the testing environment and computerized tasks.

Blood sampling and serum BDNF measurements

Serum samples from healthy controls and patients were collected between 7 and 9 a.m. at the same period following an overnight fast. The serum was separated, aliquoted, and stored at −70 °C before use. Serum BDNF levels were measured by sandwich enzyme linked immunosorbent assay using a commercially available kit. A full description of the assays has been given in our previous report (da Chen et al. 2009; Xiu et al. 2009). All samples were assayed by a technician blind to the clinical situation. The identity of all subjects was indicated by a code number maintained by the principal investigator until all biochemical analyses were completed. Inter- and intra-assay variation coefficients were 8 and 5 %, respectively.

Statistical analysis

Demographic and clinical variables of TD and non-TD groups were compared using analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. We compared RBANS scores among the three groups using ANOVA, and Fisher's least significant difference (LSD) test was performed for post-hoc pairwise comparisons (non-TD versus controls; TD versus controls; TD versus non-TD). When significance was found in ANOVA, the effect of age, education, BMI, smoking status, duration of antipsychotic treatment, and type and dose of antipsychotic drugs was tested by adding these variables to the analysis model as covariates. Relationships between variables were assessed with Pearson's product moment correlation coefficients. Z test was used to assess the significance of the difference between two correlation coefficients and z values were calculated using the Fisher r-to-z transformation. Bonferroni corrections were applied to each test to adjust for multiple testing. Multiple regression analysis using RBANS total or the index scores as the dependent variable was carried out to investigate the impact of a range of variables including BDNF level, age, education, BMI, smoking status, duration of antipsychotic treatment, type and dose of antipsychotic drugs, and PANSS total and index scores. SPSS version 17.0 was used for all statistical analyses. Data were presented as mean and standard deviation (mean±SD). All p-values were two-tailed with a significance level set at 0.05.

Results

Clinical and demographic characteristics for the schizophrenia patients with and without TD along with healthy controls are presented in Table 1. Patients with TD, without TD, and normal controls showed no differences in any characteristics except for smoking status ($p<0.01$), which was adjusted in the following analyses. Age, education, BMI, and smoking status were not associated with BDNF in TD, non-TD, and control groups, respectively (all $p>0.05$). However, in the combined patient group, BDNF was found to be associated with age ($r=-0.299$, $p=0.006$).

Between the patients with and without TD, there was no significant difference in the number of hospitalizations, antipsychotic types (between clozapine, risperidone, and typical drugs), daily antipsychotic dose (chlorpromazine equivalent), and duration of antipsychotic treatment (all $p>0.05$). Patients with TD had significantly higher levels of general psychopathology ($p<0.05$), positive symptom ($p<0.01$) subscores, total score of PANSS ($p<0.01$), and AIMS total score ($p<0.001$) than those without TD. The significant difference in AIMS total score ($p<0.001$) remained after controlling for age, BMI, education, smoking, duration of antipsychotic treatment, and type and dose of antipsychotic drugs.

Serum BDNF in healthy controls and schizophrenia with and without TD

Serum BDNF was lower in patients with TD than in those without TD (9.1±2.5 vs. 10.2±1.8 ng/ml; F=5.1, df=1, 81, p=0.027). This difference remained significant after covarying for age, education, BMI, smoking status, and antipsychotic dose (p=0.041). Furthermore, both patient groups were lower than the controls (11.6±2.5 ng/ml; Table 1) (TD vs. controls: p<0.001; non-TD vs. control: p=0.001). These differences remained significant after controlling for age, BMI, smoking, and education (TD vs. controls: p=0.001; non-TD vs. control: p<0.05). Between clozapine, risperidone, and typical drugs, there was no significant difference in BDNF levels for either the combined patients or separate TD and non-TD groups (p>0.05).

In the combined patients group or when TD or non-TD group was examined, respectively, BDNF was not associated with either the duration of antipsychotic treatment or the dose of antipsychotic medication (all p>0.05). Moreover, BDNF was not correlated with either the total score of PANSS or PANSS subscores in the combined patients group, non-TD, or TD group alone (all p>0.05).

Cognitive performance in healthy controls and schizophrenia with and without TD

The mean and standard deviation of RBANS total and index scores of 35 TD, 48 non-TD, and 52 controls are shown in Table 2. This cohort is not the same cohort as that used in our previous study (Wu et al. 2013b), and the overlapping subjects were 15 for TD, 20 for non-TD, and 25 for control groups. The RBANS total score (63.9±12 vs. 73.4±11.6, p=0.001) and all the five indexes including immediate memory (54.3±10.6 vs. 63.9±11.4, p=0.002), visuospatial/constructional index (79.5±17.9 vs. 86.8±16.6, p=0.047), language (81.5±12.5 vs. 87.8±11.5, p=0.012), attention (73.1±14.4 vs. 83.8±13.6, p=0.001), and delayed memory (65±19.3 vs. 73.4±19.5, p=0.033) were significantly lower in TD than non-TD patients. After controlling for age, education, BMI, smoking status, duration of illness, and antipsychotic treatment (type, dose, and duration of antipsychotic treatment), the differences remained significant for RBANS total score (p=0.001) and the subscales of immediate memory (p=0.009), visuospatial/constructional (p=0.007), and attention (p=0.001). Furthermore, both patient groups (TD vs. control; non-TD vs. control) scored lower on all subscales (all p<0.001 with one exception of p=0.024 for attention index in non-TD vs. controls) except for the visuospatial/constructional index than the controls. These differences remained significant after covarying for age, education, BMI, and smoking (all p<0.01 with one exception of p=0.037 for attention index in non-TD vs. controls).

Correlation between BDNF and cognitive performance

In the non-TD group, correlation analysis showed a significant positive association between BDNF and immediate memory index (r=0.324, df=46, p=0.025). For TD patients, correlation analysis showed that BDNF was negatively associated with the RBANS total score (r=−0.38, df=33, p=0.026), immediate memory (r=−0.36, p=0.033), and delayed memory (r=−0.38, p=0.044). The correlations between BDNF and immediate memory found in TD and non-TD groups were significantly different (z=3.08, p=0.002). However, there were no significant associations between BDNF and RBANS total score or any cognitive index in the combined patients group.

Multiple regression analysis showed that in TD patients, BDNF and PANSS general psychopathology (G) subscale were independent contributors to the RBANS total score (BDNF: β=−0.43, t=−2.69, p<0.05; PANSS G subscore: β=−0.44, t=−2.43, p<0.05) and the indexes of immediate memory (BDNF: β=−0.48, t=−3.31, p<0.01; PANSS G subscore: β=−0.42, t=−2.55, p<0.05) (Fig. 1) and delayed memory (BDNF: β=−0.46, t=−3.12, p<0.01; PANSS G subscore: β=−0.42, t=−2.56, p<0.05). In the non-TD group, BDNF (β=0.33, t=2.38, p<0.05) was an independent

Table 2 Comparison of total and index scores of the RBANS between schizophrenia patients with TD, without TD, and controls

Cognition	Normal controls (n=52)	Patients without TD (n=48)	Patients with TD (n=35)	F	p value	Corrected p[a]
Immediate memory	73.9±16.8	63.9±11.4	54.3±10.6**	22.2	<0.001	<0.001
Visuospatial/constructional	83.2±15.2	86.8±16.6	79.5±17.9**	2.0	0.135	0.81
Language	97.2±9.2	87.8±11.5	81.5±12.5	22.6	<0.001	<0.001
Attention	90.6±16	83.8±13.6	73.1±14.4**	14.7	<0.001	<0.001
Delayed memory	88.5±14.1	73.4±19.5	65±19.3	20.3	<0.001	<0.001
Total scale	82.4±12.5	73.4±11.6	63.9±12**	25.0	<0.001	<0.001

Asterisk indicates significance of the comparisons between TD and non-TD groups

*p<0.05; **p<0.01

[a] Refers to Bonferroni corrections

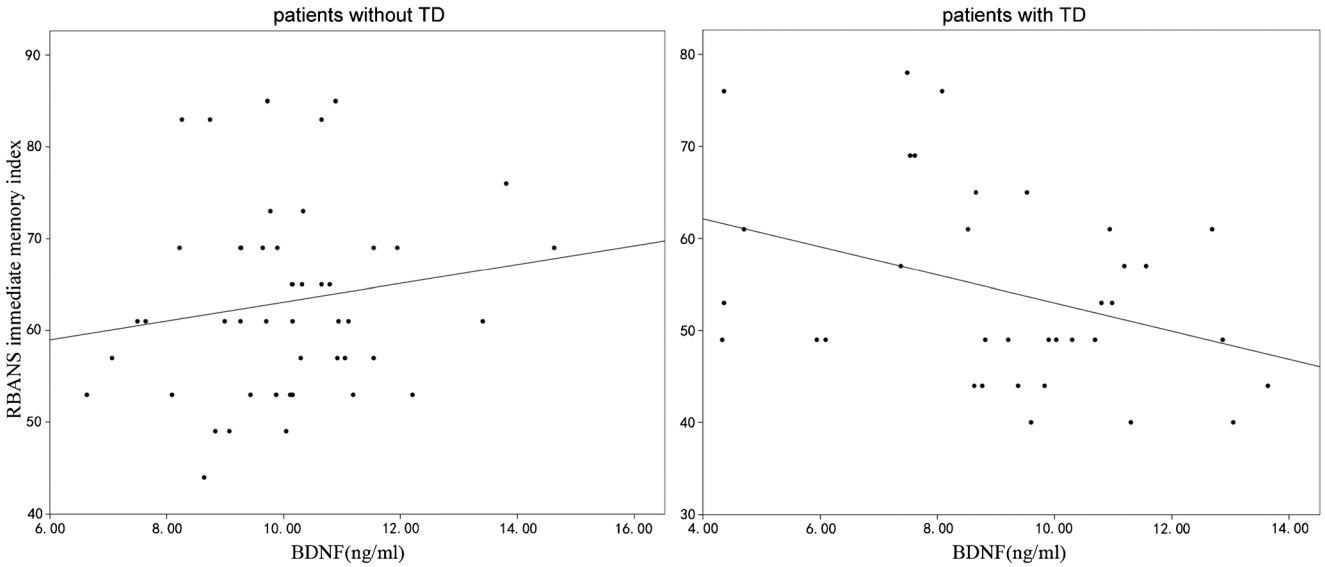

Fig. 1 Immediate memory index of RBANS was positively associated with BDNF levels in schizophrenic patients without TD and negatively in those with TD ($p<0.05$ after controlling for age, BMI, smoking, duration of illness and antipsychotic treatment)

contributor to the immediate memory index of RBANS (Fig. 1). For both TD and non-TD groups, these regression statistics were not significant after controlling for age, BMI, smoking, duration of illness, and antipsychotic treatment (type, dose and duration of antipsychotic treatment). However, in the healthy control group, BDNF was not found to be associated with any cognitive index or total score of RBANS (all $p>0.05$).

Discussion

Results from the present study revealed that (1) BDNF levels were significantly decreased in schizophrenia patients with TD than those without TD (Table 1); (2) the TD patients had significantly lower RBANS total score and subscales of immediate memory, visuospatial/constructional performance, and attention than the non-TD patients (Table 2); and (3) BDNF was positively associated with cognitive function in non-TD group and negatively in TD group (Fig. 1).

Our finding of decreased BDNF levels in either schizophrenia patients versus controls or TD versus non-TD patients (Table 1) is well consistent with previous studies. For example, a number of studies have reported lower BDNF levels in schizophrenia patients than controls (da Chen et al. 2009; Grillo et al. 2007; Ikeda et al. 2008; Palomino et al. 2006; Pirildar et al. 2004; Rizos et al. 2008; Tan et al. 2005a; Toyooka et al. 2002; Xiu et al. 2009; Zhang et al. 2007). Furthermore, we previously found lower BDNF levles in schizophrenia patients with than without TD (Tan et al. 2005b; Yang et al. 2011; Zhang et al. 2012c). However, some studies reported elevated (Gama et al. 2007; Reis et al. 2008) or indistinguishable (Huang and Lee 2006; Shimizu et al. 2003) levels of BDNF in schizophrenia patients than controls. This inconsistency may arise from numerous factors involving techniques of measuring neurotrophin levels, tested materials (serum versus plasma), and clinical and treatment status of patients. Despite the conflicting direction of the change, the majority of studies have found a significant alteration of BDNF levels in schizophrenia and TD, suggesting that BDNF may play a role in the pathogenesis of schizophrenia and TD development. While lower levels of BDNF in schizophrenia supports the hypothesis that a deficit in this neurotrophic factor may contribute to the structural and functional alterations of the brain underlying the pathophysiology of schizophrenia (Durany and Thome 2004; Shoval and Weizman 2005), the higher levels of BDNF may represent a compensatory effect imposed by a more severe cerebral damage in the early years of the disease (Gama et al. 2007; Reis et al. 2008).

For the impact of antipsychotic drugs on BDNF levels, our previous study has reported lower BDNF in patients treated with risperidone compared to those with clozapine and typical antipsychotics (Xiu et al. 2009). However, we did not find any significant difference in BDNF levels between clozapine, risperidone, and typical drugs for either the combined patients or separate TD and non-TD groups ($p>0.05$). The lack of difference could possibly be due to the relatively small sample size in this pilot study.

We also found that patients with schizophrenia scored lower on cognitive measures compared to controls on nearly all of the RBANS' five subscales except for the visuospatial/constructional index (Table 2), which is well in line with previous studies (Condray and Yao 2011; Dickerson et al. 2004; Harvey et al. 2004; Palmer et al. 2009; Sharma and Antonova 2003). Moreover, our finding that the RBANS total

score and subscales including immediate memory, visuospatial/constructional performance, and attention were significantly lower in patients with TD than those without TD (Table 2) replicated earlier findings (Davis et al. 1992; Waddington and Youssef 1986, 1996; Waddington et al. 1987; Wegner et al. 1985b; Wu et al. 2013a, b), suggesting that schizophrenia patients with TD experienced greater cognitive impairment than those without TD. Although the pathological basis of TD and its influence on cognition performance are unknown, one plausible mechanism could be that the preexisting neural substrate contributing to the development of TD (Waddington et al. 1993) may also affect the cognition performance. Recently, the neural substrate hypothesis for TD development has gained further support from a study showing significant reduction in gray matter volume in patients with TD compared to those without TD using voxel-based structural imaging (Sarro et al. 2013).

The correlation analysis indicated that serum BDNF levels were positively associated with cognitive function in patients without TD, but negatively in patients with TD. Furthermore, the correlations between BDNF and immediate memory found in TD and non-TD groups were significantly different (p=0.002). The multiple regression analysis further confirmed that BDNF was an independent contributor to immediate memory in both TD and non-TD groups. These results suggest a close relationship between cognitive function of schizophrenia and BDNF levels, and the conflicting directions as well as the significant difference of the associations detected in TD and non-TD groups may implicate distinct mechanisms underlying the findings. One plausible explanation for the positive association could be that BDNF plays an important role in neuronal survival, morphogenesis, and plasticity (Pandya et al. 2013); thus, the higher the BDNF levels, the better the cognitive performance. In line with this postulation, the neuroprotective effect of BDNF has been demonstrated by its prevention of neuronal death caused by *N*-methyl-D-aspartate receptor blockade in corticostriatal slice cultures derived from rat brains (Xia et al. 2010). Moreover, BDNF has been suggested as an important factor in the induction of LTP, a persistent strengthening of synapses associated with learning and memory (Lu and Martinowich 2008). This is further supported by the preclinical study showing that adenovirus-mediated transfection of CA1 cells with the BDNF gene can reverse the impaired LTP in mice lacking this gene (Tyler et al. 2002). In humans, a postmortem study has detected reduced BDNF production at levels of both mRNA and protein in the dorsolateral prefrontal cortex in schizophrenia compared to normal controls (Weickert et al. 2003). In chronic schizophrenia subjects, decreased BDNF levels were found to be significantly increased after neuroplasticity-based cognitive training; furthermore, BDNF levels were correlated with cognitive performance (Vinogradov et al. 2009).

In contrast, we also found that BDNF levels were negatively associated with cognition performance in TD patients. The exact mechanisms responsible for this observation are still unknown. Based on previous literature showing higher levels of BDNF in schizophrenia patients as a compensatory effect and the neuroprotective role of BDNF (Gama et al. 2007; Reis et al. 2008), we postulate that this negative association could possibly reflect a compensatory response to a more severe cerebral damage in TD patients (Sarro et al. 2013). That means, higher BDNF levels may actually reflect more severe neuronal damages in the dopaminergic and glutamatergic systems, hence a more severe cognitive dysfunction in TD patients. Similar compensatory events of BDNF have been reported in other diseases; for example, BDNF levels were elevated in the early clinical stages of Alzheimer's disease (Laske et al. 2006), and increased secretion of BDNF from brain endothelial cells was detected in response to hypoxia (Wang et al. 2006). However, it is noteworthy to point out that the beneficial effect of the compensatory increases of BDNF was not enough to counteract the impact of neuronal damages on cognitive function as demonstrated by our results where the TD group scored significantly lower on the RBANS total score and the subscales of immediate memory, visuospatial/constructional performance, and attention than the non-TD group.

Several limitations of this study should be noted. First, it is still uncertain whether peripheral BDNF reflects similar changes in the central nervous system, although there is supporting evidence (Karege et al. 2002). Moreover, we did not measure the platelet volume or platelet function to adjust for the platelet-related impact on BDNF levels in this pilot study, which could be improved in future studies. Second, our subjects consisted of a specific cohort of chronically hospitalized patients with more severe psychopathology and longer duration of illness than typical psychotic outpatients or first-episode and drug-naïve patients with schizophrenia. Therefore, whether the results from this cohort also apply to the relatively young patients with TD warrants further investigation. Third, as gender differences influence the degree of cognitive impairment in schizophrenia (Han et al. 2012) and our cohort only includes male patients, further studies are needed to assess whether our findings can be generalized to female subjects with schizophrenia. Fourth, serum BDNF differences may be related to severe stress (Smith et al. 1995), and exposure to stress hormones has an impact on brain structures involved in cognition (Lupien et al. 2009). Hence, future studies need to evaluate the role of stress on BDNF, perhaps through measuring hormone levels related to the hypothalamic–pituitary–adrenal axis. Fifth, although the statistical analysis seems valid, we did not include data reliability and validity statistics acquired from our sample, which could be improved in future studies. Finally, some patients suffering from TD switched from their previous to current

medication, for example, from high- to low-D2-affinity agents. Although it is ideal to examine the relationship between BDNF and the duration of treatment with causative or high-D2-affinity agents, in this pilot study, our patients were not recorded systematically at the beginning of their medication switch, which needs to be improved in future investigations.

In summary, BDNF was decreased in schizophrenia patients with than those without TD, and schizophrenia patients with TD experienced greater cognitive impairment than those without TD, including the RBANS total score, immediate memory, visuospatial/constructional performance, and attention index scores. BDNF levels were positively associated with immediate memory in patients without TD, but negatively in patients with TD. Multiple regression analysis identified BDNF as an independent contributor to the immediate memory index in either TD or non-TD group. The underlying mechanisms for the association between BDNF and cognitive impairment are still unknown. Based on previous literature, we postulate that the positive association in patients without TD may be attributed to the neuroprotective effect of BDNF, whereas the negative association in TD patients may reflect a compensatory response to a more severe cerebral damage. Meanwhile, it is worth noting that although this speculation is plausible with previous studies, other alternative mechanisms are also possible. Future studies using a larger sample size in both men and women in a longitudinal manner directly assessing a possible causal association are warranted. Moreover, systemic investigations of BDNF levels integrated with various factors impacting on BDNF function, including single nucleotide polymorphisms, epigenetic regulation, oxidative stress markers such as MnSOD levels (Wu et al. 2013b), and clinical data such as the duration of treatment with causative or high-D2-affinity agents, the impact of ploypharmacy, and the selective serotonin reuptake inhibitors, are sorely needed for a comprehensive understanding of the role of BDNF in schizophrenia and TD.

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