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Cognition impairment in schizophrenia patients with tardive dyskinesia: Association with plasma superoxide dismutase activity

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ABSTRACT

Long-term antipsychotic treatment for schizophrenia is often associated with the emergence of tardive dyskinesia (TD), and TD presence is also accompanied by more severe cognitive impairment. Oxidative stress-induced damage may be involved in the development of TD and contribute to cognitive deficits in schizophrenia. We examined the role of oxidative stress in relation to TD and cognitive deficits in schizophrenia using plasma manganese superoxide dismutase (MnSOD) as a biomarker. We recruited 83 male chronic patients with ($n = 32$) and without TD ($n = 51$) meeting DSM-IV criteria for schizophrenia, and 58 male control subjects. We examined the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and MnSOD activity for all subjects. Positive and Negative Symptom Scale (PANSS) and the Abnormal Involuntary Movement Scale (AIMS) were assessed in the patients. MnSOD activity was lower in patients with TD than non-TD, and either TD or non-TD group had lower MnSOD levels than controls (all $p < 0.05$). Patients with TD had lower RBANS total ($p < 0.05$) and Visuospatial/Constructional subscale scores than non-TD patients ($p < 0.01$), and either TD or non-TD group scored lower than the controls on all RBANS subscales (all $p < 0.001$) except for the Visuospatial/Constructional index. Multiple regression analysis showed that in either TD or non-TD group, MnSOD was an independent contributor to the RBANS total score (both $p < 0.05$). These findings suggest that TD patients suffered oxidative stress and cognition impairment at a more severe level than non-TD patients. Oxidative stress might serve as a functionally linking node between TD development and cognition dysfunction in schizophrenia.

1. Introduction

Long-term antipsychotic medication for schizophrenia is associated with the emergence of tardive dyskinesia (TD) (Lohr et al., 2003). While the pathophysiology of TD is not well understood, a number of risk factors including age, gender, length of antipsychotic treatment, prominent negative symptoms and thought disorder, more severe cognitive impairment, early onset extrapyramidal side effects, and diagnosis of diabetes mellitus have been identified (Sachdev, 2000). Among these factors, cognitive impairment was not only found to be more severe in schizophrenia patients with TD (Wegner et al., 1985b; Waddington and Youssef, 1986), but also specifically linked to orofacial dyskinesia (Waddington et al., 1987; Byne et al., 1998). Longitudinal perspective studies have found 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 in association with the development of orofacial dyskinesia (Waddington and Youssef, 1996). Our recent study in a larger cohort replicated these earlier findings, showing that TD was associated with greater cognitive impairment in patients with schizophrenia compared to those without TD (Wu et al., 2013).

Previous studies have evidenced that oxidative stress is associated with cognitive impairment in schizophrenia (Bitanihirwe and Woo, 2011; Yao and Keshavan, 2011) and with pathophysiology of TD (Lohr et al., 1990; Peet et al., 1993; Yamada et al., 1997; Tsai et al., 1998; Bitanihirwe and Woo, 2011; Yao and Keshavan, 2011). Preclinical and clinical studies implicated that oxidative stress-induced damage may contribute to cognitive impairment such as learning and memory (Fukui et al., 2001; Nicolle et al., 2001; Hu et al., 2006; Kapogiannis and Mattson, 2011). A recent preclinical study has found that in the DN-DISC1 mice model, the significant oxidative stress in the prefrontal cortex could elicit the activation of the nuclear GAPDH signaling cascade (Johnson et al., 2013). Augmentation of the oxidative stress-associated cascade can affect epigenetic and transcriptional machinery, which points to a mediating condition that could contribute to both cognitive

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and motivational impairments. In humans, it was reported that working memory ability was negatively correlated with protein carbonyl content (PCC), the most widely used marker of oxidative modification of proteins in schizophrenia (Asevedo et al., 2013) and serum protein oxidative stress was also elevated in siblings of patients with schizophrenia (Massuda et al., 2013). Our recent study has detected that total antioxidant status is significantly associated with attention index and RBANS total scores in schizophrenia patients, suggesting that progressive cognitive impairments in schizophrenia may be causally related to impaired antioxidant capacity resulting in increased oxidative stress (Zhang et al., 2012b). At the molecular level, the mechanism underlying the 6p25–p24 region linked to schizophrenia in families with high composite cognitive deficit scores has been pinned down to two adjacent promoter SNPs (rs7752203–rs4141761), which affected expressions of mitochondrial protein LYRM4 (Jablensky et al., 2012). LYRM4 down-regulation has been suggested as one of the mechanisms involved in inefficient oxidative phosphorylation and oxidative stress, increasingly recognized as contributors to schizophrenia pathogenesis. In relation to TD, previous studies have found lower levels of antioxidant markers superoxide dismutase (SOD) and thiobarbituric acid reactive substances (TBARS) in cerebrospinal fluid and peripheral tissues of schizophrenia patients with TD (Lohr et al., 1990; Peet et al., 1993; Yamada et al., 1997; Tsai et al., 1998). Also, our studies have found lower levels of plasma SOD, glutathione peroxidase, catalase, total antioxidant status, and higher malondialdehyde (MDA) levels in schizophrenia patients with TD compared to those without TD (Zhang et al., 2003, 2007; Chen da et al., 2010).

In view of cognitive deficits and the marked alterations in oxidative stress existed in TD patients, and the important implication of oxidative stress in cognition, it would be of interest to explore the association between cognitive impairments and oxidative stress in TD. However, to our best knowledge, no previous studies have examined this association in TD. In the current study, we compared both the cognitive performance assessed by RBANS and the activity of the key antioxidant enzyme MnSOD in blood from schizophrenia patients with TD to those without TD, as well as healthy controls in a Chinese population. Given the fact that gender differences exist in cognitive domains and oxidative stress parameters in both schizophrenia patients and controls (Halari et al., 2006; Wisner et al., 2011; Han et al., 2012; Zhang et al., 2012a), we only included male subjects in this study.

2. Methods

2.1. 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.

2.2. 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 43–70 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 30.0 ± 7.6 years, with current antipsychotic treatment for an average of 4.8 ± 5.1 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 the most common medications consisting of clozapine, risperidone, perphenazine, sulpiride, chlorpromazine, and haloperidol. 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 (Woods, 2003; Lehman et al., 2004).

Fifty-eight healthy control subjects (n = 58) were recruited from the local community in Beijing. Current mental status and personal or family history of any mental disorder was assessed by unstructured interviews. None of the healthy control subjects presented a personal or

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

Characteristic	Normal controls	Patients without TD	Patients with TD	F or X^2	p value
	(n = 58)	(n = 51)	(n = 32)		
Age (yrs)	54.0 ± 6.0	54.9 ± 4.8	56.2 ± 6.9	1.424	0.244
Education (yrs)	9.6 ± 3.2	9.1 ± 1.8	10 ± 2.2	1.097	0.337
BMI (kg/m^2)	25.3 ± 4.8	25.7 ± 5.1	24.6 ± 7.3	0.186	0.831
Smoker/nonsmoker	44/14	45/6	26/6	2.765	0.251
Age of onset (yrs)		25.3 ± 6.7	25.4 ± 6.2	0.007	0.933
Duration of Illness (yrs)		29.6 ± 7.6	30.8 ± 7.8	0.471	0.495
Number of hospitalizations		3.8 ± 2.3	4.3 ± 3.1	0.647	0.424
Antipsychotic types				0.220	0.639
Typical		12	9		
Atypical		39	23		
Daily AP dose (mg/day) (CPZ equivalent)		487.5 ± 740.1	459.1 ± 340.6	0.041	0.840
Duration of treatment (ms)		62.1 ± 65.8	51.0 ± 53.5	0.620	0.433
PANSS total score		61.0 ± 12.7	68.0 ± 11.9	6.256	0.014*
P subscore		12.2 ± 5.5	14.3 ± 4.9	3.189	0.078
N subscore		22.7 ± 6.5	24.4 ± 6.4	1.376	0.244
G subscore		26.1 ± 4.6	29.2 ± 5.7	7.659	0.007**
AIMS total score		1.4 ± 1.4	6.7 ± 2.8	131.727	<0.001**
MnSOD (U/ml)	25.7 ± 13.0	20.9 ± 13.5	15.4 ± 9.2	7.32	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.
* $p < 0.05$.
** $p < 0.01$.

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.

A 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 criteria for drug or alcohol abuse or dependence.

2.3. 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 (RDC) in DSM-IV, in combination with the criteria of Schooler and Kane (Schooler and Kane, 1982). Dyskinesia was classified as present in a particular subject with an AIMS score of at least three (moderate degree) in any body part or with at least two (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 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 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 5 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 established among controls and schizophrenic 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 individual to become acclimated to the testing environment and computerized tasks.

2.4. Plasma MnSOD activity measurement

Venous blood was obtained from each subject between 0700 and 0900 AM following an overnight fast. MnSOD activity was analyzed using established procedures. Our previous report gives a full description of the assays (Zhang et al., 2006). Plasma MnSOD activity is expressed as units per milliliter plasma (U/ml). The inter- and intra-assay coefficients of variation for SOD were 8% and 6%. A research assistant blind to the clinical situation assayed all samples. A code number maintained by the primary investigator indicated the identity of subjects.

2.5. Statistical analysis

Demographic and clinical variables of TD and non-TD groups were compared using analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. We compared RBANS scores among the three groups using ANOVA and Fisher's least significant difference (LSD) test was used to perform 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, type and dose of antipsychotic drugs was tested by adding these variables to the analysis model as covariates. Relationships between variables have been assessed with Spearman correlation coefficient. 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 MnSOD 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 analysis. Data are presented as mean and standard deviation (mean ± SD). All p-values are two tailed with significance level set at 0.05.

3. 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 age, education, body mass index (BMI), and smoking status (all $p > 0.05$). Age, education, BMI, and smoking status were not associated with MnSOD activity in the combined group, or when the associations were examined in TD, non-TD, and control groups respectively (all $p > 0.05$).

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

3.1. MnSOD activity in healthy controls and schizophrenia with and without TD

Plasma MnSOD activity was lower in patients with TD than in those without TD (15.4 ± 9.2 U/ml vs. 20.9 ± 13.5 U/ml; $F = 4.1$, $df = 1, 81$, $p = 0.046$). This difference remained significant after covarying for age, BMI, illness of duration, and antipsychotic dose ($p = 0.038$). Furthermore, both patient groups were lower than the controls (25.7 ± 13.0 U/ml; Table 1) (TD vs. controls: $p < 0.001$; non-TD vs. control: $p < 0.05$). These differences remained significant after covarying for age, BMI, and education (TD vs. controls: $p < 0.001$; non-TD vs. control: $p < 0.05$).

In the combined patient group or when TD or non-TD group was examined respectively, MnSOD activity was not associated with the duration of antipsychotic treatment, type nor dose of antipsychotic medication (all $p > 0.05$). However, MnSOD was correlated with the negative symptoms of PANSS in the combined patient group (Spearman's rho = 0.27, $df = 81$, $p = 0.01$) and TD group alone (Spearman's rho = 0.43, $df = 30$, $p = 0.01$).

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

	Normal controls (n = 58)	Patients without TD (n = 51)	Patients with TD (n = 32)	F	p value	Corrected p[a]
Immediate memory	72.7 ± 17.1	58.5 ± 11.8	54.8 ± 11.1	21.5	<0.001	<0.001
Visuospatial/constructional	82.4 ± 14.4	87.5 ± 17.2	77.3 ± 15.4*	4.2	0.017	0.102
Language	95.9 ± 9.6	87.2 ± 12.3	85.3 ± 10.7	13.2	<0.001	<0.001
Attention	89.0 ± 16.0	80.0 ± 14.2	73.5 ± 11.9	12.6	<0.001	<0.001
Delayed memory	86.6 ± 16.0	68.0 ± 17.4	66.4 ± 17.4	22.4	<0.001	<0.001
Total scale	80.7 ± 12.4	70.0 ± 10.0	64.3 ± 9.1*	26.7	<0.001	<0.001

* Indicates significance of the comparisons between TD and non-TD groups; $p < 0.05$.
[a] Refers to Bonferroni corrections.

3.2. Cognitive performance in healthy controls and schizophrenia with and without TD

The mean and standard deviation of RBANS total and index scores of 32 TD, 51 non-TD, and 58 controls are shown in Table 2. The significant differences between the TD and non-TD patients included the lower RBANS total score (64.3 ± 9.1 vs. 70.0 ± 10.0, $p = 0.022$) and subscales of Visuospatial/Constructional (77.3 ± 15.4 vs. 87.5 ± 17.2, $p = 0.005$). 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 ($p = 0.013$) and the subscales of Visuospatial/Constructional ($p = 0.035$). Furthermore, both patient groups (TD vs. control; non-TD vs. control) scored lower on all subscales (all $p < 0.001$) except for the Visuospatial/Constructional index than the controls. These differences remained significant after covarying for age, education, BMI, and smoking (all $p < 0.001$).

3.3. Correlation between MnSOD and cognitive performance

In the combined patient group, correlation analysis showed that MnSOD activity was negatively associated with the RBANS total score (Spearman's rho = −0.32, $p = 0.003$), immediate memory (Spearman's rho = −0.35, $p = 0.001$), and language (Spearman's rho = −0.24, all df = 81, $p = 0.031$). In either TD or non-TD group, MnSOD activity was also negatively associated with the RBANS total score (non-TD: Spearman's rho = −0.38, df = 49, $p = 0.006$; TD: Spearman's rho = −0.40, df = 30, $p = 0.022$) and immediate memory (non-TD: Spearman's rho = −0.36, df = 49, $p = 0.009$; TD: Spearman's rho = −0.44, df = 30, $p = 0.012$).

Multiple regression analysis showed that in either TD or non-TD group, MnSOD (non-TD: $\beta = -0.35$, $t = -2.51$, $p < 0.05$; TD: $\beta = -0.39$, $t = -2.12$, $p < 0.05$; Fig. 1) was an independent contributor to the RBANS total score. Furthermore, in the non-TD group the PANSS negative symptom ($\beta = -0.33$, $t = -2.48$, $p < 0.05$) and MnSOD ($\beta = -0.3$, $t = -2.28$, $p < 0.05$) were independent contributors to the language Index of RBANS, 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, the MnSOD activity was not found to be associated with any cognitive index or total score of RBANS (all $p > 0.05$).

4. Discussion

Results from the present study revealed that 1) plasma MnSOD activity was significantly decreased in schizophrenia patients with TD than those without TD, and for each patient group (TD versus controls, non-TD versus controls), MnSOD activity was lower than the controls (Table 1); 2) the TD patients had significantly lower RBANS total score and Visuospatial/Constructional index score than the non-TD patients, and each patient group scored lower than the controls on all subscales of RBANS except for the Visuospatial/Constructional index (Table 2); 3) decreased plasma MnSOD activity was associated with impaired cognitive function in the combined patient group, and in either TD or non-TD group (Fig. 1).

Our finding of decreased plasma MnSOD activity in either schizophrenia patients versus controls or TD versus non TD patients is consistent with previous studies (Table 1). Both Ranjekar et al. and Mukerjee et al. have observed compromised MnSOD activity in schizophrenia patients compared to normal controls (Mukerjee et al., 1996; Ranjekar et al., 2003). Lower levels of SOD in cerebrospinal fluid, peripheral tissues, and plasma were also detected from schizophrenia patients with TD compared to those without TD (Yamada et al., 1997; Tsai et al., 1998; Zhang et al., 2003). However, some studies reported elevated SOD levels in schizophrenia patients than in controls (Gama et al., 2006; Padurariu et al., 2010). The inconsistency may arise from numerous factors involving clinical and treatment status. Despite this inconsistency, our results along with previous reports unambiguously suggest an imbalance between free radical production and antioxidant levels in schizophrenia or in TD patients. The observed decline of SOD level

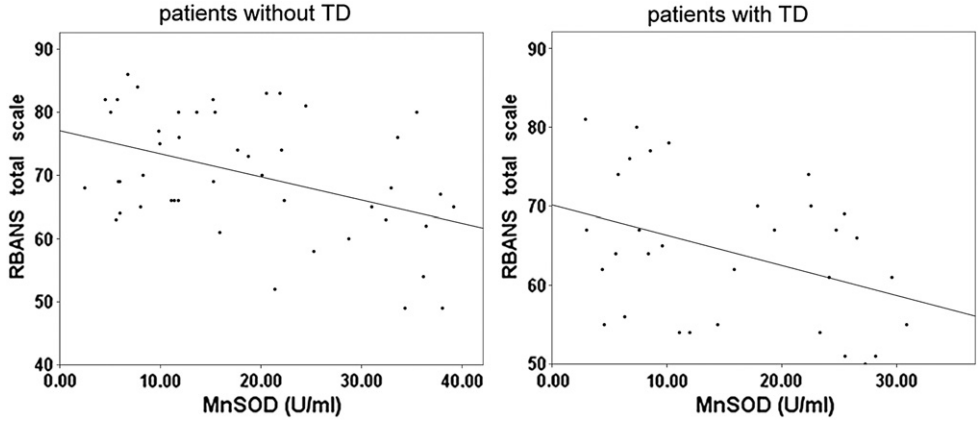

Fig. 1. RBANS total score was negatively associated with MnSOD in schizophrenic patients either without or with TD, respectively ($p < 0.05$).

could arise from either insufficient production of SOD to match the needs imposed by ongoing aerobic metabolism or the inadequacy of SOD activity to neutralize the normal oxidative processes that occur with aging in general. On the other hand, the detected increases in SOD activity or levels may reflect the compensatory processes to attain homeostasis in a system that has already failed to have sufficient SOD activity.

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 (Sharma and Antonova, 2003; Dickerson et al., 2004; Harvey et al., 2004; Palmer et al., 2009; Condray and Yao, 2011). Moreover, the RBANS total score and the subscale of Visuospatial/Constructional were significantly lower in patients with TD than those without TD (Table 2), which replicated the previous findings (Wegner et al., 1985b; Waddington and Youssef, 1986, 1996; Waddington et al., 1987; Davis et al., 1992, Wu et al., 2013 #109) and demonstrated that schizophrenic patients with TD experienced greater cognitive impairment than those without TD. Although the pathological basis of TD and its influence on Visuospatial/Constructional performance are unknown, one plausible mechanism could be that the preexisting neural substrate vulnerability hypothesized to contribute to the development of TD (Waddington et al., 1993), may also affect the neuronal networks which subserve Visuospatial/Constructional performance. This postulation was supported by the very recent study which used voxel-based structural imaging to determine whether there were regions of gray matter volume change in schizophrenia patients with TD (Sarro et al., 2013). This study found that compared to non-TD patients, those with TD showed reductions in gray matter volume that were predominantly subcortical in distribution and affected particularly the basal ganglia. Interestingly, within 4 clusters showing significant volume reduction between TD and non-TD, the temporal pole which responded to complex visual stimuli (Olson et al., 2007), was also detected. These results implicated that the pathological processes underlying TD development did involve brain structure changes in addition to neurochemical alterations, and these changes could be a contributing factor to the impaired visuospatial performance in TD patients observed in our study.

Multiple regression analysis showed that in either TD or non-TD group, MnSOD was an independent contributor to the RBANS total score (Fig. 1). These results suggest that the less effective antioxidant defense reflected by compromised MnSOD activity may play a role in the pathophysiology of schizophrenia and its associated cognitive impairment. This is consistent with our previous study (Zhang et al., 2013), and also supported by other studies showing that imbalances between local ROS and inadequate antioxidant capacity are related to cognitive decline (Davies, 2000; Liu et al., 2003; Nagai et al., 2003) and that accumulation of oxidatively modified proteins in the brain potentiates neurodegeneration linked to compromised cognitive processes (Davies, 2000; Radak et al., 2007). Taken together, based on the observations that TD patients had lower MnSOD levels, more severe cognitive dysfunction than non-TD patients, and MnSOD was an independent contributor to RBANS total score, it is plausible to postulate that oxidative stress could serve as a functionally linking node between TD development and cognition dysfunction in schizophrenia. However, this is only our speculation; this possible causal association with oxidative stress warrants further confirmation in a large cohort.

While the mechanisms underlying the association of TD with impaired cognition are still unknown, the role of oxidative stress postulated here could be one of the plausible mechanisms, which is also compatible with the well-known hypotheses of neural substrate vulnerability and state marker (Waddington et al., 1993). The former hypothesis suggested that greater cognitive impairment in schizophrenia may be due to preexisting neural substrates that may infer vulnerability to develop TD. This organic vulnerability could be imposed by long-term oxidative stress, as it has been demonstrated that accumulation of oxidatively modified proteins in the brain potentiates neurodegeneration linked to compromised cognitive processes (Davies, 2000; Radak et al., 2007). This accumulated impact of oxidative stress could also explain why increased ventricle–brain ratio were only observed among older, chronically ill schizophrenic patients with TD (Waddington et al., 1989; King et al., 1991), but not present in relatively young TD patients (Gold et al., 1991), as the vulnerability of neural substrates imposed by oxidative stress may only take effect over long period of time. On the other hand, it has been hypothesized that the associated cognitive impairment could be a state marker for TD, and our results further suggested that this state marker could actually reflect the underlying status of oxidative stress that may also play a role in cognition dysfunction.

We also found a significant association of MnSOD activity with the negative symptoms of PANSS in the combined patient group and the TD group alone. These results tentatively suggest that oxidative stress arising from the less effective antioxidant defense reflected by MnSOD level may play a role in schizophrenia patients' psychopathology. This potential role of oxidative stress was also supported by the previous study reporting the association between the PANSS negative subscore and malondialdehyde (MDA) levels (an oxidative stress marker, the end product of lipid peroxidation) in schizophrenics with TD (Zhang et al., 2007).

Several limitations of this study should be noted. First, the MnSOD activity measured here only reflects a single antioxidant enzyme status from the whole antioxidant defense system, which actually involves numerous antioxidant enzymes/molecules acting in neutralizing peripheral and central ROS. Indeed, the effective antioxidant protection is provided by SOD activity along with the sequential and cooperative actions of glutathione peroxidase (GSH-Px), catalase (CAT) and other non-enzyme antioxidant molecules (Yao et al., 2000; Reddy et al., 2003; Yao and Reddy, 2011). Thus, a systemic investigation of the activity of the primary antioxidant enzymes and antioxidant molecules in future could provide a better understanding of the dynamic status of the antioxidant defense system and its intricate balance with other biological pathways and systems in TD patients and its cognitive impairments. 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 and antioxidant efficiency in schizophrenia (Han et al., 2012; Zhang et al., 2012a) 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, the relevancy of using peripheral tissues to investigate the oxidative stress parameters in central nervous system is still uncertain though there is supporting evidence (Buckman et al., 1987, 1990; Yao and Reddy, 2011).

In summary, MnSOD activity was decreased in schizophrenia patients with than those without TD, and in the schizophrenia patients than the controls. The total RBANS score and the Visuospatial/Constructional index were lower in patients with than those without TD; the total score and all subscales except for the Visuospatial/Constructional index of RBANS were lower in the schizophrenia patients than controls. In the TD or non-TD group alone, MnSOD was associated with the RBANS total score and the index of immediate memory. Multiple regression analysis identified MnSOD as an independent contributor to the RBANS total score in either TD or non-TD group. These results suggest that TD patients had less effective antioxidant defense and suffered cognition impairment at a more severe level than non-TD patients; the compromised MnSOD activity may play a role in the pathophysiology of TD and its associated cognitive impairment. A future investigation using a larger sample size in a longitudinal manner may help to further clarify the potential causal relationship between oxidative stress, cognition dysfunction, and TD development.

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Contributors

Jing Qin Wu and Xiang Yang Zhang were responsible for study design, statistical analysis, and manuscript preparation. Da Chun Chen, Yun Long Tan, Shu ping Tan, Zhi Ren Wang, Mei Hong Xiu and Fu De Yang were responsible for recruiting the patients, performing the clinical rating and collecting the samples. Xiang Yang Zhang was involved in writing the protocol, providing the funding for the study and editing the manuscript. All authors have contributed to and have approved the final manuscript.

Conflict of interest

The authors reported no biomedical financial interests or potential conflicts of interest.

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