



Tardive dyskinesia is associated with greater cognitive impairment in schizophrenia



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ABSTRACT

Objective: Schizophrenia is a psychiatric disorder diagnosed by the presence of a number of symptoms with cognitive impairment as a core feature. Long-term antipsychotic treatment is often associated with the emergence of tardive dyskinesia (TD) and the presence of TD is linked to cognitive impairment. This study examined the relationship between TD and cognitive deficits in Chinese patients with schizophrenia.

Methods: We recruited 206 chronic patients with TD ($n = 102$) and without TD ($n = 104$) meeting DSM-IV criteria for schizophrenia and 104 control subjects who were matched on age, gender, and education. All the patients completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Positive and Negative Symptom Scale (PANSS), and the Abnormal Involuntary Movement Scale (AIMS).

Results: The PANSS total score ($p = 0.01$), N subscore ($p = 0.006$), and AIMS total score ($p < 0.001$) were significantly higher in patients with TD compared to patients without TD. Patients with TD scored lower for visuospatial/constructional, attention, and total index scores (all $p < 0.001$) on the RBANS. AIMS orofacial scores were identified as an independent contributor to RBANS total scores and attention index ($p < 0.05$), whereas AIMS limb and truncal scores were an independent determinant to the visuospatial/constructional index of RBANS ($p < 0.05$).

Conclusion: TD was associated with greater cognitive impairment in patients with schizophrenia compared to those without TD. The orofacial and limb-trunk TD specifically appeared to be a risk factor or contributor to the different aspects of cognitive deficits in schizophrenia. The association between schizophrenia and TD may be explained in part by oxidative stress.

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1. Introduction

Schizophrenia is a psychiatric disorder characterized by a range of cognitive deficits (Goff et al., 2011; Harvey et al., 2004; Heinrichs and Zakzanis, 1998) that generally persistent during the disease course (Heaton et al., 2001; Irani et al., 2011; Rajji and Mulsant, 2008). Antipsychotic medications are the standard in treating schizophrenia yet chronic use is associated with the emergence of tardive dyskinesia (TD). TD is characterized by involuntary, hyperkinetic, abnormal

movements (Correll and Schenk, 2008; de Leon, 2007; Remington, 2007), the presence of which is associated with poor quality of life, non-adherence with medications, and increased medical morbidity and mortality (Ballesteros et al., 2000; Browne et al., 1996; Youssef and Waddington, 1987). The pathophysiology of TD is not well understood and treatments lack efficacy, therefore prevention and early recognition may help improve treatment outcome (Remington, 2007; Soares and McGrath, 1999).

A number of risk factors have been associated with increased risk of developing TD. Some of these risk factors include being older, female 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 (Sachdev, 2000). Compared to the western countries, a generally low frequency of TD in Asian schizophrenia patients with inter-ethnic variations was reported in a recent study, which found that the variables including older age, male gender, more severe negative and extrapyramidal symptoms, and less anticholinergic drugs

Abbreviations: TD, tardive dyskinesia; RBANS, Assessment of Neuropsychological Status; PANSS, Positive and Negative Symptom Scale; AIMS, Abnormal Involuntary Movement Scale; CLAT, conceptual analogy test; MMSE, mini-mental state examination; ANOVA, analysis of variance; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; MDA, malondialdehyde.

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were independently associated with TD (Xiang et al., 2011). Among the aforementioned risk factors, a number of studies have consistently implicated chronic antipsychotic treatment and aging as risk factors in the development of TD (Glazer, 2000a, 2000b; Patterson et al., 2005; Zhang et al., 2009b), whereas cognitive impairment has been less frequently studied. Both Wegner et al. and Waddington et al. assessed cognition in approximately 30 individuals with schizophrenia using the conceptual analogy test (CLAT) and an abbreviated ten-question mental test and found those with TD performed worse (Waddington and Youssef, 1986; Wegner et al., 1985a). Further, two studies have linked orofacial dyskinesia and cognitive impairment as assessed by the mini-mental state examination (MMSE) (Byne et al., 1998; Waddington et al., 1987). Earlier studies found cognitive deficits preceded the onset of TD and may be a risk factor (Struve and Willner, 1983; Wegner et al., 1985b), whereas others found that TD was predictive of impaired cognitive function in association with the development of orofacial dyskinesia (Waddington and Youssef, 1996). Overall, although these studies link TD and cognitive impairment in patients with schizophrenia, they were limited by relatively small sample sizes and neuropsychological tests applied, which were either across only a limited number of cognitive domains or relatively insensitive (MMSE) (Randolph et al., 1998).

In the study presented here, we recruited three groups of more than 100 individuals each including patients with schizophrenia with and without TD, as well as age-, gender-, education-matched controls in a Chinese population. Additionally, we assessed subjects using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) across five cognitive domains in addition to the Abnormal Involuntary Movement scale (Randolph et al., 1998). To our knowledge, this was the first study to investigate possible relationships with cognitive function in schizophrenics and TD in a Chinese population.

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

Two hundred and six inpatients (Han Chinese) 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 40–73 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 of 29.9 ± 8.0 years on current antipsychotic treatment for an average of 4.2 ± 4.3 years. Patients were hospitalized for about 9 years (9.1 ± 7.2). 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 (Lehman et al., 2004; Woods, 2003). In addition, patients received one ($n = 67$), two or three ($n = 10$) different antiparkinsonian drugs.

Age-, gender-, and education-matched control subjects ($n = 104$) 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 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

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 = 104) | (n = 104) | (n = 102) | | |
| Male/female | 83/21 | 83/21 | 81/21 | 0.007 | 0.997 |
| Age (yrs) | 55.4 ± 5.7 | 55.2 ± 4.7 | 55.2 ± 7.6 | 0.043 | 0.958 |
| Education (yrs) | 9.0 ± 3.3 | 9.1 ± 2.4 | 9.4 ± 2.2 | 0.677 | 0.509 |
| Age of onset (yrs) | | 24.9 ± 6.5 | 25.5 ± 6.4 | 0.481 | 0.489 |
| Number of hospitalizations | | 4.3 ± 4.5 | 4.0 ± 2.7 | 0.432 | 0.512 |
| Antipsychotic types | | | | 0.377 | 0.539 |
| Typical | | 13 | 10 | | |
| Atypical | | 91 | 92 | | |
| Daily AP dose (mg/day) (CPZ equivalent) | | 585.4 ± 801.4 | 446.3 ± 431.3 | 2.386 | 0.124 |
| Duration of treatment (ms) | | 49.7 ± 54.3 | 51.7 ± 49.9 | 0.071 | 0.790 |
| PANSS total score | | 59.0 ± 13.8 | 63.7 ± 12.1 | 6.609 | 0.011* |
| P subscore | | 12.2 ± 6.1 | 13.1 ± 5.0 | 1.417 | 0.235 |
| N subscore | | 21.1 ± 7.1 | 23.8 ± 6.4 | 7.659 | 0.006** |
| G subscore | | 25.7 ± 5.1 | 26.9 ± 5.1 | 2.510 | 0.115 |
| AIMS total score | | 1.1 ± 1.3 | 6.7 ± 2.4 | 433.513 | <0.001** |

TD: tardive dyskinesia; 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.

* $p < 0.05$.

** $p < 0.01$.

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 (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., 2009a). 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. 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 Scheffé 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 gender, age, education, 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 Pearson's product moment correlation coefficients. Bonferroni corrections were applied to each test to adjust for multiple testing. Stepwise multivariate analysis using RBANS total or the index scores as the dependent variable was used to investigate the impact of a range of variables including gender, age, education, duration of antipsychotic treatment, type and dose of antipsychotic drugs, and AIMS orofacial and limb-trunk scores. SPSS version 17.0 was used to do all statistical analysis. Data are presented as mean and standard deviation (mean \pm SD). All p-values are two tailed with significance level set at 0.05.

3. Results

Table 1 shows the demographic data of all subjects as well as the characteristics of schizophrenic patients with and without TD. There was no significant difference in age, gender, and education between those with TD, those without TD, and normal controls (all $p > 0.05$). Compared to patients without TD, those with TD had significantly higher levels of negative symptom subscale of PANSS ($p < 0.01$) and higher PANSS total score ($p < 0.05$). These differences remained significant after adjusting for gender, age, education, age of onset, number of hospitalization, daily antipsychotic dose, and duration of treatment ($p < 0.05$). Patient's AIMS score was positively associated with the PANSS total and its subscales ($r = 0.14$ for all subscales, $r = 0.19$ for the sum; all $p < 0.05$), but not with other demographic or clinical variables (all $p > 0.05$), and only the association with PANSS total score survived Bonferroni correction (adjusted $p = 0.028$).

Between schizophrenia 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 or antiparkinsonian drugs (all $p > 0.05$). However, there was a significant difference in AIMS total score between patients with TD and without TD (6.7 ± 2.4 vs. 1.1 ± 1.3 , $F = 433.5$, $df = 1, 204$, $p < 0.001$). This difference remained significant after covarying for gender, age, education, duration of antipsychotic treatment, type and dose of antipsychotic drugs ($p < 0.001$).

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

The mean and standard deviation of RBANS total and index scores of 102 TD, 104 non-TD, and 104 controls are shown in Table 2. The significant differences in the cognition of patients with TD compared to those without TD included the lower RBANS total score (67.2 ± 12 vs. 73.1 ± 13.6 , $F = 16.8$, $df = 1, 204$, $p = 0.017$) and subscales of Visuospatial/Constructional (79.8 ± 16.7 vs. 86.2 ± 20.3 , $F = 17.1$, $df = 1, 204$, $p = 0.031$), language (84 ± 13 vs. 88.4 ± 13.1 , $F = 11.1$, $df = 1, 204$, $p = 0.041$), and attention (77 ± 13.8 vs. 84 ± 15 , $F = 21.7$, $df = 1, 204$, $p = 0.009$). After controlling for gender,

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

| | Normal controls (n = 104) | Patients without TD (n = 104) | Patients with TD (n = 102) | F | p value | Corrected p [#] |
|-----------------------------|------------------------------|----------------------------------|-------------------------------|------|---------|--------------------------|
| Immediate memory | 74.1 \pm 17.3 | 63.2 \pm 18.2 | 58.8 \pm 15.1 | 22.2 | <0.001 | <0.001 |
| Visuospatial/constructional | 80.4 \pm 14.6 | 86.2 \pm 20.3 | 79.8 \pm 16.7* | 4.3 | 0.015 | 0.089 |
| Language | 95.8 \pm 10.5 | 88.4 \pm 13.1 | 84 \pm 13* | 24.3 | <0.001 | <0.001 |
| Attention | 87.6 \pm 19.2 | 84 \pm 15 | 77 \pm 13.8** | 11.4 | <0.001 | <0.001 |
| Delayed memory | 88.3 \pm 15.1 | 74.3 \pm 20.6 | 69.2 \pm 18.9 | 29.7 | <0.001 | <0.001 |
| Total scale | 80.7 \pm 14.3 | 73.1 \pm 16.6 | 67.2 \pm 12* | 22.5 | <0.001 | <0.001 |

* indicates significance of the comparisons between TD and non-TD groups.

refers to Bonferroni corrections.

* $p < 0.05$.

** $p < 0.01$.

age, education, age of onset, number of hospitalization, daily antipsychotic dose, duration of treatment and antiparkinsonian drugs, all the differences remained significant with improved p values for RBANS total score ($p < 0.05$), the subscales of Visuospatial/Constructional ($p < 0.01$) and attention ($p < 0.05$; all $df = 1,197$), except that the significance of language index lost ($p > 0.05$). Furthermore, both schizophrenic patients with and without TD scored lower on total score and the indexes of immediate memory, language, and delayed memory than the controls (Table 2; all $p < 0.001$). These differences remained significant after covarying for sex, age, and education (all $p < 0.001$).

3.2. Correlation between AIMS score and cognitive performance

The RBANS total score and its indexes of visuospatial/constructional, attention, and language were negatively associated with the orofacial scores of AIMS (the sum of the first 4 items) for all schizophrenic patients group ($p = 0.01$, $r = -0.18$; $p = 0.02$, $r = -0.16$; $p = 0.004$, $r = -0.2$; and $p = 0.003$, $r = -0.2$; all $df = 204$), respectively. In addition, the attention index of RBANS was also negatively associated with AIMS limb and truncal scores (sum of the items 5–7; $r = -0.14$, $df = 204$, $p = 0.04$). However, there were no significant associations between RBANS total score or its indexes and AIMS facial or limb and truncal scores in either TD or non-TD group alone (all $p > 0.05$).

Stepwise multivariate regression analysis using RBANS and its index scores as dependent variables was performed for all patients to investigate possible independent determinants from variables including age, gender, education, age of onset, number of hospitalization, antipsychotic agent type, dose and duration of treatment, AIMS orofacial and limb and truncal score, and PANSS and its subscales. This analysis identified negative symptom of PANSS ($\beta = -0.273$, $t = -4.005$, $p < 0.0005$), gender ($\beta = 0.267$, $t = 4.035$, $p < 0.0005$), antipsychotic dose ($\beta = -0.211$, $t = -3.162$, $p = 0.002$), age ($\beta = -0.215$, $t = -3.186$, $p = 0.002$), age of onset ($\beta = 0.166$, $t = 2.447$, $p = 0.015$), and AIMS orofacial score ($\beta = -0.147$, $t = -2.172$, $p = 0.031$) as independent contributors to RBANS total score, which together accounted for 27% of the variance in RBANS total score. AIMS orofacial score was also found to be an independent contributor to the attention index of RBANS (Fig. 1; $\beta = -0.176$,

$t = -2.480$, $p = 0.014$). Similarly, AIMS limb and truncal score was detected as an independent determinant of visuospatial/constructional index (Fig. 1; $\beta = -0.150$, $t = -2.047$, $p = 0.04$) along with other two contributors including education ($\beta = 0.212$, $t = 2.901$, $p = 0.004$) and negative symptom scores of PANSS ($\beta = -0.197$, $t = -2.683$, $p = 0.008$).

4. Discussion

Our data showed that cognitive scores on the RBANS total scale and three subscales (language, immediate and delayed memory) were significantly lower in schizophrenic patients than in normal controls (Table 2). The RBANS total score and two subscales (visuospatial/constructional and attention) were significantly lower in patients with TD compared to those without TD. Interestingly, AIMS orofacial scores were identified as an independent contributor to RBANS total scores and its attention index, whereas AIMS limb and truncal scores were found to be an independent determinant to the visuospatial/constructional index of RBANS (Fig. 1). This suggests that the orofacial TD and the limb and trunk TD may play a differential role in the cognitive deficits seen in schizophrenia. To the best of our knowledge, this is the first study to associate two major subsyndromes of TD with specific cognitive impairments in Han Chinese schizophrenic patients.

Our finding that schizophrenic patients had lower RBANS total scales with or without TD compared to normal controls (Table 2) is in line with previous studies (Condray and Yao, 2011; Palmer et al., 2009; Sharma and Antonova, 2003). These results are particularly consistent with a report by Dickerson et al., which showed significant differences on the RBANS total score and all of the measured domains in schizophrenia compared to normal controls (Dickerson et al., 2004). Unlike Dickerson et al., we did not detect significantly lower scores on the visuospatial/constructional index in schizophrenic patients, which may arise from the differences in demographic and clinical status between the two samples such as age and duration of treatment.

We also found lower cognitive performance on RBANS total score and its two indices (the visuospatial/constructional and attention) in patients with TD compared to patients without TD (Table 2). The

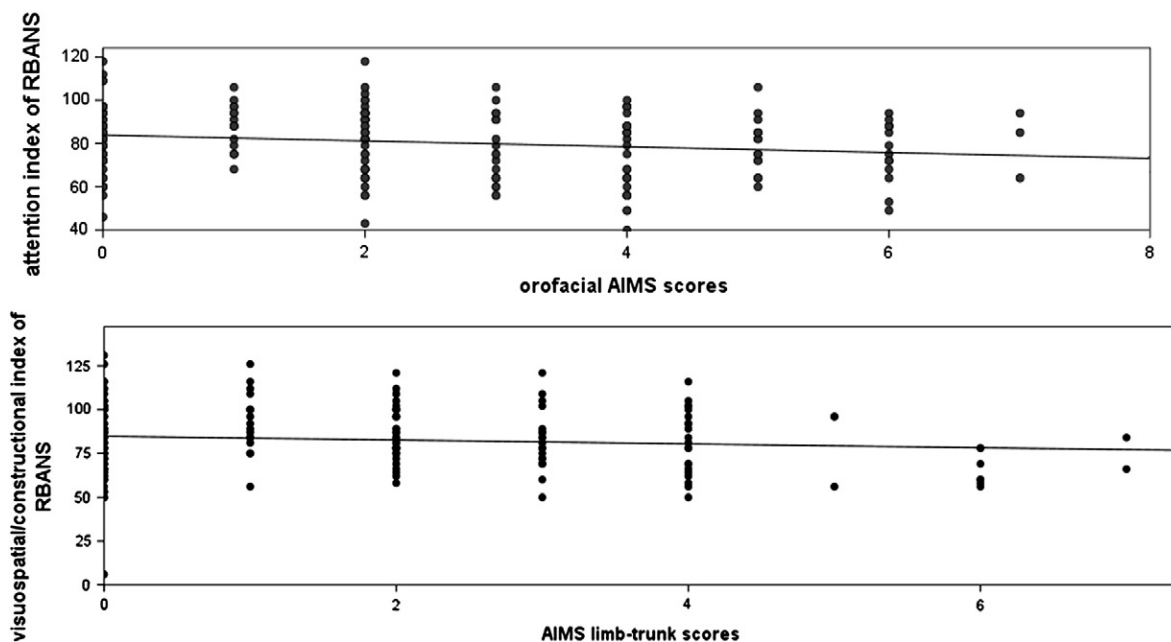


Fig. 1. RBANS attention and visuospatial/constructional indexes were negatively associated with AIMS orofacial and limb–trunk scores in schizophrenic patients, respectively ($p < 0.05$).

present study employed a larger cohort (Table 1) compared to previous studies yet effectively replicated earlier findings that patients with schizophrenia and TD exhibited significant deficits in cognitive performance on neuropsychological tests (Davis et al., 1992; Waddington and Youssef, 1986, 1996; Waddington et al., 1987; Wegner et al., 1985b). While most of these studies used a cross sectional design to show that patients with TD suffered more preexisting cognitive impairment than did patients without TD (Davis et al., 1992; Waddington and Youssef, 1986; Waddington et al., 1987; Wegner et al., 1985b), two studies further investigated this relationship using a longitudinal design. Wegner et al. observed that patients who developed TD showed greater preexisting cognitive impairment prior to the onset of TD compared to those that did not develop TD (Wegner et al., 1985b). Additionally, Waddington et al. found that patients demonstrating the progressive onset of emergence of TD over time also showed a marked deterioration in cognitive function (Waddington and Youssef, 1996). These studies, by studying the same patients over time to remove cohort effects and increase detecting power, further confirmed the association between cognitive dysfunction and TD.

We investigated the association between TD and cognition using multivariate analysis and found that AIMS orofacial score was an independent contributor to RBANS total scores and its attention index, whereas AIMS limb and trunk score was an independent determinant to the visuospatial/constructional index (Fig. 1). These results suggest that the orofacial TD may be the risk factor or contributor for general cognitive deficits and attention, whereas the limb-trunk TD may be the risk factor or contributor for visuospatial/constructional cognition. Consistent with our finding, Waddington et al. has demonstrated that the presence of either marked cognitive dysfunction or muteness bore a consistent and highly significant primary association with both the presence and the overall severity of orofacial dyskinesia (DeWolfe et al., 1988; Waddington et al., 1987). In addition, DeWolfe et al. has reported that facial and limb TD symptoms significantly correlated with 11 and 2 WAIS (Wechsler Adult Intelligence Scale) scores, respectively. Taken together, our and previous results suggest that two major subsyndromes of TD based upon topography, the orofacial and limb-trunk dyskinesia, may differentially contribute to specific cognitive deficits in schizophrenia.

The mechanisms underlying the association of TD with impaired cognition are still open to a variety of interpretations, one of which is that greater cognitive impairment in schizophrenia may be due to preexisting neural substrates that may infer vulnerability to develop TD in response to antipsychotic treatment (Waddington et al., 1993). Evidence in favor of this hypothesis is supported by increased ventricle-brain ratio among older, chronically ill schizophrenic patients with persistent orofacial TD (King et al., 1991; Waddington et al., 1989), which is not present in relatively young patients with TD (Gold et al., 1991). It is possible however that the association between cognitive impairment and TD may reflect not a neural-based vulnerability but rather a state marker for TD (Waddington et al., 1993). Indeed, a longitudinal study found that poor initial cognitive function was not predictive of the subsequent emergence of TD in older, chronically schizophrenic patients without TD, and only those who went on to develop orofacial TD were distinguished by cognition deterioration over the same time-frame their TD emerged (Waddington et al., 1990). Thus the aforementioned two hypotheses of organic vulnerability to versus state marker for TD are competing for interpreting the nature of the association between cognitive dysfunction and TD.

Increasing evidence however implicates oxidative stress as a major contributor to the pathophysiology of schizophrenia (Bitanirwe and Woo, 2011; Yao and Keshavan, 2011) and TD (Lohr et al., 1990; Peet et al., 1993; Tsai et al., 1998; Yamada et al., 1997). Based on this evidence, it is possible that oxidative stress may contribute to the observed association between TD and cognition dysfunction. For example, studies

have found lower levels of antioxidant markers superoxide dismutase (SOD) and thiobarbituric acid reactive substances (TBARS) in cerebrospinal fluid and peripheral tissues of schizophrenic patients with TD (Lohr et al., 1990; Peet et al., 1993; Tsai et al., 1998; Yamada et al., 1997). Our lab has also previously found lower levels of plasma SOD, glutathione peroxidase, catalase, total antioxidant status and higher malondialdehyde (MDA) levels in schizophrenic patients with TD compared to those without TD (Chen et al., 2010; Zhang et al., 2003, 2007). Moreover, total antioxidant status was significantly associated with attention index and RBANS total scores in schizophrenia patients (Zhang et al., 2012). Further, the oxidative stress marker, GSH-Px has been found to be negatively correlated with CT measures of brain atrophy in chronic schizophrenic patients (Buckman et al., 1987, 1990). Compromised oxidative stress mechanisms may explain, in part, why those patients who develop orofacial TD experience cognition deterioration over the same time-frame their TD emerged (Waddington et al., 1990), since these two symptoms may both be due to oxidative stress. Although our speculation that oxidative stress may be linked to the development of TD and progressive cognitive decline is supported by some evidence, studies directly assessing a possible causal association are warranted.

In addition to the association between TD and cognition, we also found that the schizophrenia patients with TD displayed significantly higher levels of negative symptoms than those without TD, which replicated earlier work reporting significant association between TD and the negative symptoms on the PANSS (Davis et al., 1992; Waddington et al., 1987; Wang et al., 2012; Zhang et al., 2009b). Recently, a study further investigated whether patients who had the primary negative symptoms of schizophrenia (deficit schizophrenia) were more likely to experience TD than those without deficit schizophrenia (Telfer et al., 2011). A significant association between deficit features and TD was detected, suggesting that the pathological process underlying deficit schizophrenia can predispose to the development of TD (Telfer et al., 2011). Coincidentally, we previously showed that the negative symptoms reflected by PANSS negative subscore were also significantly correlated with MDA levels (oxidative stress marker) in schizophrenics with TD (Zhang et al., 2007). Taken together, it is plausible to speculate that oxidative stress could be one of the pathological processes underlying deficit schizophrenia, predisposing to the development of TD and this hypothesis warrants further investigation.

There are several factors that limit the findings of the present study. First, this study uses a cross-sectional and retrospective design as the psychometric assessments are completed after the development of TD. Thus, it is unknown whether cognitive impairment precedes the motor disorder or vice versa. Second, the ability to generalize our study is limited by our sample 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. Third, the age of patients included in our sample was wide ranging (40–73 yrs) and generally older compared to other studies (mean 55 yrs). The impact of aging on cognitive decline is clear and in our sample, age is an independent contributor to RBANS total score. Nevertheless, after statistically controlling for the effects of age, the association between TD and cognition remained significant. In addition, it is worthy of mentioning that age factor also has implications in abnormal movements, specifically in spontaneous dyskinesias which are more common in older individuals and can be mistaken for TD, even though we had two assessments of TD diagnosis for each subject. Fourth, our study linking TD to symptoms did not exclude the possibility that individuals who have TD are being masked by antipsychotic treatment, and would only be evident in the case of dose reduction or discontinuation. For example, atypical antipsychotic drug clozapine has been reported to exert a favorable effect on TD in a proportion of patients, and it has even been claimed to be the drug of choice for patients with

TD (Remington, 2007), which may attenuate or sometimes eliminate or 'mask' TD. Finally, we did not screen patients for non-prescription drug use which has been shown to have a significant impact on cognitive performance (Pace-Schott et al., 2008).

5. Conclusion

Our results demonstrate that schizophrenic patients with TD experienced greater cognitive impairment than those without TD. AIMS orofacial score was an independent contributor to RBANS total scores and its attention index, whereas AIMS limb-truncal score was an independent determinant to the visuospatial/constructional index. Development of orofacial and limb-trunk TD may be a risk factor for the degree of cognitive impairment in schizophrenia. While the mechanisms underlying the association of TD with impaired cognition are still open to a variety of interpretations, we hypothesize that oxidative stress may contribute significantly to the observed association between TD and cognition dysfunction. This postulation is compatible with popular hypotheses of neural substrate vulnerability or state marker due to antipsychotics. Nevertheless, the speculative role of oxidative stress serving as a functionally linking node between TD and impaired cognition warrants further investigation.

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