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RESEARCH ARTICLE

# Plasma total antioxidant status and cognitive impairments in first-episode drug-naïve patients with schizophrenia

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## Abstract

Accumulating evidence suggest that excessive reactive oxygen species-induced oxidative damage may underlie neurodegeneration and cognitive impairment in several disorders including schizophrenia. In this study we examined the association of oxidative stress with cognitive deficits in first-episode drug-naïve (FEDN) patients with schizophrenia. We recruited 54 FEDN patients and 50 age- and sex-matched healthy controls and examined the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus cognitive Battery (MCCB) and plasma total antioxidant status (TAS). Psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale. The results showed that plasma TAS levels were significantly lower in the patients than those in the healthy subjects (94.7 $\pm$ 25.0 U/ml vs 156.6 $\pm$ 46.7 U/ml, $p < 0.0001$). The patients scored lower than healthy controls on the MCCB total score, speed of processing, attention/vigilance and managing emotion test index and STROOP test. For the patients, TAS was associated with some domains of cognitive deficits in schizophrenia, such as speed of processing, attention/vigilance and emotion managing. Our results suggested that oxidative stress may be involved in the pathophysiology of schizophrenia at the early of stage and its cognitive impairment.

**Keywords** Schizophrenia · Cognitive function · MCCB · Oxidative stress · Total antioxidant capacity

## Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| ATD | Acute tryptophan depletion |
| BVMT | Brief Visuospatial Memory Test |
| FEDN | First-episode drug-naïve |
| FEP | First-episode patients |
| FRAP | Ferric reducing antioxidant potential |
| HVLT | Hopkins Verbal Learning Test |
| LTP | Long time potentiation |
| MCCB | Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus cognitive Battery and plasma |
| MSCEIT | Mayer–Salovey–Caruso Emotional Intelligence Test |
| NAB | Neuropsychological assessment battery |
| OS | Oxidative stress |
| PANSS | Psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale |
| ROS | Reactive oxygen species |
| SCID | Structured clinical interview for DSM-IV |
| TAS | Total antioxidant status |
| TPTZ | Tripyridyl triazine |

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## Introduction

Schizophrenia is a severe mental illness characterized by hallucinations, delusions, negative symptoms, and often a range of cognitive deficits in executive function, attention, working memory and emotion processing (Green et al. 2015; Harvey 2014; Palmer et al. 2009; Rajji et al. 2014). These disturbances in cognition are increasingly recognized as cardinal features of the illness (Erlenmeyer-

Kimling 2000), they often precede the symptoms of psychosis, are orthogonal to positive and negative symptoms (Nieuwenstein et al. 2001), and generally persistent during the course of the disorder (Irani et al. 2011; Rajji and Mulsant 2008). Moreover, poor functional outcome is associated more closely with the extent of cognitive impairments than with the severity of psychopathology symptoms, showing lower performance in basic activities of daily living, social problem solving, occupational functioning, community outcome, and quality of life (Keefe et al. 2008). However, cognitive decline in schizophrenia is generally unaffected by currently available antipsychotics medication (Mintz and Kopelowicz 2007) and the pathophysiological mechanisms underlying these cognitive deficits are still unclear.

Free radicals, such as hydroxyl, peroxyl, alkoxyl and inorganic radicals, are highly reactive chemical species generated during normal metabolic processes, and, if excess, can cause lipids, proteins, and DNA damage, leading cell dysfunction or even death (Miller et al. 1993). Oxidative stress (OS), resulting from an imbalance between oxidant molecules and antioxidant defenses, can cause increased oxidative stress as well as initiation of lipid peroxidation (Kohen and Nyska 2002; Yao and Keshavan 2011). Under normal physiological conditions, free radical-induced oxidative stress is combated by a complex antioxidant defense system (Bitanihirwe and Woo 2011; Halliwell 2006; Valko et al. 2007; Yao and Reddy 2011). The major antioxidant defenses in plasma include ascorbate, protein thiol, albumin, uric acid, bilirubin, $\alpha$-tocopherol and $\beta$-carotene account for about 85% of the total human antioxidant capacity (Reddy 2003). Determination of total antioxidant status (TAS) provides a measurement of all antioxidants, although we can yield valuable information by measuring levels of specific antioxidant molecules (Yao et al. 1998).

Numerous preclinical and clinical studies have shown that oxidative damage produced by excessive reactive oxygen species (ROS) may underlie cognitive impairment and neurodegeneration, especially in aging (Davies 2000; Hu et al. 2006; Nicolle et al. 2001; Radak et al. 2007). Aging is related to a slow deterioration of cognitive performance particularly on learning and memory (Kolosova et al. 2006). ROS plays a modulatory role in the signaling events underlying long time potentiation (LTP), a cellular model of learning and memory (Poo 2001) and formation of memory in young adult mice, plays an important role in the damage of memory in the aged and diseased brain (Massaad and Klann 2011). A lot of researches have indicated that the accumulation of oxidative damage especially the oxidized proteins and peroxided lipid underlies the molecular basis of brain aging and neurodegeneration (Kolosova et al. 2006). A previous study reported that overexpression of Cu/Zn-SOD, a key enzyme in the metabolism of oxygen free radicals in transgenic mice leaded to chronic oxidative stress as well as impaired ability to express LTP and spatial memory. Moreover, these effects were abrogated by treatment of free radical scavenger catalase or the antioxidant (Gahtan et al. 1998).

Oxidative stress caused by ROS may be in part related to the pathophysiology of schizophrenia (Lohr et al. 2003; Yao and Reddy 2011). Several studies report that patients with schizophrenia have altered the peripheral activities of antioxidant enzymes (Zhang et al. 2013a), reduced levels of antioxidants and increased levels of lipid peroxidation in serum, plasma, red blood cells (Flatow et al. 2013) and cerebrospinal fluid (Padurariu et al. 2010). Moreover, numerous studies suggest the activities of critical antioxidant enzymes (Zhang et al. 2015) or levels of lipid peroxidation (Akiibinu et al. 2012; Gunes et al. 2016) are related to the psychopathology in schizophrenia, including positive symptoms, negative symptoms (Raffa et al. 2011; Virit et al. 2009; Wu et al. 2012) and cognitive deficits (Zhang et al. 2012a, b, 2013a).

The aim of this study was to examine the relationship between oxidative stress and cognitive deficits in schizophrenia. Only a few studies have investigated their relationship in chronic patients with schizophrenia (Virit et al. 2009; Zhang et al. 2012a, b). However, no study has explored their relationship in first-episode and drug-naïve (FEDN) patients with schizophrenia. We hypothesized that excessive oxidative stress may be related to cognitive impairment in FEDN patients.

## Methods

### Subjects

Fifty-four inpatients (22 men and 32 women), diagnoses were confirmed with the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994) by agreement of two senior psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) were recruited from Beijing Huilongguan Hospital, a city-run psychiatric hospital in Beijing, China. All patients were first-episode and had no previous exposure to antipsychotics. The patients had a mean age of 25.9 ± 6.0 years, a mean total duration of illness of 28.6 ± 30.2 months, and a mean education of 13.0 ± 2.4 years.

Fifty healthy subjects (20 men and 30 women) were recruited from the local community, and matched for the age and gender to the patients. Axis I psychiatric disorders were ruled out in these controls by psychiatric review evaluation implemented by a psychiatrist. Demographic data for patients and normal controls are summarized in

**Table 1** Demographics of patients and normal control subjects

| | Schizophrenia ($n$ = 54) | Control subjects ($n$ = 50) | $F/\ \chi^2$ | *df* | *p* |
|---|---|---|---|---|---|
| Sex, M/F | 22/32 | 20/30 | 0.01 | 1 | 0.94 |
| Age (year) | 25.9 ± 6.0 | 25.9 ± 6.7 | $3.85 \times 10^{-4}$ | 1, 102 | 0.98 |
| Education (year) | 13.0 ± 2.4 | 12.6 ± 2.4 | 0.46.0 | 1, 102 | 0.50 |
| Smokers | 21 (35.2%) | 17 (34.0%) | 0.27 | 1 | 0.61 |
| Smoked cigarettes daily | 14.0 ± 8.9 | 12.6 ± 7.2 | 0.40 | 1, 36 | 0.45 |
| Age of onset (years) | 23.6 ± 5.1 | NA | | | |
| Duration of illness (ms) | 28.6 ± 30.2 | NA | | | |
| *PANSS* | | | | | |
| *P*—score | 23.8 ± 5.8 | NA | | | |
| *N*—score | 21.9 ± 5.1 | NA | | | |
| *G*—score | 39.3 ± 8.1 | NA | | | |
| Total score | 85.1 ± 14.6 | NA | | | |

All data were reported as mean ± SD unless otherwise indicated. There was no significant difference among schizophrenics and control controls in any characteristic by $\chi^2$ test, *t*-test and analysis of variance (ANOVA), followed by post hoc tests (Fisher's LSD test)

Table 1. A complete medical history and physical examination, laboratory tests including a urine and blood screen, and electrocardiogram were obtained from all participants. All subjects were physical healthy, without any neurological or other medical diseases. Neither the patients nor the control subjects had a diagnosis of alcohol or illicit drug abuse or dependence.

The study was approved by the ethics committee of Beijing Huilongguan Hospital. After a complete description of the study to all participants, the written informed consents were obtained.

## Clinical measures

The patient's psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) on the day of the blood drawing, which was conducted independently by two psychiatrists. To ensure consistency and reliability of ratings during study, this two psychiatrists had simultaneously participated in training courses on the use of the PANSS before this study started. After training, a correlation coefficient was higher than 0.8 and maintained for the PANSS total score by repeated assessment.

## Blood sampling and plasma TAS measurements

Plasma samples were collected between 6 and 8 AM following an overnight fast. Samples were obtained simultaneously for patients and controls within one-month period. The plasma samples were separated, aliquoted and then stored at − 70 °C.

A full description of the assays for TAS levels was reported in our previous study (Li et al. 2011). Briefly, the plasma TAS was measured using a commercially available kit within 1 week by ferric reducing antioxidant potential (FRAP). In this assay, TAS was regarded as reductant of $Fe^{3+}$ to $Fe^{2+}$, which are chelated by TPTZ to form a $Fe^{2+}$-TPTZ complex absorbing at 593 nm (Benzie and Strain 1996) and recorded using the Mutiskan microplate reader (Flow-labs, McLean, VA, USA). Activity was expressed as units per milliliter (U/ml). All were assessed by the same technician, who was blind to the diagnostic status of participants. The identity of all subjects was indicated by a code number maintained by the investigator until all biochemical analyses were completed. Inter- and intra-assay variation coefficients were 6% and 5%, respectively.

## Cognitive tests

Cognitive function was evaluated by the measurement and treatment research to improve cognition in schizophrenia (MATRICS) consensus cognitive battery (MCCB) (Green and Nuechterlein. 2004). 10 tests were selected for the MATRICS Consensus Cognitive Battery (MCCB) that is used to determine functioning in 7 cognitive domains and a global composite score. The MCCB battery includes Trial Making Test Part A; Brief Assessment of cognition in Schizophrenia: Symbol Coding; Hopkins Verbal Learning Test (HVLT); Wechsler Memory Scale Spatial Span; Letter-number Span; Neuropsychological Assessment Battery (NAB): Maze; Brief Visuospatial Memory Test (BVMT); Category Fluency; Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotion; and the Continuous Performance Test-Identical Pair (CPT-IP). The seven cognitive domains are: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual

Learning, Reasoning/Problem-solving, and Social Cognition (Barch et al. 2009). Our group has translated MCCB into Chinese and this academic version was converted into a tool to be available for clinical trials and other professional purposes in clinical settings. Its clinical validity and test–retest reliability has been established in controls and schizophrenia patients (Zou et al. 2009).

Stroop Test: We implement a computerized version of the Stroop test in this study. During the test, the subjects were presented with 100 words with the 4 colors names printed in incongruent colors (for example, the "word" is printed in red ink). The subjects were asked to name the color of the each word as quickly and accurately as possible during 1 min, ignoring the word name itself. The number of corrected and uncorrected errors was recorded.

Each participant came in the neurocognitive testing room on separate day. A research member introduced each subject to the general cognitive testing procedures to attend a brief (about 5 min) training session so as to acclimate them to the testing environment and computerized tasks. In order to reduce or eliminate potential deficits in cognitive function resulting from smoking withdrawal, subjects who smoked were allowed to smoke prior to and during testing breaks. Breaks were taken on request at the end of each domain test of the MATRICS.

### Statistical analysis

Demographic and clinical variables of the patient and healthy control groups were compared using the parametric Student's $t$ test or one-way of analysis of variance (ANOVA) for continuous variable and $\chi^2$ for categorical variables. Since the TAS was Gaussian distributed in patients and controls (Kolmogorov–Smirnov one sample test: both $p > 0.05$), the principal outcome analysis was made up of one-way ANOVA. We compare scores of cognitive domains between the patient and control groups using ANOVA too. When ANOVA results were significant, the effects of age, sex, education and smoking were tested by entering these variables into the analysis model as covariates. Relationships between plasma TAS and MCCB total and cognitive domains scores in patients and healthy controls were assessed with Pearson's correlation coefficients, especially in the patients to see if it is correlated to the severity of cognitive impairment, correlations between plasma TAS and scores of PANSS subscales were also analyzed with Pearson's correlation coefficients, with partial correlation when controlling for the effects of other additional variables such as age, sex, education and smoking. Data were presented as mean ± SD and statistical significance was defined as $p < 0.05$.

## Results

Demographic and clinical characteristics for the schizophrenia patients and healthy controls are showed in Table 1. No significant differences were noted between patients and normal control groups in any demographic characteristic.

There was no significant correlation between TAS levels and age in controls and patients (all $p > 0.05$). TAS levels were not associated with onset age of illness, duration of illness in patients (all $p > 0.05$). Moreover, TAS levels did not differ either between smoker and nonsmoker subjects or between male and female in all participants, controls or schizophrenics.

### Plasma TAS in patients and healthy controls

Plasma TAS levels were significantly lower in schizophrenia than controls (94.7 ± 25.0 U/ml vs. 156.6 ± 46.7 U/ml, $F_{1,\ 102} = 79.88$, $p < 0.001$), and not attenuated after covariance for age, sex, education, smoking ($F_{1,\ 102} = 70.02$, $p < 0.001$). We found that no sex difference in TAS levels for patients and healthy controls. Plasma TAS levels had a significant positive correlation with the general symptom subscore of PANSS ($r = 0.288$, $p = 0.040$), but not with positive and negative symptom ($p > 0.05$).

### Cognitive performance in schizophrenics and healthy controls

Table 2 shows MCCB total and cognitive domains scores of patients and healthy controls. The unadjusted results showed that the first-episode drug-naïve patients with schizophrenia performed significantly worse compared to healthy controls on MCCB total score ($F_{1,\ 102} = 9.85$, $p = 0.002$), Speed of processing total score ($F_{1,\ 102} = 7.02$, $p = 0.005$), Attention/Vigilance score ($F_{1,\ 102} = 32.89$, $p < 0.0001$), MSCEIT total ($F_{1,\ 102} = 5.05$, $p = 0.027$), and Stroop test ($F_{1,\ 102} = 9.99$, $p = 0.002$). After controlling for age and education, these results remained significant for MCCB total score ($F_{1,\ 102} = 8.18$, $p = 0.005$), Speed of processing total score ($F_{1,\ 102} = 7.02$, $p = 0.009$), Attention/Vigilance score ($F_{1,\ 102} = 28.39$, $p < 0.001$), MSCEIT total ($F_{1,\ 102} = 5.05$, $p = 0.027$), and Stroop test ($F_{1,\ 102} = 7.21$, $p = 0.009$). There were no significant differences in other cognitive performances ($p > 0.05$).

Furthermore, we did not find the age or education correlated with all cognitive performances for schizophrenia patients and healthy subjects. There was no significant

**Table 2** Cognitive domain scores and the serum TAS levels in patients and normal control subjects

| | Schizophrenia ($n$ = 54) | Control subjects ($n$ = 50) | Adjusted $F^a$ | $p$ |
|---|---|---|---|---|
| MCCB total score | 50.5 ± 12.3 | 61.4 ± 11.7 | **8.18** | **0.005** |
| Speed of processing | 49.1 ± 11.5 | 56.6 ± 12.7 | **7.02** | **0.009** |
| Attention/vigilance | 43.0 ± 11.2 | 55.9 ± 11.5 | **28.39** | **< 0.001** |
| Working memory | 55.0 ± 13.1 | 58.1 ± 13.9 | 1.38 | 0.24 |
| HVLT | 51.1 ± 13.0 | 58.1 ± 14.8 | 2.74 | 0.10 |
| BVMT | 51.0 ± 11.9 | 56.1 ± 13.8 | 2.57 | 0.11 |
| NAB | 55.2 ± 17.1 | 61.4 ± 12.9 | 2.33 | 0.13 |
| MSCEIT | 45.1 ± 14.5 | 51.3 ± 11.0 | **5.05** | **0.027** |
| TROOP | 46.9 ± 11.8 | 54.7 ± 13.0 | **7.21** | **0.009** |
| TAS | 94.7 ± 25.0 | 156.6 ± 46.7 | **70.02** | **< 0.001** |

[a]Adjusted *F* means that *F* value was controlled for sex, age, smoking and education

*MCCB* Measurement and treatment research to improve cognition in schizophrenia (MATRICS) consensus cognitive battery, *HVLT* hopkins verbal learning test, *BVMT* brief visuospatial memory test, *NAB* neuropsychological assessment battery, *MSCEIT* Mayer–Salovey–Caruso emotional intelligence test, *TAS* total antioxidant status

**Table 3** Pearson's correlation between TAS and PANSS scores in schizophrenia patients

| PANSS | TAS ($n$ = 54) | |
|---|---|---|
| | $r$ value | $P$ value |
| *P*—score | − 0.215 | 0.13 |
| *N*—score | 0.033 | 0.818 |
| *G*—score | − 0.288 | **0.040** |
| Total score | − 0.236 | 0.096 |

**Table 4** Relationships between TAS and Cognitive domain scores in schizophrenia patients

| Cognitive | TAS ($n$ = 54) | |
|---|---|---|
| | $r$ value | $P$ value |
| MCCB total score | 0.32 | **0.003** |
| Speed of processing | 0.42 | **$5.98 \times 10^{5}$** |
| Attention/vigilance | 0.42 | **$2.43 \times 10^{5}$** |
| Working memory | 0.13 | 0.25 |
| HVLT | 0.27 | **0.014** |
| BVMT | 0.16 | 0.16 |
| NAB | 0.20 | 0.07 |
| MSCEIT | 0.16 | 0.15 |
| TROOP | 0.19 | 0.08 |

correlation between onset age or duration of illness and cognitive index.

### TAS and PANSS scores in schizophrenia patients

A weak negative relationship ($r = -0.288$, $p = 0.040$) was found between TAS levels and *G*-score of PANSS in the patients with schizophrenia ($n = 54$) after controlling for age, sex and smoke, but not with *P*-score, *N*-score or total-score as shown in Table 3.

### TAS and cognitive performance

Correlation analysis showed that TAS levels were not related to all cognitive performances for the healthy controls. In the patients with schizophrenia ($n = 54$), TAS levels were positively correlated with MCCB total score ($r = 0.467$, $p = 0.001$), Attention/Vigilance ($r = 0.308$, $p = 0.028$), working memory ($r = 0.286$, $p = 0.042$), HVLT score ($r = 0.517$, $p = 0.001$), BVMT score ($r = 0.340$, $p = 0.015$), and NAB ($r = 0.315$, $p = 0.024$). Further partial correlation analysis revealed that the correlation mainly existed between TAS levels and MCCB total ($r = 0.32$, $p = 0.003$), Attention/Vigilance ($r = 0.42$, $p < 0.001$), HVLT score ($r = 0.27$, $p = 0.014$) respectively as controlling for age, sex, education and duration of illness, there were potentially significant correlations between TAS levels and BVMT score ($r = 0.16$, $p = 0.16$) and Stroop test score ($r = 0.19$, $p = 0.08$) as shown in Table 4.

## Discussion

This study found that (1) plasma TAS levels were significantly lower in first-episode drug naïve schizophrenia patients than controls; (2) schizophrenia patients had significantly lower scores on global composite score, speed of processing, attention/vigilance, social cognition of MCCB and Stroop test than controls; (3) TAS levels were positively correlated with the speed of processing, attention/vigilance, verbal learning and memory indices and the MCCB total score in patients. Previous studies have found that the oxidative stress is associated with cognitive impairments which were assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in chronic schizophrenia (Zhang et al. 2012a, b). Although the RBANS is becoming a widely used screening instrument in neuropsychological assessment, it also has some limitations. For example, because it is a brief test battery, it is unable to evaluate all of the cognitive functions that may be altered in patients, such as motor abilities or executive functioning of MCCB. As we know, this is first report to research the correlation between oxidative stress biomarker and cognitive deficits which were assessed by the MCCB in first-episode drug-naïve patients with schizophrenia.

Our finding of decreased levels of plasma TAS in first-episode drug-naïve schizophrenia patients accords with previous findings (Ruiz-Litago et al. 2012; Li et al. 2011; Martinez-Cengotitabengoa et al. 2012; Reddy 2003). Other studies reported that the plasma TAS levels were decreased in chronic schizophrenic patients (Virit et al. 2009; Zhang et al. 2012a, b). A deficit in the antioxidant defence system of patients with psychosis has been reported by other researchers. Subsequent studies confirmed this association between FEP and decreased antioxidant capacity (Reddy 2003; Li et al. 2011; Li 2006) reported that patients with schizophrenia have increased levels of oxidative stress, and antipsychotic drugs can ease the activity decreases of antioxidant enzymes such as SOD and CAT (Miljevic et al. 2018). These results suggested that antioxidants were reduced in schizophrenia. They concluded that there is dysregulation of free radical metabolism and poor activity of the antioxidant defense system in patients with schizophrenia. In the present study, we observed significantly lower levels of TAS in FEDN compared with healthy controls. There were some reports shows smoking, sex, age, duration of illness can influence TAS levels (Bitanihirwe and Woo 2011; Zhang et al. 2012a, b), while no sex difference in TAS levels between patients and healthy controls was found in our study, it was not attenuated after covariance for sex, age, education and smoking. Therefore, oxidative stress mechanisms may be common pathophysiological pathways in schizophrenia (Li 2006). Impairment in the antioxidant system may be a common pathway of several psychiatric, metabolic and neurological disorders (An et al. 2018; Martinez-Cengotitabengoa et al. 2012). Specific markers of oxidative stress as a sensor of oxidation associated with schizophrenia might provide a key link connecting mechanisms underlying numerous processes described in schizophrenia. Some studies investigating the cognitive effects of serotonin depletion suggested that low serum tryptophan Levels and acute tryptophan depletion (ATD) impair cognitive function (Ramos-Chavez and Roldan-Roldan 2018) like verbal recall and recognition (Mace et al. 2008). Its metabolite kynurenine has been shown to cause cell death through the ROS pathway in nature killer (NK) cells (Wang et al. 2016). Mitochondrial dysfunction triggers extensive generation of free radicals leading to oxidative/nitrative stress, abnormalities, and pathologic consequences. Patients with schizophrenia present an increase in oxidative damage to lipids, proteins, and DNA, in both central and peripheral tissues with deficits of antioxidant defense (Boskovic et al. 2011). However, this impairment in antioxidant defense seems to be non-specific, since it has also been described in patients with affective disorders (Ozcan et al. 2004).

We also found plasma TAS levels had a significant positive relationship with the general symptom subscore of PANSS which is consistent with previous reports (Zhang et al. 2012a, b, 2013b), but not with positive and negative symptom. Therefore, TAS and oxidative stress may play a role in the psychopathology of schizophrenia.

Our unadjusted results showed that the first-episode drug-naïve patients with schizophrenia performed significantly worse compared to healthy controls on MCCB total score, Speed of processing total score, Attention/Vigilance score, MSCEIT total, and Stroop test, which is also consistent with previous findings (McCleery et al. 2014; Rajji et al. 2013; Tan et al. 2014). However, McCleery's study found schizophrenic patients showed impaired performance across all MCCB domains relative to controls. This difference may reflect the different sample size of the two samples, since McCleery's included 105 patients and 300 controls. In contrast, we had less sample size, while our controls were younger and matched on age ($25.9 \pm 6.0$, $25.9 \pm 6.7$), their controls were substantially older ($22.1 \pm 3.7$, $42.6 \pm 11.6$), which likely led to different presentation on the MCCB tests. Rajji et al. (2013) reported that there was an aging effect on all ten tests with aging associated with poor performance except for MSCEIT on which aging was associated with better performance. There was also an education and sex effect on all cognitive tests. MCCB findings were simply an artifact of the psychometric properties. In our study, after controlling for age and education, these results remained significant for MCCB total score, Speed of processing total score, Attention/Vigilance score, MSCEIT total, and Stroop test. Meanwhile, we did not find the age or education correlated with all cognitive performances for schizophrenia patients and healthy subjects. There was no significant correlation between onset age or duration of illness and cognitive indexes.

Interestingly, TAS was found to be positively related to MCCB total score, Attention/Vigilance, working memory, HVLT score, BVMT score, and NAB. Further partial correlation analysis revealed that the correlation mainly existed between TAS levels and MCCB total score, Attention/Vigilance, HVLT score and Stroop respectively as controlling for age, sex, education and duration of illness, there were potentially significant correlations between TAS levels and BVMT score. The association was alternate to our expected direction that OS was the conventional risk factors of cognitive impairment, indicating that OS-induced damage may be important and independent in schizophrenia. Lower TAS being positively associated with impaired cognitive function in schizophrenia is consistent with some previous studies showing positive relationship between TAS and cognitive deficits. (Martinez-Cengotitabengoa et al. 2012; McCleery et al. 2014; Tan et al. 2014; Wu et al. 2014; Zhang et al. 2012a, b). An imbalance between the production and elimination of free radicals can damage DNA during aging (Mendoza-Nuñez et al. 1999). Those with normal antioxidant levels showed a higher frequency of DNA damage than subjects with low antioxidant levels (Mendoza-Nuñez et al. 1999, 2001). Therefore, DNA damage leads to increased levels of antioxidant in order to prevent cells from further damage and promote recovery. A study found Polygonum minus possesses antioxidant and anticholinesterase activity and demonstrated enhanced cognition in vivo, in vitro and ex vivo cellular (George et al. 2014). The extract was shown to possess strong antioxidant capacity, Furthermore, the antioxidants of the standardized extract can protect cells from oxidative damage, as shown by the cellular antioxidant protection assay. In the animal model of cognitive function, these properties can also be seen, since the brain has a high level of metabolism and oxygen use, thus, it is susceptible to OS. We suggests that OS involves in the pathophysiology of schizophrenia, it may be correlated to cognitive impairment. Supplement of antioxidants may Improve cognitive impairment in schizophrenia.

The speed of processing domain may be more reliably measured than other MCCB domains for it consists of three tests. However, while the test–retest reliability for it may be higher than that of verbal learning and visual learning. Thus, there is no significant differences between speed of processing and other MCCB domains (Keefe et al. 2011).

The Stroop test is viewed as a useful tool to examine executive in neuropsychological research, with lower scores on the Stroop task indicating the possibility of impairment in executive function (Alvarez and Emory 2006; Dalby et al. 2012). Moreover, this test is widely used as a measure of frontal lobe functioning since frontal lobe lesions appear to negatively impact Stroop performance (Stuss et al. 2001). In general, performance on the Stroop test has been viewed as a sensitive, but not specific, indicator of prefrontal function. The Stroop test is also regarded as a useful tool to assess executive function which involves in processing speed and attention (Alvarez and Emory 2006), the performance was reported to be impaired in schizophrenia (Kim et al. 2014).

Furthermore, first-episode patients with schizophrenia showed significant weakness in speed of information processing, even early in the illness (Kern et al. 2011), but did not exhibit weakness in verbal learning domains, perhaps using a word list learning task contributes to the lack of particular weakness in verbal learning on MCCB (Mccleery et al. 2014). Longitudinal study found that working memory was less impaired than other cognitive domains at initial assessment (Barder et al. 2013). Kern reported that all MCCB domains were impaired in schizophrenia patients but with less relative impairment in reasoning and problem solving compared to the remaining MCCB domains (Kern et al. 2011).

Our study has several limitations. First, the study sample was small. Second, the peripheral markers of oxidative stress and cognitive function were assessed only once, and third the patients seem only modestly impaired. Although we found associations between oxidative stress markers, TAS, and cognitive functioning, causality cannot be assumed and further research is needed.

## Conclusion

In summary, plasma TAS levels were significantly lower in the first-episode drug-naïve schizophrenia patients, the schizophrenic patients scored lower than healthy controls on the MCCB total score, attention/vigilance and managing emotion test index and Stroop test. For the patients, TAS was correlated with some cognitive domains' deficits in schizophrenia, such as speed of processing, Attention/Vigilance and emotion managing. It is possible that our finding that plasma TAS may have a specific role in cognitive dysfunction, especially in speed of processing, in schizophrenia suggested schizophrenic patients had less effective antioxidant defense and suffered cognition impairment at a more severe level than controls; the unbalanced antioxidant status may play a role in the pathophysiology of schizophrenia and it is associated with 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 and cognition dysfunction. Beyond this cross-sectional study, longitudinal studies of MCCB performance after psychiatric medication of schizophrenia are needed to determine whether it is associated with plasma TAS.

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**Authors' contributions** TX collect the subjects and clinical rating, wrote the protocol, conducted the analysis and wrote the article. QL conducted the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus cognitive Battery (MCCB) and plasma total antioxidant status (TAS) data analysis. XL, LT and ZW gave the critical comment for the study design. ST, SC and GY reference search and gave the idea for study design. HA, FY, XZ, YT gave the idea for study design.

## Compliance with ethical standards

**Conflict of interests** The authors declare that they have no competing interests and consent for publication is available.

**Ethics approval** The study was approved by the ethics committee of Beijing Huilongguan Hospital. After a complete description of the study to all participants, the written informed consent was obtained.

**Availability of data and material** All data are fully available without restriction.

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