Article

Age of Onset Moderates the Association Between Total Antioxi-Dant Capacity and Cognitive Deficits in Patients With Drug-Naïve Schizophrenia

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Age of Onset Moderates the Association between Total Antioxidant Capacity and Cognitive Deficits in Patients with Drug-Naïve Schizophrenia

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Abstract: Schizophrenia patients with an earlier age of onset have been found to have more serious negative symptoms and cognitive deficits. Oxidative stress is thought to be implicated in cognitive impairment in schizophrenia. Total antioxidant capacity (TAOC) is an essential indicator of oxidative stress. However, the association between age of onset, TAOC, and cognitive performance in schizophrenia is still unexplored. In this study, 201 patients (age: 26.5±9.6 years, male: 53.2%) with drug naïve schizophrenia were recruited. Clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS). Cognitive functioning was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Plasma TAOC levels were analyzed using established procedures. Results showed that early-onset (EO) patients had higher TAOC levels, more severe negative symptoms and performed worse on Visuospatial/Constructional, Language and RBANS total score compared with non-EO patients. After Bonferroni correction, only non-EO patients showed a significant inverse relationship between TAOC levels and RBANS language, attention, and total scores. Our findings suggest that early /late age of onset may be correlated with psychopathological symptoms, cognitive impairment and oxidative responses in schizophrenia. Furthermore, the age of onset may moderate the relationship between TAOC and cognitive function in patients with schizophrenia. These findings suggest that improving oxidative stress status in non-EO schizophrenia patients may enhance their cognitive function.

Keywords: schizophrenia; age of onset; TAOC; cognitive function; oxidative stress

1. Introduction

Schizophrenia is one of the psychiatric disorders covering a broad range of psychiatric symptoms, with an estimated global prevalence of 0.28% [1]. Individuals with schizophrenia typically exhibit disorganized formal thoughts, delusions, hallucinations, catatonic symptoms, affective disorders, and neurocognitive deficits [2]. Schizophrenia is a diverse disorder, and one aspect of its diversity is age of onset. Because the presentation of schizophrenia can vary significantly across ages, age of onset is generally used to anticipate schizophrenia outcomes [3]. A common definition of early-onset (EO) schizophrenia is that the patient develops psychotic symptoms before the age of 21 [4]. Early-onset schizophrenia patients were shown to have more serious clinical symptoms and more impaired cognitive performance [5,6]. Mechanisms for these associations may involve neurotrophic factors [6], oxidative stress [7,8], differences in neurodevelopment [9], and differences in lifestyle and dietary patterns between ages [10].

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Schizophrenia is associated with cognitive impairments in working memory, attention, and visual and verbal learning [11]. Around 98% of schizophrenia patients experience cognitive impairment, which severely negatively impacts the overall functioning of the patient and hinders the recovery process [12]. As the three main characteristics of schizophrenia, positive symptoms, negative symptoms and cognitive deficits are closely correlated [13]. Studies have shown that the severity of negative and cognitive symptoms is associated with impairments in semantic memory, verbal memory and executive functioning, whereas positive symptoms are associated with semantic memory [14]. Schizophrenia usually develops during adolescence or young adulthood, when the most dramatic cognitive decline may be observed [12]. In contrast, cognitive function is better preserved in patients with late-onset schizophrenia [15]. Several studies have found that earlier age of onset in schizophrenia is related to more positive symptoms, negative symptoms, poorer immediate memory, attention, social cognition, and verbal learning functions [5,16,17].

Disturbances in the oxidative stress system are suggested to influence the etiology and cognitive impairment of schizophrenia [18]. Several studies have suggested that in early-onset schizophrenia patients, glutathione levels are decreased and lipid peroxidation (LOOH) levels are higher, indicating disturbances in the oxidative stress system might have an impact on the earlier age of onset of schizophrenia [8,19]. Total antioxidant capacity (TAOC), reflecting the contribution of plasma/serum water-soluble molecules to antioxidant capacity, including albumin, caeruloplasmin, transferrin, protein thiols, uric acid, ascorbic acid and bilirubin, as well as some α-tocopherols, is an essential indicator of oxidative stress [20]. TAOC is thought to be involved in cognitive impairment in several groups such as patients with Alzheimer's disease (AD), and patients with early onset first psychosis [21–23]. Previous study has found that TAOC levels in patients with paranoid schizophrenia are significantly lower than in healthy controls, suggesting a defect in the antioxidant system of schizophrenic patients [24]. Another study showed that TAOC levels were related to several areas of cognitive deficits in schizophrenia patients, such as processing speed, attention/vigilance, and emotion management [25]. One possible mechanism is that, due to deficiencies in antioxidant defense, patients with schizophrenia exhibit more oxidative damage to lipids, proteins, and DNA in both central and peripheral tissues, thereby impairing cognitive function-related neurons [26]. In addition, TAOC levels are currently a fairly important predictor of antipsychotic efficacy, suggesting that higher TAOC levels may predict better treatment response to antipsychotics [27,28].

Given that TAOC levels might act as a biomarker of cognitive functions and are associated with oxidative stress, and the close relationship between cognitive function and age of onset in schizophrenia, in this study, our goal is to further investigate their inter-relationship between the age of onset, cognitive function and TAOC levels in schizophrenia patients. In this study, cognitive function mainly represents five key domains: immediate memory, delayed memory, visuospatial/constructional, attention, and language. As far as we are concerned, this is the first study to examine the relationship between the age of onset, cognitive function, and TAOC levels in drug-naïve schizophrenia patients. Our hypotheses were that 1) there would be differences in cognitive performance and TAOC levels between EO and non-EO schizophrenia patients, and 2) there would be a positive correlation between TAOC levels and cognitive performance in the EO group. Therefore, the primary goals of our research were to investigate 1) whether clinical symptoms, cognitive functioning, and TAOC levels would differ between EO and non-EO schizophrenia patients, and 2) whether the age of onset would affect the association between TAOC levels and cognitive functioning of schizophrenia patients.

2. Methods

2.1. Participants

In this study, we recruited 201 drug naïve schizophrenia patients from a psychiatric hospital in China. Patients were diagnosed with schizophrenia on the basis of the Structured Clinical Interview I for DSM-IV (SCID-I) criteria by two independent psychiatrists. Inclusion criteria were: 1) Han Chinese; 2) aged 16–45 years; 3) illness duration no more than 60 months; 4) no history of

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antipsychotic or antidepressant treatment. Exclusion criteria were: 1) having major somatic diseases; 2) having a history of autoimmune diseases, allergies, hypertension, or diabetes; 3) being pregnant or breastfeeding. 4) current diagnosis of other psychiatric disorder, such as major depressive disorder or anxiety disorder. All subjects provided a comprehensive medical history as well as demographic data.

This study was approved by the Ethics Committee of Beijing Huilongguan Hospital (Ethics No. 2013-10). Each subject offered written informed consent before enrollment.

2.2. Definition of EO and non-EO patients

Based on medical records, the age of first onset was determined as the age at which the participant first met DSM-IV criteria for schizophrenia. In this sample, the mean age of onset was 25.8 ± 9.6 years, with a range of 14 to 53 years. Depending on the age of onset, we classified these patients into two groups: < 21 was the early-onset (EO) group and ≥ 21 was the non-early-onset (NEO) group [29,30]. This age criterion was effective in identifying early-onset schizophrenia in previous studies [6].

2.3. Assessment of Psychiatric Symptoms and Cognitive Functions

Each patient answered a complete questionnaire about their sociodemographic features as well as medical and psychological status. Existing medical documents and supplementary data were used to gather further information. Participants whose data were lost or ambiguous underwent further interviews.

The Positive and Negative Syndrome Scale (PANSS) [31] was expert-based and was used by four trained psychiatrists to assess psychopathology. Repeated post-training assessments showed an inter-rater correlation coefficient of kappa = 0.84 for the PANSS total score.

Individual assessments of cognitive performance were conducted using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) [32]. The 12 subtests that make up the RBANS were used to create a total score, as well as five age-adjusted index scores to measure five dimensions of cognitive functioning, including immediate memory, visuospatial/constructional, language, attention, and delayed memory. Trained psychiatrists scored patient's performance on the RBANS test.

2.4. Blood Sampling and TAOC Measurement

After an overnight fast, each subject had their venous blood sampled between 7:00 AM and 9:00 AM. TAOC was then analyzed using established procedures [33]. The assay was fully described in our previous paper [27,33]. Briefly, TAOC levels were tested as reductants from Fe3+ to Fe2+, which were then chelated by TPTZ to produce a Fe2+-TPTZ complex, measured with a Multiskan microplate reader (FlowLabs, McLean, VA, USA). Blood TAOC levels were presented as units per milliliter of plasma (U/ml). The participants' identities were disclosed by the code number kept by the lead investigator.

2.5. Statistical Analysis

First, we checked the normality of continuous variables using the Kolmogorov-Smirnov one-sample test, accompanied by log transformation for variables that did not follow a normal distribution. Demographic, clinical, and cognitive characteristics were compared between the EO and non-EO groups using analysis of variance (ANOVA) for continuous variables and chi-square analysis for categorical variables. With Pearson correlation coefficients, associations between TAOC and demographic, clinical, and cognitive characteristics were assessed for the whole sample and separately for EO and non-EO groups. Bonferroni correction was conducted to adjust for multiple testing.

To predict clinical features, a series of multiple linear regression analyses were performed. Initial requirements for conducting multiple regression analyses were met [34,35]: N = 201 > 100; predictors

can explain the dependent variables (e.g. R = 0.482, R^2 = 0.233); the number of predictors: 6; 10 × 6 = 60 < N (200); the Durbin–Watson coefficient was 1.94, suggesting that the residuals of the predictors were independent. In addition, the variance inflation factors (VIF) were used to assess multicollinearity, with the values between 1.04 and 1.17, indicating little risk of multicollinearity. These analyses were performed with PANSS total or index scores, or RBANS total or index scores being the dependent variables to examine the effects of several variables, including age, gender, education, smoking status, BMI, and TAOC levels.

SPSS®, version 23.0 (IBM Corporation, Armonk NY; USA) for Windows® was used for all statistical analyses. Data are shown as mean ± SD. All P values were two-tailed and the significance level was set at 0.05.

3. Results

3.1. Demographic, Clinical and Cognitive Parameters in EO and non-EO Patients

Table 1 presents demographic, clinical and cognitive variables of patients with EO and non-EO schizophrenia. The EO group included of 90 patients (47 males and 43 females), while the NEO group included 111 patients (60 males and 51 females). The EO group had significantly lower age ($p < 0.001$), lower smoking rate ($p<0.001$), lower education level ($p = 0.007$), lower BMI ($p = 0.003$), higher negative symptom subscore ($p = 0.013$, $\eta^2=0.01$), lower visuospatial/constructional subscore ($p = 0.003$, $\eta^2=0.04$), lower language subscore ($p < 0.001$, $\eta^2=0.095$) and lower RBANS total score ($p = 0.025$, $\eta^2=0.03$). Among all these significant variables, only differences in age, smoking rate and language remained significant after Bonferroni correction (all corrected $p < 0.05$).

Table 1. Demographics, clinical and cognitive variables in early-onset and non-early-onset patients with schizophrenia.

	EO (n=90)	Non-EO (n=111)	F or X^2	df	P value	Partial η^2
Age (y)	18.56±1.69	33.01±8.44	255.711	200	<0.001	0.56
Sex						
Male (%)	47/90 (52.22%)	60/111 (54.05%)	0.067	1	0.887	/
Female (%)	43/90 (47.78%)	51/111 (45.95%)				
Education (y)	8.37±2.33	9.78±4.40	7.524	197	0.007	0.04
BMI (kg/m²)	20.31±3.52	21.79±3.25	8.990	186	0.003	0.05
Smoker (%)	10/90 (11.11%)	39/111 (35.14%)	13.992	1	<0.001	/
Age of onset (y)	17.79±1.53	32.26±8.48	255.259	200	<0.001	0.56
PANSS						
Positive symptoms	20.68±5.66	21.40±6.11	0.748	200	0.388	0.004
Negative symptoms	19.79±6.94	17.44±6.38	6.272	200	0.013	0.01
General psychopathology	34.48±8.38	35.08±8.75	0.246	200	0.621	0.001
Total Score	74.84±14.66	73.64±15.72	0.310	200	0.579	0.002
RBANS						
Immediate Memory	64.12±14.99	66.00±17.59	0.647	200	0.422	0.003
Visuospatial/Constructional	73.38±13.81	80.39±18.38	9.015	200	0.003	0.04
Language	67.91±18.21	79.33±17.15	20.927	200	<0.001	0.095
Attention	76.34±18.30	72.86±21.03	1.538	200	0.216	0.01
Delayed Memory	66.41±19.94	70.86±20.14	2.453	200	0.119	0.01
Total Score	63.31±13.34	68.29±17.05	5.134	200	0.025	0.03
TAOC (U/mL)	244.48±76.06	220.08±67.05	5.861	200	0.016	0.03

Note: EO = early-onset; Non-EO = non-early-onset; BMI = body mass index; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TAOC = Total Antioxidant Capacity

3.2. TAOC Levels in EO and non-EO Schizophrenia Patients

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TAOC levels were considerably higher in the EO group than in the non-EO group (p = 0.016, η^2=0.03) (Table 1 and Figure 1). Moreover, Pearson's correlation analysis indicated a marginally significant correlation between TAOC levels and patients' age of onset (p = 0.056) (Table 2). Nevertheless, there was no considerable relationship between age of onset and TAOC levels in either EO group or non-EO group (p>0.05).

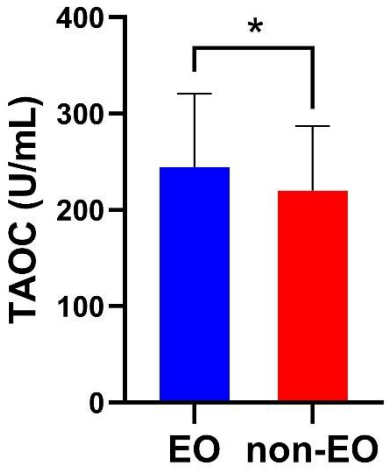

Figure 1. Comparison of TAOC levels between EO and non-EO groups

3.3. Association between TAOC Levels and Cognitive Function in EO and non-EO Groups

The results of the correlation between TAOC and clinical or cognitive variables for EO group, non-EO group and all participants are shown in Table 2.

In the EO group, Pearson's correlation analysis showed that TAOC levels were significantly correlated with attention (r=-0.217, p = 0.04). Nevertheless, this association did remain its significance after the Bonferroni correction. Further multiple linear regression showed no remarkable association between PANSS total and index scores, RBANS total and index scores and TAOC levels.

In the non-EO group, Pearson correlation analysis showed that TAOC levels were significantly related to the following variables: positive symptoms (r = -0.342, P < 0.001), general psychopathology (r = -0.265, P = 0.005), PANSS total score (r = -0. 346, P < 0.001), immediate memory (r = -0.253, P = 0.007), visuospatial/constructional (r = -0.202, P = 0.033), language (r = -0.357, P < 0.001), attention (r = -0.289, P = 0.002) and RBANS total scores (r = -0.290, P = 0.002). Correlations between TAOC and cognitive functions in non-EO group are shown in Figure 1. After Bonferroni correction, only the associations between TAOC levels and positive symptoms, PANSS total score, language, attention and RBANS total score continued to be significant (all corrected p<0.05). Furthermore, using each clinical score as the dependent variable, multiple linear regression suggested that TAOC levels were independently correlated with: positive symptoms (β= -0.273, t = -2.498, p = 0.014), negative symptoms (β= -0. 320, t = -2.996, p = 0.004), general psychopathology (β= -0.236, t = -2.116, p = 0.037), and PANSS total scores (β= -0.373, t = -3.453, p = 0.001) and language (β= -0.192, t = -2.038, p = 0.044).

Table 2. Correlations between TAOC and clinical and cognitive variables in early-onset, non-early onset and all patients with schizophrenia

	EO (n=90)	Non-EO (n=111)	All participants (n=201)
Education (y)	-0.363 (0.000)	-0.382 (0.000)	-0.374 (0.000)
Age of onset	0.121 (0.256)	-0.039 (0.685)	-0.135 (0.056)
BMI (kg/m^2)	-0.176 (0.109)	-0.180 (0.068)	-0.212 (0.003)
PANSS			
Positive symptoms	-0.180 (0.089)	-0.342 (0.000)	-0.273 (0.000)
Negative symptoms	0.038 (0.719)	-0.158 (0.096)	-0.029 (0.681)

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General psychopathology	0.016 (0.883)	-0.265 (0.005)	-0.138 (0.050)
Total Score	-0.042 (0.693)	-0.346 (0.000)	-0.196 (0.005)
RBANS			
Immediate Memory	-0.112 (0.295)	-0.253 (0.007)	-0.196 (0.005)
Visuospatial/Constructional	-0.064 (0.548)	-0.202 (0.033)	-0.173 (0.014)
Language	-0.134 (0.208)	-0.357 (0.000)	-0.284 (0.000)
Attention	-0.217 (0.040)	-0.289 (0.002)	-0.236 (0.001)
Delayed Memory	-0.105 (0.323)	-0.163 (0.086)	-0.151 (0.032)
total Score	-0.172 (0.104)	-0.290 (0.002)	-0.258 (0.000)

Note: TAOC = Total Antioxidant Capacity; EO = early-onset; Non-EO = non-early-onset; BMI = body mass index; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status;

Pearson's correlation coefficients were used to assess the correlations between TAOC levels and the other variables mentioned above, shown as r (p).

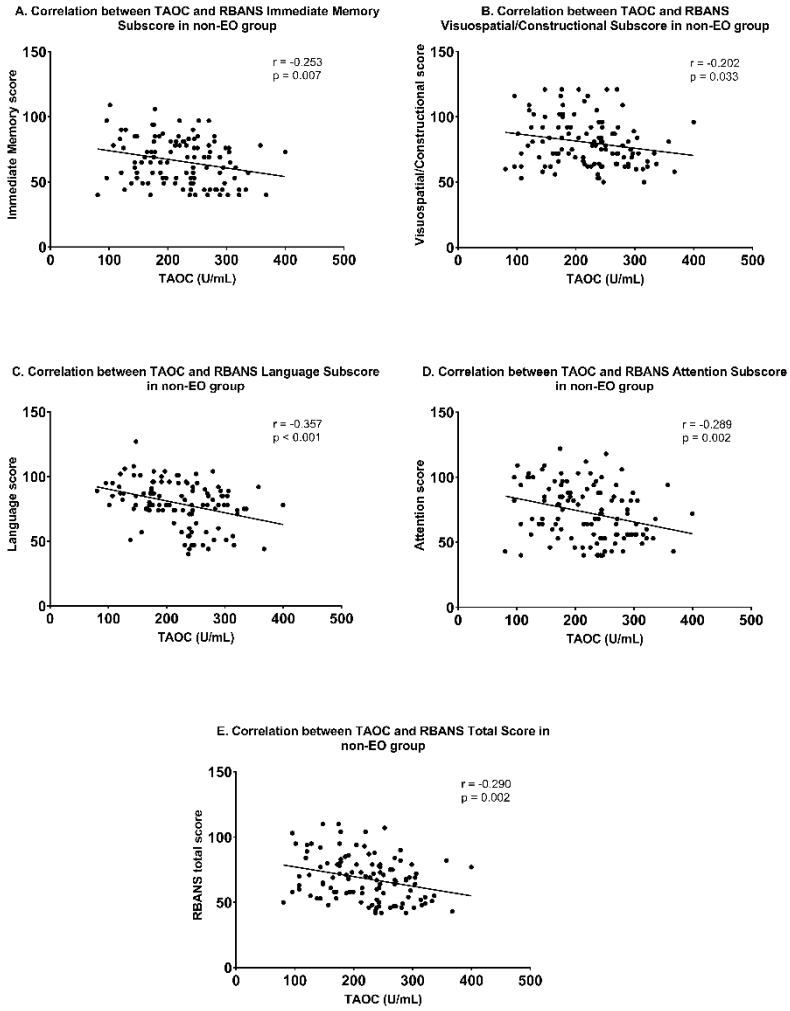

Figure 2. Correlations between TAOC and cognitive functions in non-early-onset group

4. Discussion

There are three main findings in this research: 1) patients in the EO group had significantly more serious negative symptoms and more impaired cognitive performance than patients in the non-EO group; 2) TAOC levels were considerably higher in the EO group than in the non-EO group; and 3) after Bonferroni correction, TAOC levels were negatively correlated with positive symptoms, total

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PANSS scores, language, attention, and total RBANS scores only in the non-EO group. Our results suggest a difference in the relationship between TAOC levels and cognitive function in EO and non-EO patients, age of onset may further moderate the relationship between TAOC levels and cognitive function in drug naïve schizophrenia patients.

In the present study, it was found that EO patients had poorer cognitive functioning than non-EO patients, especially in the visuospatial/constructional and language domains. Our findings align with previous research that found people with EO schizophrenia had more severe impairments in various cognitive functions, such as verbal learning and verbal memory [15,16]. Furthermore, our results suggested that EO patients had more serious negative symptoms than non-EO patients, which is also in line with the results of some earlier research [17,36]. However, some researchers have failed to find significant differences in cognition between EO and late-onset schizophrenia [37,38]. This inconsistency may be brought about by the small sample sizes in some previous research, different measures of cognitive functioning, different stages of disease progression (e.g., first-episode versus chronic), different disease durations, and different treatment statuses (e.g., unmedicated versus medicated). In addition, different genetic backgrounds may play a vital role in the manifestation of the disease in EO patients and non-EO patients [39]. It can be assumed that EO may be the result of a monogenic disorder, whereas the manifestation of non-EO patients may be polygenic in nature, and may have different genetic causes for their phenotypic manifestations in different populations of subjects, resulting in different degrees of cognitive symptoms.

Several studies have shown a strong association between age of onset and cognitive functioning in schizophrenia patients [15]. According to several reports, an earlier age of onset in schizophrenia patients is correlated with worse immediate memory, attention, social cognition, and verbal learning functions [5,16]. In addition, earlier age of onset is associated with narrower hindbrain segments [40] and larger ventricles [41]. It has also been shown that loss of cortical gray matter is noticed in the frontal lobes of patients with childhood-onset schizophrenia and that earlier age of onset predicts cognitive impairment due to frontal lobe damage [42,43]. This evidence suggests that earlier onset of schizophrenia may lead to more severe cognitive impairment by affecting brain structure and tissue damage. Furthermore, earlier onset is associated with more males, more negative symptoms, and higher doses of antipsychotic medication, which is often thought to indicate neurodevelopmental impairment [17]. In addition, more pronounced cognitive deficits in EO individuals may also be associated with higher rates of chromosomal abnormalities in schizophrenia and higher familial rates of schizophrenia spectrum disorders [44]. Age of onset has also been associated with the BDNF Val66Met gene polymorphism, which is related to poorer cognitive performance in schizophrenia [45,46]. The developing brain may be negatively affected by genetic and environmental risk factors, which might result in an earlier age of onset and poorer cognitive performance [17]. More studies are needed to determine the exact mechanisms by which cognitive performance is worse in patients with EO schizophrenia than in non-EO patients.

We also found that TAOC levels were considerably different between the EO and non-EO groups, with EO patients having significantly higher TAOC levels than non-EO patients. Previous studies have shown considerable heterogeneity among studies regarding changes in antioxidant biomarker levels in patients with EO schizophrenia, even with opposite results [7]. These contradictory findings may be due to differences between subjects, different assessment and analysis methods, and clinical factors that may alter the levels of oxidative parameters (e.g., different levels of antipsychotic drug exposure). In the current research, higher TAOC levels were found in EO patients, possibly due to a compensatory effect on the acute rise in the pro-oxidant state, which is usually present in young schizophrenia patients [47]. Another possible reason is that oxidative stress levels in vivo naturally decrease with age [48], which may also partially explain the lower TAOC levels in non-EO patients.

It is worth noting that a negative correlation was found between TAOC levels and RBANS language, attention, and total score only in the non-EO group, which was out of our expectations. In non-EO patients, high TAOC may be compensatory, represent high levels of oxidative stress, and be associated with poorer cognitive function. Some previous reports have suggested that TAOC levels

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are correlated with cognitive dysfunction in schizophrenia patients in several domains, suggesting that oxidative stress might have an impact on the pathological process of cognitive dysfunction in schizophrenia patients [25]. However, some previous studies found no significant relationship between TAOC and cognitive impairment in schizophrenia, suggesting heterogeneity in the relationship between TAOC levels and cognitive function across studies [7]. Our findings indicated that age of onset might have a moderating effect on the correlation between TAOC and cognitive function in schizophrenia patients. It was found that perineuronal networks (PNNs) mature in an experience-dependent way during late postnatal development, covering the prodromal/onset time of schizophrenia [49]. During adulthood, PNNs play a regulating role in neuronal properties, including sensitivity to oxidative stress [49]. Patients with EO schizophrenia often have PNNs that are not yet fully mature and have experienced damage due to the disease. In this case, the effect of oxidative stress indicators on cognitive function might become less significant. In addition, environmental factors such as long-term smoking and alcohol consumption accelerate telomere erosion as well as aging and affect the body's oxidative stress levels [50]. Patients with relatively late onset schizophrenia may experience long-term disruption of the oxidative stress system due to these environmental factors, which may also make the effects of oxidative stress on cognitive function more pronounced. In addition, the low sample size may be one of the possible reasons for the lack of association between TAOC levels and RBANS scores in the EO group. However, these are only our speculations and deserve further exploration in future studies.

Our study has the following limitations. Firstly, the cross-sectional design hindered causal reasoning about the association between cognitive impairments and TAOC levels in EO and non-EO schizophrenia patients. Future longitudinal studies are necessary to investigate the causal relationship between cognitive deficits and TAOC levels. Second, in this study, considerable differences were found between the EO and non-EO groups in education, BMI, and smoking status. Although we controlled for these variables in the statistical analysis, matched subjects with similar demographic characteristics and socioeconomic status would be better in future studies. Third, this study primarily used TAOC as a representative marker of the antioxidant defense system. To gain more insight into the role of oxidative stress in cognitive impairment in schizophrenia, researchers need to systematically analyze all important synergistic oxidative stress markers in a larger cohort in future studies. Fourth, previous studies have shown that a higher ratio of total oxidant to total antioxidant status (oxidative stress index, OSI) reflects an unbalanced antioxidant status, which occurs in the early stages of schizophrenia and may play an important role in the negative symptoms of schizophrenia [51]. However, due to the limitations of blood sample analysis, our study did not include oxidative stress index. Future studies needed to explore the association between age of onset, OSI, and cognitive deficits in patients with schizophrenia. Fifth, we do not know the exact source of TAOC in our participants. It remains unclear whether the TAOC in the blood samples comes from the central nervous system (CNS) and whether the TAOC levels in the peripheral system are the same as those in the cerebrospinal fluid. Finally, our study did not collect data on the duration of the prodromal period of patients in clinical practice; thus, we cannot use the prodromal period as a confounder in statistical analysis.

In conclusion, in the current study, we suggested that EO patients had significantly more serious negative symptoms and cognitive impairment than non-EO patients. We also found higher levels of TAOC in the EO group. In addition, a remarkable association between TAOC levels and patients' clinical symptoms and cognitive function was found only in the non-EO group. TAOC levels may play a different role in cognitive deficits between EO and non-EO schizophrenia patients. This study provides clinical suggestions for the treatment of non-EO schizophrenia, namely that reducing patients' oxidative stress levels may help improve their cognitive symptoms. In future studies, effective drugs could be developed to alleviate the negative effects of free radical products on cognitive function in schizophrenia. These findings may also help us better understand the relationship between oxidative stress and cognitive deficits in schizophrenia and the role of age of onset in their relationship, providing more knowledge for future personalized treatment.

Author Contributions: Conceptualization, Jiaxin Li, Deyang Li, Junru Guo, and Dongmei Wang; Formal analysis, Jiaxin Li and Deyang Li; Funding acquisition, Xiangyang Zhang; Investigation, Jiaxin Li, Deyang Li, Junru Guo; Project administration, Dongmei Wang and Xiangyang Zhang; Resources, Xiangyang Zhang; Supervision, Dongmei Wang and Xiangyang Zhang; Writing – original draft, Jiaxin Li and Deyang Li; Writing – review & editing, Dongmei Wang and Xiangyang Zhang. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Beijing Huilongguan Hospital (Ethics No. 2013-10).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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References

1. Charlson, F.J.; Ferrari, A.J.; Santomauro, D.F.; Diminic, S.; Stockings, E.; Scott, J.G.; McGrath, J.J.; Whiteford, H.A. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr. Bull.* **2018**, *44*, 1195-1203.
2. Alizadeh, M.; Delborde, Y.; Ahmadpanah, M.; Seifrabiee, M.A.; Jahangard, L.; Bazzazi, N.; Brand, S. Non-linear associations between retinal nerve fibre layer (RNFL) and positive and negative symptoms among men with acute and chronic schizophrenia spectrum disorder. *J. Psychiatr. Res.* **2021**, *141*, 81-91.
3. Immonen, J.; Jääskeläinen, E.; Korpela, H.; Miettunen, J. Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Interv. Psychiatry* **2017**, *11*, 453-460.
4. Hafner, H.; Nowotny, B. Epidemiology of early-onset schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* **1995**, *245*, 80-92.
5. Linke, M.; Jankowski, K.S.; Ciołkiewicz, A.; Jędrasik-Styła, M.; Parnowska, D.; Gruszka, A.; Denisiuk, M.; Jarema, M.; Wichniak, A. Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? *Psychiatry Res.* **2015**, *225*, 197-201.
6. Xu, H.; Wang, J.S.; Zhou, Y.J.; Chen, D.C.; Xiu, M.H.; Wang, L.; Zhang, X.Y. BDNF affects the mediating effect of negative symptoms on the relationship between age of onset and cognition in patients with chronic schizophrenia. *Psychoneuroendocrinology* **2021**, *125*, 105121.
7. Fraguas, D.; Díaz-Caneja, C.M.; Rodríguez-Quiroga, A.; Arango, C. Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis. *Int. J. Neuropsychopharmacol.* **2017**, *20*, 435-444.
8. Kostyak, J.C.; Kris-Etherton, P.; Bagshaw, D.; DeLany, J.P.; Farrell, P.A. Relative fat oxidation is higher in children than adults. *Nutr. J.* **2007**, *6*, 19.
9. Kyriakopoulos, M.; Dima, D.; Roiser, J.P.; Corrigall, R.; Barker, G.J.; Frangou, S. Abnormal functional activation and connectivity in the working memory network in early-onset schizophrenia. *J. Am. Acad. Child Adolesc. Psychiatry* **2012**, *51*, 911-920.e912.
10. Vancampfort, D.; Stubbs, B.; Mitchell, A.J.; De Hert, M.; Wampers, M.; Ward, P.B.; Rosenbaum, S.; Correll, C.U. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* **2015**, *14*, 339-347.
11. Heinrichs, R.W.; Zakzanis, K.K. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **1998**, *12*, 426-445.

12. Mihaljević-Peleš, A.; Bajs Janović, M.; Šagud, M.; Živković, M.; Janović, Š.; Jevtović, S. Cognitive deficit in schizophrenia: an overview. *Psychiatr. Danub.* **2019**, *31*, 139-142.
13. Boudriot, E.; Schworm, B.; Slapakova, L.; Hanken, K.; Jager, I.; Stephan, M.; Gabriel, V.; Ioannou, G.; Melcher, J.; Hasanaj, G.; et al. Optical coherence tomography reveals retinal thinning in schizophrenia spectrum disorders. *Eur. Arch. Psychiatry Clin. Neurosci.* **2022**.
14. Bozikas, V.P.; Kosmidis, M.H.; Kioperlidou, K.; Karavatos, A. Relationship between psychopathology and cognitive functioning in schizophrenia. *Compr Psychiatry* **2004**, *45*, 392-400.
15. Rajji, T.K.; Ismail, Z.; Mulsant, B.H. Age at onset and cognition in schizophrenia: meta-analysis. *Br. J. Psychiatry* **2009**, *195*, 286-293.
16. Tuulio-Henriksson, A.; Partonen, T.; Suviusaari, J.; Haukka, J.; Lonnqvist, J. Age at onset and cognitive functioning in schizophrenia. *Br. J. Psychiatry* **2004**, *185*, 215-219.
17. van der Werf, M.; Kohler, S.; Verkaaik, M.; Verhey, F.; van Os, J.; Investigators, G. Cognitive functioning and age at onset in non-affective psychotic disorder. *Acta Psychiatr. Scand.* **2012**, *126*, 274-281.
18. Wang, D.M.; Du, Y.X.; Zhu, R.R.; Tian, Y.; Chen, J.J.; Chen, D.C.; Wang, L.; Zhang, X.Y. The relationship between cognitive impairment and superoxide dismutase activity in untreated first-episode patients with schizophrenia. *World J. Biol. Psychiatry* **2022**, *23*, 517-524.
19. Mico, J.A.; Rojas-Corrales, M.O.; Gibert-Rahola, J.; Parellada, M.; Moreno, D.; Fraguas, D.; Graell, M.; Gil, J.; Irazusta, J.; Castro-Fornieles, J.; et al. Reduced antioxidant defense in early onset first-episode psychosis: a case-control study. *BMC Psychiatry* **2011**, *11*, 26.
20. Erel, O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clin. Biochem.* **2004**, *37*, 277-285.
21. Alghadir, A.H.; Gabr, S.A.; Anwer, S.; Li, H. Associations between vitamin E, oxidative stress markers, total homocysteine levels, and physical activity or cognitive capacity in older adults. *Sci. Rep.* **2021**, *11*, 12867.
22. Martinez-Cengotitabengoa, M.; Mico, J.A.; Arango, C.; Castro-Fornieles, J.; Graell, M.; Paya, B.; Leza, J.C.; Zorrilla, I.; Parellada, M.; Lopez, M.P.; et al. Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study. *Schizophr. Res.* **2014**, *156*, 23-29.
23. Palomar-Bonet, M.; Atienza, M.; Hernandez-Ledesma, B.; Cantero, J.L. Associations of Salivary Total Antioxidant Capacity With Cortical Amyloid-Beta Burden, Cortical Glucose Uptake, and Cognitive Function in Normal Aging. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, 1839-1845.
24. Morera-Fumero, A.L.; Diaz-Mesa, E.; Abreu-Gonzalez, P.; Fernandez-Lopez, L.; Cejas-Mendez, M.D. Low levels of serum total antioxidant capacity and presence at admission and absence at discharge of a day/night change as a marker of acute paranoid schizophrenia relapse. *Psychiatry Res.* **2017**, *249*, 200-205.
25. Xie, T.; Li, Q.W.; Luo, X.G.; Tian, L.; Wang, Z.R.; Tan, S.P.; Chen, S.; Yang, G.G.; An, H.M.; Yang, F.D.; et al. Plasma total antioxidant status and cognitive impairments in first-episode drug-naive patients with schizophrenia. *Cogn. Neurodyn.* **2019**, *13*, 357-365.
26. Bošković, M.; Vovk, T.; Kores Plesničar, B.; Grabnar, I. Oxidative stress in schizophrenia. *Curr. Neuropharmacol.* **2011**, *9*, 301-312.
27. Wang, K.Q.; Xiu, M.H.; Su, X.R.; Wu, F.C.; Zhang, X.Y. Association between Changes in Total Antioxidant Levels and Clinical Symptom Improvement in Patients with Antipsychotic-Naive First-Episode Schizophrenia after 3 Months of Risperidone Monotherapy. *Antioxidants* **2022**, *11*, 646.
28. Al-Chalabi, B.M.; Thanoon, I.A.J.; Ahmed, F.A. Potential effect of Olanzapine on total antioxidant status and lipid peroxidation in sSchizophrenic patients. *Neuropsychobiology* **2009**, *59*, 8-11.
29. Basso, M.R.; Nasrallah, H.A.; Olson, S.C.; Bornstein, R.A. Cognitive deficits distinguish patients with adolescent- and adult-onset schizophrenia. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **1997**, *10*, 107-112.
30. Greig, T.C.; Bell, M.D.; Kaplan, E.; Bryson, G. Object relations and reality testing in early- and late-onset schizophrenia. *J. Clin. Psychol.* **2000**, *56*, 505-517.
31. Kay, S.R.; Fiszbein, A.; Opler, L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* **1987**, *13*, 261-276.
32. Randolph, C.; Tierney, M.C.; Mohr, E.; Chase, T.N. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J. Clin. Exp. Neuropsychol.* **1998**, *20*, 310-319.
33. Li, X.F.; Zheng, Y.L.; Xiu, M.H.; Chen, D.C.; Kosten, T.R.; Zhang, X.Y. Reduced plasma total antioxidant status in first-episode drug-naive patients with schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 1064-1067.

34. Golshani, S.; Najafpour, A.; Hashemian, S.S.; Goudarzi, N.; Shahmari, F.; Golshani, S.; Babaei, M.; Firoozabadi, K.; Duersteler, K.M.; Bruehl, A.B.; et al. When Much Is Too Much-Compared to Light Exercisers, Heavy Exercisers Report More Mental Health Issues and Stress, but Less Sleep Complaints. *Healthcare* **2021**, *9*, 1289.
35. Brosius, F. *SPSS: umfassendes Handbuch zu Statistik und Datenanalyse*; MITP-Verlags GmbH & Co. KG: 2018.
36. Bellino, S.; Rocca, P.; Patria, L.; Marchiaro, L.; Rasetti, R.; Di Lorenzo, R.; Paradiso, E.; Bogetto, F. Relationships of age at onset with clinical features and cognitive functions in a sample of schizophrenia patients. *J. Clin. Psychiatry* **2004**, *65*, 908-914.
37. Jeste, D.V.; Harris, M.J.; Krull, A.; Kuck, J.; McAdams, L.A.; Heaton, R. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *Am. J. Psychiatry* **1995**, *152*, 722-730.
38. Sachdev, P.; Brodaty, H.; Rose, N.; Cathcart, S. Schizophrenia with onset after age 50 years. 2: Neurological, neuropsychological and MRI investigation. *Br. J. Psychiatry* **1999**, *175*, 416-421.
39. Goldberg, X.; Fatjo-Vilas, M.; Munoz, M.J.; Campanera, S.; Miret, S.; Minano, M.J.; Aguilera, M.; Miralles, M.L.; Navarro, M.E.; Lazaro, L.; et al. Increased familiarity of intellectual deficits in early-onset schizophrenia spectrum disorders. *World J. Biol. Psychiatry* **2012**, *13*, 493-500.
40. Crow, T.J.; Colter, N.; Frith, C.D.; Johnstone, E.C.; Owens, D.G. Developmental arrest of cerebral asymmetries in early onset schizophrenia. *Psychiatry Res.* **1989**, *29*, 247-253.
41. Raz, S.; Raz, N. Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerized imaging. *Psychol. Bull.* **1990**, *108*, 93-108.
42. Caldiroli, A.; Serati, M.; Orsenigo, G.; Caletti, E.; Buoli, M. Age at onset and social cognitive impairment in clinically stabilized patients with schizophrenia: An ecological cross-sectional study. *Iran. J. Psychiatry* **2018**, *13*, 84-93.
43. Vidal, C.N.; Rapoport, J.L.; Hayashi, K.M.; Geaga, J.A.; Sui, Y.; McLemore, L.E.; Alaghband, Y.; Giedd, J.N.; Gochman, P.; Blumenthal, J.; et al. Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Arch. Gen. Psychiatry* **2006**, *63*, 25-34.
44. Rapoport, J.L.; Giedd, J.N.; Gogtay, N. Neurodevelopmental model of schizophrenia: update 2012. *Mol. Psychiatry* **2012**, *17*, 1228-1238.
45. Notaras, M.; Du, X.; Gogos, J.; van den Buuse, M.; Hill, R.A. The BDNF Val66Met polymorphism regulates glucocorticoid-induced corticohippocampal remodeling and behavioral despair. *Transl. Psychiatry* **2017**, *7*, e1233.
46. Zhou, D.H.; Yan, Q.Z.; Yan, X.M.; Li, C.B.; Fang, H.; Zheng, Y.L.; Zhang, C.X.; Yao, H.J.; Chen, D.C.; Xiu, M.H.; et al. The study of BDNF Val66Met polymorphism in Chinese schizophrenic patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2010**, *34*, 930-933.
47. Girgis, R.R.; Kumar, S.S.; Brown, A.S. The cytokine model of schizophrenia: emerging therapeutic strategies. *Biol. Psychiatry* **2014**, *75*, 292-299.
48. Nandi, A.; Yan, L.J.; Jana, C.K.; Das, N. Role of catalase in oxidative stress- and age-associated degenerative diseases. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 9613090.
49. Berretta, S.; Pantazopoulos, H.; Markota, M.; Brown, C.; Batzianouli, E.T. Losing the sugar coating: potential impact of perineuronal net abnormalities on interneurons in schizophrenia. *Schizophr. Res.* **2015**, *167*, 18-27.
50. Solana, C.; Pereira, D.; Tarazona, R. Early senescence and leukocyte telomere shortening in SCHIZOPHRENIA: A role for cytomegalovirus infection? *Brain. Sci.* **2018**, *8*, 188.
51. Copoglu, U.S.; Virit, O.; Kokacya, M.H.; Orkmez, M.; Bulbul, F.; Erbagci, A.B.; Semiz, M.; Alpak, G.; Unal, A.; Ari, M.; et al. Increased oxidative stress and oxidative DNA damage in non-remission schizophrenia patients. *Psychiatry Res.* **2015**, *229*, 200-205.