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Superoxide Dismutase, BDNF, and Cognitive Improvement in Drug-Naive First-Episode Patients With Schizophrenia: A 12-Week Longitudinal Study

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Abstract

Objective: Cognitive improvement after antipsychotic agents in patients with schizophrenia (SCZ) appears to involve redox regulation through neurotrophins such as brain derived neurotropic factor (BDNF). This study examined whether cognitive improvement was associated with the increase in superoxide dismutase (SOD) and whether higher levels of BDNF could have a permissive role in allowing SOD to improve cognition.
Methods: We examined this hypothesis in 183 drug-naïve first-episode SCZ patients taking risperidone monotherapy for 12 weeks. We measured total copper-zinc SOD (CuZn-SOD), manganese SOD (Mn-SOD), and SOD activities and BDNF levels in these patients and compared their levels with 152 healthy controls. We assessed cognitive functioning and clinical symptoms at baseline and 12-week follow-up.
Results: After treatment with risperidone, CuZn-SOD activity was significantly increased, and BDNF levels were slightly increased. Increased CuZn-SOD activity was associated with the cognitive effectiveness of risperidone monotherapy. The BDNF levels and SOD activities were correlated at baseline but not after 12-week treatment. Furthermore, baseline CuZn-SOD activity positively correlated with improvement on the delayed memory subscale of the Repeatable Battery for the Assessment of Neuropsychological Status only in the high BDNF subgroup.
Conclusions: Our longitudinal study suggests that risperidone can enhance SOD activity and that, in combination with higher baseline BDNF levels acting in a permissive role, can improve cognitive impairments in SCZ. Greater baseline CuZn-SOD activity also may have predictive value for cognitive improvement of delayed memory in SCZ patients receiving risperidone treatment.

Keywords: BDNF, cognitive functioning, risperidone, schizophrenia, superoxide dismutase

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Significance Statement

To advance the precision medicine treatment of cognitive impairment in schizophrenia, we tested whether SOD and BDNF are related to the improvement of clinical symptoms after treatment. Data from a 12-week longitudinal clinical study of risperidone monotherapy in patients with schizophrenia showed that the increase in CuZn-SOD activity was associated with the cognitive effectiveness of risperidone treatment. Moreover, CuZn-SOD activity at baseline was correlated with greater improvement in patients' delayed memory but only in individuals with high baseline BDNF levels. However, more research is needed to evaluate the combination of other oxidative stress markers with BDNF as a predictor of a robust response to risperidone treatment in the early stages of the disease.

INTRODUCTION

Cognitive decline is a core symptom in patients with schizophrenia (SCZ) and is associated with the prognosis and functional outcomes of patients (Harvey, 2009). It is evident in the early phase of the illness and worsens in the late phase (Giuliano et al., 2012). SCZ patients exhibit cognitive decline in several domains of cognition, including working memory, sustained attention, and executive functioning (Harvey et al., 2004; Xiu et al., 2016; Wei et al., 2019). Compared with healthy patients, cognitive functioning is moderately to severely impaired in SCZ from 1 to 3 SDs (Buchanan et al., 2011). Although some studies support that antipsychotics can alleviate neurocognitive impairment, the results of large-scale clinical trials are inconsistent (Goff et al., 2011).

The effect of antipsychotic drugs on cognitive functioning in SCZ varies across antipsychotics. Typical antipsychotic drugs lead to cognitive deterioration, while atypical antipsychotics such as risperidone have fewer extrapyramidal side effects and potential cognitive improvement (Gallhofer et al., 1996; Halim et al., 2004). However, the effects of risperidone treatment on cognitive functioning were diverse and heterogeneous. Early meta-analyses found that risperidone showed little effect on cognitive decline in first-episode patients (Meltzer and McGurk, 1999; Krakowski et al., 2008), but a recent study in first-episode SCZ patients found significantly improved cognitive functioning except for verbal learning and memory with 6 months of risperidone (Hou et al., 2020). This study focuses on variation in oxidative stress and the neurotrophin signaling pathway as factors related to cognitive improvement after risperidone treatment.

Cognitive impairments in SCZ may reflect redox dysregulation in a critical period of neurodevelopment (Do et al., 2009; Hardingham and Do, 2016). Redox regulation involves antioxidant enzymes, such as superoxide dismutase (SOD), which defends against oxidative stress (Crapo et al., 1992) through superoxide disproportionation and the rapid conversion of O_2– to H_2O_2 (Shimoda-Matsubayashi et al., 1997; Romuk et al., 2019). The neurons in the brain are vulnerable to oxidative stress because of their high oxygen utilization, high levels of oxidizable polyunsaturated fatty acids, and the presence of redox active metals (Do et al. 2009). Mounting evidence has shown abnormal SOD activities in peripheral blood and brain of SCZ patients (Flatow et al., 2013; Upthegrove and Khandaker, 2019) as well as in cerebrospinal fluid (Coughlin et al., 2017). More specifically, first-episode drug-naive (DNFE) patients with SCZ have abnormal SOD enzyme activity related to SCZ-positive symptoms and cognitive impairments (Wu et al., 2012; Xiu et al., 2020).

Low brain derived neurotropic factor (BDNF) is widely regarded as the cause of cognitive impairment in SCZ due to its multiple roles in neuroplasticity required for learning and memory (Notaras and van den Buuse, 2020). For example, clinical studies have shown that SCZ patients with cognitive impairment have diminished BDNF levels (Xiao et al., 2017; Heitz et al., 2018; Xiu et al., 2019). Another study has found that lower BDNF levels and higher SOD activities are correlated with cognitive deficits in both DNFE patients and chronic patients (Xiu et al. 2020). In addition, SOD and BDNF have an interactive effect on the cognitive impairment of SCZ patients (Xiu et al., 2020).

Risperidone and olanzapine regulate oxidative stress markers and BDNF levels in some studies, but other studies report that risperidone has no effect on BDNF levels or oxidative stress markers (Bai et al., 2003; Dietrich-Muszalska and Kolinska-Lukaszuk, 2018; Hendouei et al., 2018; Yu et al., 2019). Considering the close interrelationships between BDNF, antioxidant enzymes, and neurocognitive decline in DNFE SCZ patients, we hypothesize that cognitive functioning will improve with an increase of SOD activities and BDNF levels after risperidone monotherapy. To test this hypothesis, we will assess BDNF level and SOD activity (including CuZn-SOD, Mn-SOD, and total SOD) in SCZ patients after risperidone treatments for 12 weeks. Further analyses will examine the relationship between SOD enzymes and BDNF at baseline and follow-up as well as their association with change in cognitive functioning and clinical symptoms. These associations include (1) using these baseline levels of BDNF and SOD enzyme activities as predictors of cognitive improvement or clinical symptoms after treatment, and (2) using these changes in biomarkers during treatment as correlates of the improvement in cognitive functioning and clinical symptoms.

METHODS

Study Overview

We carried out this 12-week clinical trial at 2 large psychiatric hospitals in China: Beijing Huilongguan Hospital and Henan Zhumadian Hospital. The protocol of this trial was approved by the local ethics committee. All participants signed the informed consent before the clinical trial. After the screening procedure, eligible patients were treated with flexible dosing of risperidone (4–6 mg/d) for 3 months according to the standard protocol. Anti-depressants and mood stabilizer were not allowed during the trial.

Participants

In this study, DNFE SCZ patients aged 16 to 45 years were recruited and diagnosed with SCZ according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) using the Chinese version of Structured Clinical Interview for DSM-IV (SCID) (Phillips et al., 2009). The definition of first-episode and drug-naïve was described as in a previous study (Lieberman et al., 2003; Phillips et al. 2009). The patients met

the following criteria: Han nationality, age 16–45 years, disease course <5 years, cumulative use of antipsychotic drugs <2 weeks, without major medical comorbidities, and no abuse or substance dependence except for tobacco. We also recruited 152 control participants from local communities by advertisement. We interviewed them using the SCID to rule out axis I psychiatric disorders and antipsychotic treatment.

We performed a physical exam and laboratory tests on all participants at the second day of admission. Clinical psychiatrists also collected medical, psychological, and sociodemographic information.

Outcome Measures

The primary outcome measure was the cognitive functioning measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) (Randolph et al., 1998). The RBANS comprises 12 subtests used to calculate 5 age-adjusted index scores and a total score. Test indices are immediate memory, visuospatial/constructional, language, attention, and delayed memory. Our group previously translated RBANS into Chinese and established the clinical validity and test-retest reliability of the Chinese version in healthy controls and SCZ patients (Zhang et al., 2009). The severity of symptom assessed by the Positive and Negative Syndrome Scales (PANSS) was the secondary outcome measure (Kay et al., 1987). To ensure consistency and reliability of ratings across the study, the psychiatrists simultaneously attended a training session on using the PANSS before the start of the study. After training, they maintained an interrater correlation coefficient >0.8 for the PANSS total score. At baseline and at follow-up after 12-week risperidone monotherapy, all participants were assessed on the PANSS scale for psychotic symptoms and the RBANS scale for cognitive functioning.

Measurement of BDNF Level and SOD Activity

Usually, we drew blood from the patients between 7:00 AM and 9:00 AM on the second day of admission after fasting, and fasting blood samples were collected in a blood collection tube. Separated plasma and serum samples were stored at –80°C. BDNF levels were measured using a commercially available kit (R&D, USA) as reported earlier by a blinded technician who did not know the number of the sample (Xiu et al., 2009). We detected superoxide enzymes using a spectrophotometer and commercially available kits as described in prior literature (Zhang et al., 2013). The inter- and intra- variation coefficients between the assays were all <10% in the present study. To minimize the decay of plasma and serum in this study, the samples were batch-processed, and BDNF levels and SOD enzyme activities were measured every half-year.

Statistical Analysis

Initial analyses included all patients at baseline and controls. All biomarkers were tested for normality of distribution. ANOVA analysis was carried out to assess the group difference in sociodemographic characteristics. Regression analysis was conducted to investigate the relationships between SOD activity, BDNF level, the interactive effects (BDNF × SOD activity), and clinical symptoms or cognitive functioning in patients and controls. In this model, clinical symptoms or RBANS scores were dependent variables, and superoxide enzyme activity, BDNF levels, and BDNF × superoxide enzyme activity were independent variables. Covariates include sex, age, education, and BMI.

The next analysis included patients with baseline and 12-week follow-up data. Patients were classified into response group and non-response group according to the improvements in clinical symptoms and cognitive functions after treatment. To investigate whether 12 weeks of risperidone monotherapy altered SOD activity and BDNF levels and whether there were differences in SOD activity and BDNF levels between response and non-response groups, a 2 × 2 (time point by group) repeated-measure MANOVA analysis (RM MANOVA) was performed with SOD activity and BDNF levels as the outcome measures. After a statistically significant omnibus multivariate test of significance, individual univariate analysis of biomarkers was performed.

Lastly, our previous study showed that there was an interaction effect between the baseline SOD and BDNF after controlling for confounding factors. Considering the close relationship between BDNF and SOD, therefore, a median split of baseline BDNF level was conducted and all patients were divided into low BDNF subgroup (low-BDNF) and high BDNF subgroup (high-BDNF), as our previous study (Wu et al., 2020). Pearson correlation analysis was performed between the baseline biomarkers or change of biomarkers and the improvement of symptoms or cognitive functions in patients. Regression analysis was used to detect whether the baseline biomarkers could predict the response to risperidone after controlling for the confounders, with the clinical and cognitive responses to risperidone as a dependent variable.

Bonferroni corrections were used for multiple tests. We set the significance levels at $P < .05$.

RESULTS

Of the patients in the initial study, 293 patients consented to a 12-week treatment with risperidone. Cognitive functioning score and biomarkers were available from 183 patients, which were included in the further analysis.

Peripheral Biomarkers in DNFE Patients at Baseline and at 12-Week Follow-up

As shown in Table 1, the patients performed worse in RBANS total score and its subscales except for visuospatial/constructional subscale (Bonferroni corrected $P_{all} < .05$) after controlling for age, sex, BMI, and education. As reported in our previous study, compared with controls, higher SOD and CuZn-SOD activities and a lower level of BDNF were found in patients (all $P < .01$) (Xiu et al., 2020). Our previous study adopted a cross-sectional design, whereas this study was a prospective longitudinal cohort study design.

Risperidone treatment significantly increased the CuZn-SOD activity ($P < .05$) and slightly increased the BDNF levels in patients after 12 weeks of treatment but had no influence on Mn-SOD and total enzyme activities (all $P > .05$). BDNF levels were significantly associated with Mn-SOD activity at baseline but not at follow-up ($P > .05$).

Relationships Between Biomarkers and Clinical Response After Risperidone Monotherapy

As shown in Figure 1, after 12 weeks of risperidone monotherapy, the PANSS total score and its 3 subscores significantly decreased (all $P_{Bonferroni} < .01$). According to a previous literature, we defined a patient as a responder if his or her PANSS total score showed a 30% or more reduction from baseline to week 12 (Li et al., 2021). MANOVA analysis revealed that there was no

significant interaction effect of group × time on the clinical response to risperidone monotherapy ($P > .05$).

Relationships Between Biomarkers and Cognitive Response After Risperidone Monotherapy

We found that after treatment, attention, delayed memory, immediate memory subscales, and RBANS total score were significantly increased (Bonferroni corrected $P_{all} < .05$). In addition, there was a significant association between the reduction in the PANSS total score and the increase in the RBANS total score ($r = 0.20$, $P = .009$). Further analysis showed that the improvement of immediate memory was associated with the improvement of negative symptoms ($r = 0.24$, $P = .001$). The improvement of delayed memory was associated with the improvement of positive symptoms ($r = 0.22$, $P = .003$) and PANSS total score ($r = 0.17$, $P = .024$). However, after Bonferroni correction, only the association between the improvement in immediate memory and negative symptom remained significant ($P < .05$).

DNFE patients were further defined as cognitive responders if the increase of cognitive functioning was higher than 1-SD value after treatment (Lam et al., 2016; Schiller et al., 2019). RM MANOVA analysis found a significant time effect (Wilks' lambda $F = 4.6$, $P = .005$) and a significant interaction of group × time effect (Wilks' lambda $F = 4.4$, $P = .021$) but no group effect (Wilks' lambda $F = 1.4$, $P = .24$). Univariate analyses showed a significant interactive effect of group × time for CuZn-SOD ($F = 5.1$, $P = .026$) and a main effect of time for CuZn-SOD ($F = 3.9$, $P = .04$) (Table 2). However, BDNF levels, total SOD enzyme activity, and Mn-SOD activity in the RM MANOVA analysis showed no main effect of time, group, or an interactive effect.

Logistic regression analysis was performed with response or non-response as the dependent variable and with age, sex, baseline BMI, and PANSS total score as the covariates. We found that the change in CuZn-SOD activity was correlated with the response ($\beta = -0.025$, Wald $X^2 = 4.922$, $P = .027$, odds ratio $= 0.975$, 95% confidence interval = 0.954–0.997)

Table 1. Demographic Characteristics, Clinical Data, Cognitive Function and Biomarkers in DNFE Patients With Schizophrenia and Healthy Controls

Variable	DNFE patients (n = 183)	Healthy controls (n = 152)	P
Sex (male/female)	103/80	79/73	.44
Age (y)	27.0 ± 9.0	28.3 ± 7.7	.12
Education (y)	9.7 ± 3.7	10.5 ± 3.0	.25
Smokers (%)	28.3	31.5	.26
Body mass index (kg/m^2)	21.2 ± 3.4	23.9 ± 4.9	.001
BDNF (ng/mL)	9.8 ± 4.4	11.8 ± 2.5	<.001
CuZn-SOD (U/mL)	53.8 ± 15.7	46.0 ± 15.5	<.001
Mn-SOD (U/mL)	22.0 ± 14.7	22.8 ± 15.9	.81
total SOD (U/mL)	75.3 ± 9.7	65.3 ± 12.7	<.001
Age of onset (y)	25.7 ± 9.1		
Cognitive function, mean ± SD			
Immediate memory	67.1 ± 16.9	75.6 ± 17.6	<.001
Visuospatial/ constructional	79.2 ± 17.4	79.8 ± 15.4	.066
Language	77.6 ± 18.0	94.1 ± 13.2	<.001
Attention	76.8 ± 20.0	87.5 ± 19.9	<.001
Delayed memory	72.1 ± 19.3	86.5 ± 15.0	<.001
Total score	68.7 ± 15.7	80.2 ± 15.0	<.001

Abbreviations: DNFE, drug-naive first episode.

Relationships Between Baseline Biomarkers and Clinical or Cognitive Improvement After Treatment

To further investigate the association between baseline biomarkers and the improvement of cognitive functioning, we performed Pearson product moment analysis in patients using the baseline BDNF subgroups. Our previous studies have shown that baseline BDNF levels were associated with cognitive improvement in the high-BDNF subgroup (Wu et al. 2020). In this study, we also found that CuZn-SOD activity at baseline was associated with improved memory impairments in the high-BDNF subgroup ($r = 0.23$, $P = .047$). Further linear regression analysis showed that baseline CuZn-SOD activity was a significantly predictive biomarker for cognitive improvement on the delayed memory scale ($\beta = .26$, $t = 2.4$, $P = .02$). In the low-BDNF subgroup, no significant associations between the improvement of cognitive functioning and biomarkers were found (all $P > .05$).

Moreover, baseline BDNF levels and SOD enzyme activity were not associated with the improvement of clinical symptoms in both low-BDNF and high-BDNF subgroups (all $P > .05$).

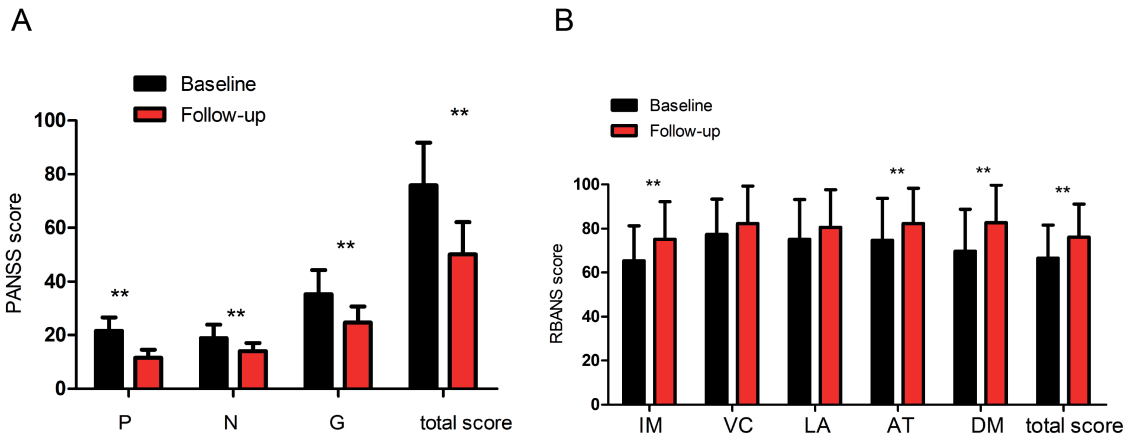

Figure 1. Comparison of Positive and Negative Syndrome Scales (PANSS) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores between baseline and follow-up (12th week). (A) PANSS subscore and total score at baseline and 12-week follow-up. Abbreviations: G, general psychopathology; N, negative subscore; P, positive subscore. (B) RBANS subscale and total score at baseline and 12-week follow-up. Abbreviations: AT, attention; DM, delayed memory; IM, immediate memory; LA, language; VC, visuospatial/constructional. **$P < .05$. Error bars represent 1 SD.

Table 2. BDNF Levels and Antioxidant Enzymes in Responders and Non-Responders

	Baseline		Follow-up		Effect		
	Response n = 50	Non-response n = 133	Response n = 50	Non-response n = 133	Time F(p)	Response F(p)	Interaction F(p)[a]
Mn-SOD	20.7 ± 15.6	22.2 ± 14.7	21.4 ± 11.3	18.8 ± 10.0	1.9 (0.18)	0.4 (0.54)	0.9 (0.35)
CuZn-SOD	57.2 ± 17.2	53.7 ± 14.3	57.0 ± 13.1	60.5 ± 12.5	3.9 (0.04)	0.02 (0.9)	5.1 (0.026)
Total SOD	76.6 ± 12.1	75.0 ± 8.9	77.5 ± 11.2	76.8 ± 8.5	0.5 (0.47)	0.7 (0.40)	0.4 (0.51)
BDNF (ng/mL)	10.2 ± 5.1	10.0 ± 4.1	9.9 ± 3.4	11.0 ± 6.0	0.4 (0.52)	0.2 (0.63)	0.5 (0.50)

*a*Adjusted *F* value controlling for sex, age, and BMI.

DISCUSSION

This prospective, open-label, 12-week observation trial comprehensively assessed several superoxide enzyme activities and BDNF level in DNFE patients and had the following major findings: (1) risperidone treatment significantly increased the CuZn-SOD activity, but not BDNF level and Mn-SOD activity; (2) the relationship between BDNF levels and CuZn-SOD activity was observed at baseline, but not at follow-up; and (3) in the high-BDNF group, baseline CuZn-SOD activity was associated with improved cognitive functioning on the delayed memory scale.

In line with previous studies by our group or others on first-episode and antipsychotics-naïve SCZ patients, we found that 12 weeks of risperidone monotherapy improved clinical symptoms and cognitive impairment (Wu et al. 2020; Li et al. 2021; Yu et al., 2021). There is currently controversy regarding the discovery of the effect of risperidone on the cognitive function of SCZ. Previous meta-analyses indicated that treatment with antipsychotic drugs (such as risperidone, clozapine, olanzapine) may improve general cognitive abilities, including processing speed, learning, or long-term memory (Keefe et al., 1999; Mishara and Goldberg, 2004; Woodward et al., 2005; Thornton et al., 2006). However, few clinical studies have found that risperidone treatment has no effect on cognitive impairment in SCZ (Keefe et al., 2007; Davidson et al., 2009; Maneeton et al., 2018). Keefe et al. (2007) suggest that the duration of the disease may affect cognitive function. Our current study supports that risperidone treatment for 12 weeks shows a pro-cognitive effect in the early stages of SCZ. Considering that the SOD enzymes and BDNF were associated with clinical symptoms and cognitive impairments of DNFE patients (Wu et al., 2013; Fernandes et al., 2015), we further examined the effect of risperidone treatment on these biomarkers. The results showed that risperidone treatment significantly increased CuZn-SOD activity and slightly increased BDNF levels in patients. In those patients who did not show cognitive improvement on RBANS, CuZn-SOD activity further increased. However, BDNF levels and Mn-SOD activity were not significantly different between patients with improved cognitive impairment (e.g., responders) and patients without improvement (non-responders). We cannot give an exact explanation for this finding that only CuZn-SOD changed significantly after treatment. It is well known that CuZn-SOD mainly exists in the cytoplasm, while Mn-SOD exists in the mitochondria (Indo et al., 2015). Our study suggests that risperidone treatment had more influence over oxidative state of the cell than the cytoplasm. Maybe the pharmacological properties of risperidone make it relatively easier to activate CuZn-SOD activity in the cytoplasm.

We found that cognitive improvement was associated with the CuZn-SOD activity and BDNF levels, and regression analysis supported this association, providing further evidence that BDNF and SOD enzymes at baseline can be useful biomarkers for the cognitive response to risperidone monotherapy in patients. This association of BDNF and cognition rather than clinical symptoms also is consistent with a previous study of 12 weeks of antipsychotic treatment. That study showed that patients with decreased BDNF levels at baseline had significantly increased levels after treatment and that the increase in BDNF levels significantly correlated with their improvement on the RBANS total score, but not improvement on clinical symptom scores (Zhang et al., 2018). Mechanistically, our findings are consistent with BDNF regulation of synaptic plasticity and influence on cognitive functioning (Egan et al., 2003; Qin et al., 2017; Zhang et al. 2018). However, contrary to our expectation, after treatment, CuZn-SOD activity was not decreased to the normal levels in those patients who had cognitive improvement. Moreover, the increase of CuZn-SOD activity in patients with non-response to treatment was higher than in responders after treatment, and cognitive improvement was negatively associated with the increase of CuZn-SOD activity. We speculated that because these CuZn-SOD increases at baseline were modest and remained within normal levels, they may reflect a continued compensatory response to excess free radicals and pro-oxidants, which stay at this level as part of SCZ in spite of risperidone treatment. Furthermore, since the brain is particularly susceptible to oxidative stress due to its high oxygen consumption and low antioxidant capacity, a decrease in CuZn-SOD activity may require considerable time (Martinez-Cengotitabengoa et al., 2012). However, the continued increase of CuZn-SOD activity in non-responders is harmful, which may reflect the maladjustment of compensatory response to excessive free radicals and pro-oxidants in those with no response.

Another suggestive finding of the relationship between BDNF and CuZn-SOD activity as a marker of oxidative stress is their association at baseline and lack of association after successful treatment. There was no significant correlation between these 2 biochemical indicators in healthy controls. When the patient's cognitive function and clinical symptoms were improved after treatment, the patients were comparable with the healthy controls, showing that there was no correlation between these 2 biochemical indicators. Our findings indicated that the interrelationship between BDNF and CuZn-SOD was also an important predictor of SCZ cognitive improvement. The neurotrophic factors and phospholipid metabolism/oxidative stress hypotheses of SCZ have been intensively studied for more than 20 years (Mahadik and Mukherjee, 1996; Horrobin, 1998; Mahadik et al., 2001; Angelucci et al., 2004; Buckley, 2007; Green et al., 2011). Similarly, a large amount of evidence from animal and human studies has shown that second-generation antipsychotic drugs such as risperidone and olanzapine increase the levels of antioxidant defense enzymes and neurotrophins in the central nervous system and periphery, which are corrected

with mild to moderate improvements in psychopathology in patients with SCZ. Therefore, the results obtained here are consistent with the previously published data, but are incremental in terms of the procognitive mechanism of atypical antipsychotics. The interesting aspect of our study is that the intercorrelation between these biomarkers may have predictive value for risperidone treatment response.

A final observation to consider is that only those patients with high BDNF at baseline, but not those with low BDNF, showed a correlation of BDNF and CuZn-SOD levels with improvement in cognitive functioning after risperidone treatment. Moreover, the high-BDNF patients had less severe cognitive impairments and their redox regulation appeared better balanced. This better balance perhaps reflected a physiologically well-regulated antioxidant defense system and kept balance in their CuZn-SOD activity better than the rapid increase in those patients with low BDNF levels, since neurotrophic factors, especially BDNF, regulate antioxidant activity (Glerup et al., 2016). Future studies need to investigate potential mechanisms relating elevated BDNF levels and CuZn-SOD activity to cognitive improvement in SCZ patients, perhaps over longer periods of time than 12 weeks and with the broad hypothesis of "normalization" of oxidative damaged brain processes as symptoms and cognition improve through effective medications.

Our study has several limitations. First, we measured peripheral, not brain, BDNF levels and SOD enzyme activities, and the extrapolation of changes in the blood to the brain are uncertain. Second, we assessed a limited number of antioxidant enzymes and did not include a full exploration of oxidative stress markers. Third, we do not know how many days of antipsychotic treatment occurred before the study, since the average duration of illness was 24 months with an onset extending to almost 5 years before enrollment in this study. Fourth, it would have been better if participants were randomly assigned to risperidone or placebo instead of being split into responders and non-responders. However, in this study we did not do this because of consideration from the standpoint of the ethical boundaries. Fifth, we do not know the exact mechanism of changes in plasma SOD activity under baseline conditions and following risperidone monotherapy. In addition, we did not measure the levels of TBARS and/or hydroxyalkenals. Another possible mechanism for changes in enzyme activity may be the consequence of changes in protein levels, which were not estimated in this study.

We found a substantial effect of risperidone treatment on BDNF and SOD activity in SCZ. The baseline SOD activity and BDNF level, as well as a relationship between BDNF and CuZn-SOD, could predict improvement of the cognitive impairments. The relationship between CuZn-SOD enzyme activity and BDNF level at baseline, but not at follow-up, suggested "normalization" in the relationship between the SOD and BDNF in successful treatment of SCZ, since the healthy controls also showed no association between these 2 biochemical measures. Our findings that BDNF and CuZn-SOD can be useful biomarkers for the cognitive response to risperidone monotherapy in patients with cognitive impairment at baseline deserve replication and extension with the broad hypothesis of "normalization" of oxidative damage of brain as symptoms and cognition improve through effective medications for SCZ.

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Interest Statement

No conflict of interest was disclosed for any author.

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