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Differential Impacts of Endogenous Antioxidants on Clinical Symptoms and Cognitive Function in Acute and Chronic Schizophrenia Patients

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Abstract

Background: Impaired antioxidant defense is implicated in the pathophysiology of schizophrenia, and superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) are 3 first-line endogenous antioxidants. Various cognitive functions decline differently during the schizophrenia course. The characteristic roles of the 3 antioxidants in clinical and cognitive profiles in acute and chronic phases of schizophrenia require study.

Methods: We recruited 311 patients with schizophrenia, including 92 acutely exacerbated patients who had been off antipsychotics for at least 2 weeks and 219 chronic patients who had been stable on medication for at least 2 months. Blood SOD, CAT, and GSH levels; clinical symptoms; and 9 cognitive test scores were measured.

Results: Blood CAT levels were higher in the acute patients than in the chronic patients, whereas SOD and GSH levels were similar to one another. Higher CAT levels were correlated with less positive symptoms, better working memory and problem solving in the acute phase, and less negative symptoms, less general psychopathology, better global assessment of function, and better cognitive function (in speed of processing, attention, problem solving) in the chronic period. Higher SOD levels were correlated with better global assessment of function in the acute phase and better speed of processing, working memory, and verbal learning and memory in the chronic period. GSH influenced neither clinical nor cognitive manifestations.

Conclusions: This study showed that blood CAT affected different clinical and cognitive domains between acute and chronic stages of schizophrenia, SOD influenced cognitive functions in chronic state, but GSH affected none. Further studies are needed to explore the underlying mechanisms.

Keywords: Antioxidants, cognitive functions, negative symptoms, positive symptoms, schizophrenia

Significance Statement

Impaired antioxidant defense is implicated in schizophrenia. Superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) are 3 first-line endogenous antioxidants. Various cognitive functions decline differently during schizophrenia course. This study in 311 patients with schizophrenia (92 acutely exacerbated patients and 219 chronic patients) showed that blood CAT affected different clinical and cognitive domains between acute and chronic stages of schizophrenia, SOD influenced cognitive functions in chronic state, but GSH affected none.

INTRODUCTION

Schizophrenia, one of the most disabling brain disorders, is characterized by positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., affective blunting, asociality, and avolition), and deficits in cognitive domains (including speed of processing, attention, working memory, visual learning and memory, verbal learning and memory, and problem solving) (Green et al., 2000; Nam et al., 2009; Lin et al., 2013; Jeganathan and Breakspear,

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2021). Importantly, cognitive dysfunction has been regarded as a core feature of schizophrenia and the main determinant for functional outcome of patients with schizophrenia (Cervellione et al., 2007; Nam et al., 2009; Zanelli et al., 2019; Lin et al., 2022). Further, cognitive functions decline during the illness course of the patients with schizophrenia (Zanelli et al., 2019).

While schizophrenia is multifactorial, oxidative stress plays a key role in its pathophysiology (Bitanihirwe and Woo, 2011; Fraguas et al., 2019; Lin and Lane, 2019; Ermakov et al., 2021; Chen et al., 2023), declining course, and poor outcome (Khan et al., 2002; Murray et al., 2021). To curb excessive oxidative stress, there is a complex set of endogenous antioxidant defense (Pizzino et al., 2017; Murray et al., 2021). Superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) are 3 first-line endogenous antioxidants (Pigeolet et al., 1990; Liu and Ng, 2000; Islam, 2017; Ighodaro and Akinloye, 2018). Schizophrenia is associated with an alteration of these antioxidants; however, how they affect specific symptoms of the patients remains unclear, with inconsistent and even contradictory findings from previous studies (Fraguas et al., 2019; Ermakov et al., 2021; Murray et al., 2021) in SOD (Zhang et al., 2009; Wu et al., 2012; Gonzalez-Liencres et al., 2014; Bai et al., 2018; Chien et al., 2020; Huo et al., 2021), CAT (Juchnowicz et al., 2021; Yang et al., 2023), and GSH (Yao et al., 1999; Matsuzawa et al., 2008; Chien et al., 2020). The previous research about their influences on cognitive functions in schizophrenia has mainly focused on SOD and GSH; however, the results have been inconclusive too (Gonzalez-Liencres et al., 2014; Huo et al., 2021).

Several reasons have been suggested for the aforementioned inconsistent findings, including antipsychotic medication confound, variable disease phases (Sarandol et al., 2015; Đorđević et al., 2017; Chien et al., 2020; Murray et al., 2021), and different cognitive assessments (Gonzalez-Liencres et al., 2014; Huo et al., 2021; Wu et al., 2022). This study aimed to explore the role of the 3 first-line endogenous antioxidants (SOD, CAT, and GSH) in clinical symptoms and comprehensive cognitive tests in patients with acute and chronic schizophrenia, separately.

METHODS

The study was approved by the institutional review board of China Medical University Hospital in Taiwan and conducted in accordance with the Declaration of Helsinki.

Participants

Han Taiwanese patients with schizophrenia aged from 18 to 65 years who had adequate education to communicate effectively were screened. Experienced research psychiatrists confirmed the diagnosis of schizophrenia using the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). We enrolled (1) acutely exacerbated patients who had been drug free for at least 2 weeks; and (2) chronic medicated patients who had been stabilized with antipsychotics for at least 2 months but remained symptomatic. All the enrolled patients had normal physical examinations, neurological examinations, and laboratory screening tests.

Patients with other comorbid psychiatric disorders, serious medical or neurological illness, and those who were unable to cooperate with the assessments for the study were excluded. All the individuals were recruited after they agreed to participate in the study and written informed consent was obtained from each.

Clinical Assessments

Patients' clinical symptoms were measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Scale for Assessment of Negative Symptoms-20 items (SANS) (Andreasen, 1983).

The functional outcome was measured with the Global Assessment of Functioning (GAF) Scale of the DSM-IV. Previous study indicated that the GAF is a valid tool for assessing global psychological, social, and occupational functioning for clinically stable patients with schizophrenia (Startup et al., 2002). All the clinical ratings were conducted by trained and experienced research psychiatrists.

Measurements of Cognitive Function

Cognitive functions were thoroughly assessed in the 6 neurocognitive domains (measured by 9 cognitive tests): (1) speed of processing, which included 3 tests: category fluency, Trail Making A (Reitan et al., 1958), and Wechsler Adult Intelligence Scale-Third Edition, digit symbol-coding (Wechsler, 1997a); (2) sustained attention (measured by continuous performance test [CPT], clear version) (Chen et al., 1998; Lin et al., 2013); (3) working memory, including verbal (backward digit span) (Silver et al., 2003) and nonverbal (Wechsler Memory Scale-Third Edition [WMS-III], Spatial Span) (Wechsler, 1997b); (4) verbal learning and memory (WMS-III, word listing) (Wechsler, 1997b); (5) visual learning and memory (WMS-III, visual reproduction) (Wechsler, 1997b); and (6) problem solving (Wechsler Intelligence Scale for Children-Third Edition), Maze) (Wechsler, 1991).

Laboratory Measurements

Three endogenous antioxidants in peripheral blood were measured using commercially available kits, as previously described (Lane et al., 2023).

SOD levels in plasma were analyzed using the kit according to the manufacturer's recommended protocol (Merck, Kenilworth, NJ, USA; catalog no. 574601). The detailed method has been described elsewhere (Lin et al., 2018, 2020).

CAT levels in plasma were measured using the kit according to the manufacturer's recommended protocol (Cayman, Ann Arbor, MI, USA; catalog no. 707002). The detailed method has been described elsewhere (Lin et al., 2018, 2020).

GSH levels in plasma were measured using the kit according to the manufacturer's recommended protocol (Cayman, Ann Arbor, MI, USA, Catalog number: 703002). The detailed method has been described elsewhere (Lin and Lane, 2021).

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Inc.) to analyze the data in this study. Fisher exact test was used to compare the between-group differences of the categorical variable (gender) and *t* test (or Mann-Whitney U test if the distribution was not normal) for continuous variables (Table 1).

Correlations between laboratory and clinical measures (or cognitive tests) in acutely ill and chronically stable patients with schizophrenia were analyzed by zero-order correlations (Tables 2 and 3). The significance level for statistical tests was $P < .05$.

RESULTS

Demographic, Clinical, Cognitive, and Laboratory Data

We recruited 311 patients with schizophrenia, including 92 acutely ill patients who had been drug free for at least 2 weeks and 219 chronic patients who had been stabilized with antipsychotics for at least 2 months.

Table 1. Demographic, Clinical, Cognitive, and Laboratory Characteristics of Acutely Ill and Chronic Schizophrenia Patients

Parameter	Acute (n = 92)	Chronic (n = 219)	P
Gender			.900[a]
Male	52 (56.5%)	126 (57.5%)	
Female	40 (43.5%)	93 (42.5%)	
Age (y)	31.5 ± 9.5	37.7 ± 9.8	<.001[b]
Education (y)	13.3 ± 2.7	12.0 ± 2.8	<.001[b]
Age at illness onset (y)	24.8 ± 7.1	23.6 ± 6.8	.183[b]
Illness duration (m)	74.4 ± 74.8	159.9 ± 106.6	<.001[b]
PANSS-total score	89.5 ± 17.2	83.3 ± 14.6	.008[b]
PANSS-positive score	21.1 ± 5.7	19.2 ± 4.9	.007[b]
PANSS-negative score	22.5 ± 7.1	23.1 ± 6.4	.193[b]
PANSS-general score	45.8 ± 6.8	41.0 ± 6.9	<.001[b]
SANS score	46.4 ± 20.5	48.1 ± 20.1	.327[b]
GAF score	51.2 ± 7.2	48.1 ± 9.9	.027[b]
Category fluency	26.8 ± 8.7	24.7 ± 9.1	.074[c]
Trail making A	2.9 ± 1.2	2.1 ± 1.2	<.001[b]
Digit symbol coding	6.5 ± 3.7	5.0 ± 3.5	.001[b]
CPT-clear version	3.3 ± 1.3	3.1 ± 1.4	.302[b]
Backward digit span	8.2 ± 3.8	7.3 ± 3.5	.140[b]
Spatial span	7.6 ± 3.7	7.2 ± 3.5	.493[b]
Word listing	7.3 ± 3.4	6.7 ± 3.1	.081[b]
Visual reproduction	6.0 ± 3.0	6.0 ± 3.5	.591[b]
Maze	20.3 ± 5.3	17.2 ± 6.4	<.001[b]
CAT level (nmol_min_ml)	61.7 ± 52.3	40.4 ± 31.4	.004[b]
SOD level (U_ml)	0.06 ± 0.06	0.06 ± 0.07	.600[b]
GSH level (μM)	4.4 ± 4.3	4.4 ± 3.9	.667[b]

Abbreviations: CAT, catalase; CPT, cognitive performance test; GAF, Global Assessment of Functioning; GSH, glutathione; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms-20 items; SOD, superoxide dismutase.
[a]Fisher's Exact test.
[b]Mann-Whitney U test.
[c]t test.

As shown in Table 1, the 2 groups were similar in gender distribution (male: 56.5% vs 57.5%) and age at illness onset (24.8 ± 7.1 vs 23.6 ± 6.8 years). The acutely ill patients were younger than the chronic patients (31.5 ± 9.5 vs 37.7 ± 9.8 years) and had more education (13.3 ± 2.7 vs 12.0 ± 2.8 years) and a shorter illness duration (74.4 ± 74.8 vs 159.9 ± 106.6 months).

Compared with the chronic patients, the acutely ill patients displayed more severe clinical symptoms (except negative symptoms, with higher scores on PANSS-total, PANSS-positive, and PANSS-general psychopathology) but better general function (with higher GAF scores) and cognitive performances (including Trail Making A, digit symbol-coding, and Maze, but not other tests [without statistical significance]) (Table 1).

In the laboratory, the acutely ill patients had higher CAT levels than the chronic patients. The 2 groups were similar in terms of SOD and GSH levels (Table 1).

Correlations Between Laboratory and Clinical/Cognitive Measures

Among all 311 patients, illness duration was negatively correlated with blood CAT levels ($r = -0.127$, $P = .025$) and SOD levels ($r = -0.158$, $P = .005$) but positively correlated with GSH levels ($r = 0.115$, $P = .042$).

Higher blood CAT levels were correlated with less severe positive symptoms, better spatial span (for measuring nonverbal working memory), and better Maze performance (for problem solving) in the acute phase; and less severe symptoms (including overall symptoms, negative symptoms, and general psychopathology), better global function, and better cognitive performance (in category fluency [for speed of processing], CPT [for sustained attention], and Maze) in the chronic period (Tables 2 and 3).

Higher SOD levels were correlated with higher GAF scores in the acute phase and better digit symbol coding (for speed of processing), spatial span, and word listing (verbal learning and memory) in the chronic period (Tables 2 and 3).

GSH levels were not associated with clinical or cognitive manifestations in both acute and chronic phases (Tables 2 and 3).

Correlations Between Laboratory Measures, Between Clinical Profiles, and Between Cognitive Tests

CAT levels were correlated with neither SOD nor GSH levels in acutely ill patients; on the other hand, CAT levels were positively correlated with GSH levels, but not with SOD levels, in chronic patients. SOD levels were negatively correlated with GSH levels in both acutely ill patients and chronic patients (Tables 2 and 3).

Each clinical symptom item (including PANSS-total, PANSS-positive, PANSS-negative, PANSS-general psychopathology, and SANS) was positively correlated with every other symptom item and negatively correlated with GAF in both acutely ill patients and chronic patients (Tables 2 and 3).

Each cognitive test (including category fluency, Trail Making A, digit symbol-coding, CPT, backward digit span, spatial span, word listing, visual reproduction, and Maze) score was positively correlated with every other cognitive test score in both acutely ill patients and chronic patients, except category fluency vs Maze (without statistical significance) in acutely ill patients (Tables 2 and 3).

DISCUSSION

To our knowledge, this is the first study to investigate the relationships between 3 first-line endogenous antioxidants (CAT, SOD, and GSH) and clinical/cognitive profiles in patients with both acute and chronic schizophrenia.

Main Findings

Blood CAT levels in acute patients exceeded the levels in chronic patients, whereas SOD and GSH levels were similar between the 2 groups of patients.

Higher CAT levels were correlated with less positive symptoms, better nonverbal working memory, and better problem solving in the acute phase and with less negative symptoms, less general psychopathology, better global function, faster speed of processing (by category fluency), better sustained attention, and better problem solving in the chronic period.

Higher SOD levels were correlated with better global function in the acute phase and with better speed of processing (by digit symbol-coding), nonverbal working memory, and verbal learning and memory in the chronic period.

GSH did not influence any clinical or cognitive parameters.

Implication of CAT Findings

Previous study indicated that CAT concentrations were numerically (not statistically significantly) higher in first-episode

Table 2. Zero-Order Correlations of Laboratory and Clinical Measures in Acutely Ill and Chronic Schizophrenia Patients

	1	2	3	4	5	6	7	8	9
Acute group (n = 92)									
1 CAT level	—								
2 SOD level	−.182	—							
3 GSH level	.118	−.428[b]	—						
4 PANSS-total	−.135	−.103	.068	—					
5 PANSS-positive	−.249a	.015	.078	.842[b]	—				
6 PANSS-negative	−.049	−.133	−.027	.896[b]	.631[b]	—			
7 PANSS-general	−.086	−.134	.145	.894[b]	.641[b]	.699[b]	—		
8 SANS	−.177	−.113	.078	.813[b]	.619[b]	.854[b]	.660[b]	—	
9 GAF	−.003	.229[a]	−.107	−.807[b]	−.602[b]	−.751[b]	−.761[b]	−.646[b]	—
Chronic group (n = 219)									
1 CAT level	—								
2 SOD level	−.093	—							
3 GSH level	.235b	−.402[b]	—						
4 PANSS-total	−.156[a]	−.047	−.047	—					
5 PANSS-positive	−.102	−.039	.071	.693[b]	—				
6 PANSS-negative	−.133[a]	−.047	−.055	.793[b]	.274[b]	—			
7 PANSS-general	−.133[a]	−.029	−.099	.886[b]	.502[b]	.555[b]	—		
8 SANS	−.150[a]	−.097	−.012	.753[b]	.337[b]	.829[b]	.583[b]	—	
9 GAF	.233b	.013	.076	−.657[b]	−.344[b]	−.642[b]	−.548[b]	−.705[b]	—

Abbreviations: CAT, catalase; GAF, Global Assessment of Functioning; GSH, glutathione; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms-20 items; SOD, superoxide dismutase.
[a]P < .05.
[b]P < .001.

patients (n = 47) than in chronic patients (n = 49) (Juchnowicz et al., 2021). The current study, with a larger sample size, demonstrated that CAT levels were significantly higher in acutely exacerbated patients (n = 92) than in chronic stable patients (n = 219), implying that CAT concentration may be able to serve as a state marker if more studies confirm the findings in the future.

In a recent study, no significant association was revealed between CAT concentration and every PANSS subscale score (all $P > .05$) in patients with chronic schizophrenia (n = 49) (Yang et al., 2023). In another study, CAT concentrations were negatively related with negative symptoms in patients with schizophrenia (n = 96) (Juchnowicz et al., 2019). The current study found for the first time—to our knowledge—that CAT levels were negatively correlated with positive symptoms (measured by PANSS-positive) in acutely ill patients and also negatively correlated with negative symptoms by both PANSS-negative and SANS), general psychopathology (PANSS-general), and overall symptoms (PANSS-total) in the chronic patients. In addition, CAT levels were positively correlated with GAF in the patients with chronic schizophrenia. Due to the different sample sizes, heterogeneity of patients, medication effects, etc. among previous studies, more research is warranted to further explore the role of CAT in clinical symptoms of patients with schizophrenia at various stages.

Importantly, this study also for the first time, to our knowledge, showed that CAT levels were correlated with cognitive function of patients with schizophrenia and, moreover, with different cognitive domains between patients with acute schizophrenia and those with chronic schizophrenia. Future replication studies are needed.

Overall, the differential associations of CAT levels with better clinical/cognitive features between the acute and chronic phases may reflect an adaptive or compensatory mechanism to reduce clinical symptoms and preserve general and cognitive functions across the illness course.

Implication of SOD Findings

The present study found that patients with acute schizophrenia and those with chronic schizophrenia had similar SOD levels, partially supporting the previous notion that SOD may be a trait marker of schizophrenia (Flatow et al., 2013).

The findings of previous studies regarding the relationships between SOD levels and clinical symptoms of patients with schizophrenia appeared contradictory: a positive relationship with positive, negative, or overall symptoms (Zhang et al., 2009 [n = 78]; Bai et al., 2018 [n = 40 first-episode, drug-free and 40 chronically medicated patients]; Huo et al., 2021 [n = 32 geriatric male patients]; Wang et al., 2021 [n = 67 female patients]), a negative relationship with positive symptoms (Wu et al., 2012 [n = 78 never-medicated first-episode and 100 medicated chronic patients]), or no relationship with overall symptom severity (Gonzalez-Liencres et al., 2014 [n = 41]). In the current study, with a larger-sized sample, no relationship between SOD levels and any clinical symptom domain was observed for both acutely exacerbated patients (n = 92) and chronically medicated patients (n = 219). Instead, SOD levels were positively with global function in the acutely ill patients.

SOD levels were not associated with cognitive function in a previous study (Gonzalez-Liencres et al., 2014, n = 41) but were

Table 3. Zero-Order Correlations of Laboratory and Cognitive Measures in Acutely Ill and Chronic Schizophrenia Patients

	1	2	3	4	5	6	7	8	9	10	11	12
Acute group (n = 92)												
1 CAT level	—											
2 SOD level	−.182	—										
3 GSH level	.118	−.428[c]	—									
4 Category fluency	−.018	.026	−.059	—								
5 Trail making A	.132	.057	−.163	.541[c]	—							
6 Digit symbol-coding	.138	.091	−.172	.598[c]	.557[c]	—						
7 CPT	.100	.105	−.009	.541[c]	.582[c]	.553[c]	—					
8 Backward digit span	.149	.114	−.094	.374[b]	.262[a]	.389[c]	.227a	—				
9 Spatial span	.231a	−.030	.083	.583[c]	.475[c]	.578[c]	.494[c]	.417[c]	—			
10 Word listing	.087	.175	−.081	.596[c]	.529[c]	.632[c]	.442[c]	.463[c]	.520[c]	—		
11 Visual reproduction	.186	.093	−.017	.530[c]	.522[c]	.579[c]	.426[c]	.327[b]	.503[c]	.705[c]	—	
12 Maze	.329[b]	.133	−.042	.171	.318[b]	.398[c]	.399[c]	.285[b]	.435[c]	.341[b]	.493[c]	—
Chronic group (n = 219)												
1 CAT level	—											
2 SOD level	−.093	—										
3 GSH level	.235c	−.402[c]	—									
4 Category fluency	.153[a]	.097	.054									
5 Trail making A	.125	.067	−.053	.462[c]	—							
6 Digit symbol-coding	.083	.138[a]	.045	.506[c]	.657[c]	—						
7 CPT	.157[a]	.037	.096	.471[c]	.412[c]	.500[c]	—					
8 Backward digit span	.002	.104	−.027	.392[c]	.416[c]	.459[c]	.377[c]	—				
9 Spatial span	.103	.164[a]	−.063	.453[c]	.490[c]	.563[c]	.467[c]	.534[c]	—			
10 Word listing	.050	.140[a]	−.019	.395[c]	.316[c]	.500[c]	.288[c]	.415[c]	.449[c]	—		
11 Visual reproduction	.121	.108	−.062	.440[c]	.344[c]	.455[c]	.301[c]	.434[c]	.499[c]	.535[c]	—	
12 Maze	.170[a]	.057	.027	.435[c]	.450[c]	.462[c]	.487[c]	.401[c]	.517[c]	.255[c]	.495[c]	—

Abbreviations: CAT, catalase; CPT, cognitive performance test; GSH, glutathione; SOD, superoxide dismutase.
[a]P < .05.
[b]P < .01.
[c]P < .001.

inversely associated with immediate memory, language, and Repeatable Battery for the Assessment of Neuropsychological Status total scores in another one (Huo et al., 2021; n = 32 geriatric male patients). The current study for the first time, to our knowledge, found that higher SOD levels were correlated with better speed of processing, nonverbal working memory, and verbal learning and memory in patients with chronic schizophrenia (n = 219).

The reasons for these discrepancies may include different sample sizes, methods of measurement, medication status, age, gender, and other factors. More research is needed to elucidate the role of SOD in clinical manifestations of schizophrenia and its potential as a biomarker.

Implication of GSH Findings

The present study indicated that patients with acute and chronic schizophrenia had similar GSH levels, partially supporting the previous notion that GSH may be a trait marker of schizophrenia (Juchnowicz et al., 2021).

A negative correlation was reported between GSH levels in the brain and negative symptoms in patients with schizophrenia, perhaps suggesting that lower GSH levels may result in oxidative stress and consequently negative symptoms (n = 20) (Matsuzawa et al., 2008). On the other hand, another study found that patients with residual symptoms (principally negative symptoms) had lower GSH levels in the brain than the patients with nonresidual schizophrenia (n = 28) (Kumar et al., 2020). However, GSH levels in blood were not correlated with clinical symptoms or cognitive function in schizophrenia patients (n = 41) (Gonzalez-Liencres et al., 2014), similar to the findings of the current study.

Certainly, blood levels of GSH may be unable to reflect the levels in the brain. More studies with larger-size samples for measuring both blood and brain levels are helpful in clarifying the role of GSH in phenotypes of schizophrenia and the relationship between blood and brain levels.

Implication of Relationships of CAT, SOD, and GSH

Among the acutely ill patients, GSH levels were negatively correlated with SOD levels. Among the chronic patients, GSH levels were negatively correlated with SOD and positively correlated with CAT. Consistently, according to earlier studies, SOD, GSH, and CAT cooperate to prevent oxidative stress from damaging cells (Weydert and Cullen, 2010; Gusti et al., 2021). SOD transforms

superoxide into hydrogen peroxide and oxygen; thereafter, GSH and CAT change hydrogen peroxide into water and oxygen (Weydert and Cullen, 2010; Gusti et al., 2021). The homeostasis among these enzymes depends on their cellular distribution (Morris et al., 2014; Ighodaro, 2018). SOD is found in various compartments such as the cytosol, mitochondria, and extracellular space (Weydert and Cullen, 2010). GSH is primarily located in the cytosol and mitochondria, and CAT is mainly in the peroxisomes (Weydert and Cullen, 2010; Ighodaro, 2018). Since both SOD and GSH exist in the cytosol and mitochondria, it is expected that GSH levels show a negative correlation with SOD to keep a balanced redox status. It is also logical for GSH levels to have a positive correlation with CAT levels because both antioxidants work together through similar mechanisms across different organelles. The lack of correlation between SOD and CAT levels is also understandable because of their different locations.

The insignificant relationship between GSH levels and CAT levels in the acutely ill patients may have arisen from the rather small sample size or just the acute (not yet stabilized) state. Future larger study is required for the answer.

Clinical Relevance of Correlations Between Clinical Profiles and Between Cognitive Tests

Previous studies suggest that various symptom domains and GAF can be transformed with close approximation (Suzuki et al., 2015; Grot et al., 2021). In accordance, the current study demonstrated that each clinical symptom item was positively correlated with every other symptom item and negatively correlated with GAF in both acutely ill and chronic patients.

Also consistent with previous studies that indicated that cognitive deficits were present across multiple domains (Targum and Keefe, 2008; Lin et al., 2022), the current study demonstrated that each cognitive test score was correlated with every other cognitive test score in the chronic patients; and most cognitive test scores, except category fluency vs maze (without statistical significance), were correlated with each other in the acute patients.

Strength and Limitation

The main strength of the current study is that we applied 9 comprehensive cognitive tests in measuring 6 cognitive domains. In addition, the sample size was rather large; it is, to date, the largest (92 acutely ill patients and 219 chronically medicated patients). However, the sample can be larger, especially for the acute patients.

There are also other limitations of the present study. First, schizophrenia is a complex disease. Further studies are warranted to establish the joint role of the current 3 antioxidants plus other biomarkers in clinical symptoms and cognitive functions of schizophrenia. Second, it has been reported that antipsychotic drugs can enhance the antioxidant system by acting on the dopaminergic system (Goh et al., 2022). In the current study, the possible medication effect in the patients with chronic schizophrenia may have confounded the finding. Third, the question of whether the blood levels of the 3 antioxidants can reflect their levels in brain deserves study. Fourth, no healthy individuals were enrolled. Whether the findings can be extrapolated to healthy individuals remains unclear. Fifth, though we enrolled patients with both acute and chronic schizophrenia, longitudinal studies should be designed in the future. Sixth, further studies are required to explore the underlying mechanisms of the influences of the 3 endogenous antioxidants on clinical symptoms and cognitive domains through various phases of schizophrenia. Finally, we enrolled only Han Taiwanese patients in this study. More studies are needed to examine whether ethnic difference may change the result.

CONCLUSIONS

This study revealed that blood CAT influenced clinical and some cognitive domains in both acute and chronic phases of schizophrenia, SOD altered cognitive functions in the chronic phase, but GSH did not alter any. More studies are necessary to discover the underlying mechanisms.

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Interest Statement

The authors declare that there is no conflict of interest.

Data Availability Statement

Data available: No.

References

American Psychiatric Association (1994) *Structured clinical interview for DSM-IV*. Washington, DC: American Psychiatric Press.

Andreasen NC (1983) *Scales for the assessment of negative symptoms (SANS)*. Iowa City: University of Iowa.

Bai ZL, Li XS, Chen GY, Du Y, Wei ZX, Chen X, Zheng GE, Deng W, Cheng Y (2018) Serum oxidative stress marker levels in unmedicated and medicated patients with schizophrenia. *J Mol Neurosci* **66**:428–436.

Bitanihirwe BK, Woo TU (2011) Oxidative stress in schizophrenia: an integrated approach. *Neurosci Biobehav Rev* **35**:878–893.

Cervellione KL, Burdick KE, Cottone JG, Rhinewine JP, Kumra S (2007) Neurocognitive deficits in adolescents with schizophrenia: longitudinal stability and predictive utility for short-term functional outcome. *J Am Acad Child Adolesc Psychiatry* **46**:867–878.

Chen MY, Zhang Q, Liu YF, Zheng WY, Si TL, Su Z, Cheung T, Jackson T, Li XH, Xiang YT (2023) Schizophrenia and oxidative stress from the perspective of bibliometric analysis. *Front Psychiatry* **14**:1145409.

Chen WJ, Liu SK, Chang CJ, Lien YJ, Chang YH, Hwu HG (1998) Sustained attention deficit and schizotypal personality features in nonpsychotic relatives of schizophrenic patients. *Am J Psychiatry* **155**:1214–1220.

Chien YL, Hwu HG, Hwang TJ, Hsieh MH, Liu CC, Lin-Shiau SY, Liu CM (2020) Clinical implications of oxidative stress in schizophrenia: acute relapse and chronic stable phase. *Prog Neuropsychopharmacol Biol Psychiatry* **99**:109868.

Đorđević VV, Lazarević D, Ćosić V, Knežević M, Đorđević VB (2017) Age-related changes of superoxide dismutase activity in patients with schizophrenia. *Vojnosanit Pregl* **74**:31–37.

Ermakov EA, Dmitrieva EM, Parshukova DA, Kazantseva DV, Vasilieva AR, Smirnova LP (2021) Oxidative stress-related mechanisms in schizophrenia pathogenesis and new treatment perspectives. *Oxid Med Cell Longev* **2021**:8881770.

Flatow J, Buckley P, Miller BJ (2013) Meta-analysis of oxidative stress in schizophrenia. *Biol Psychiatry* **74**:400–409.

Fraguas D, Díaz-Caneja CM, Ayora M, Hernández-Álvarez F, Rodríguez-Quiroga A, Recio S, Leza JC, Arango C (2019) Oxidative stress and inflammation in first-episode psychosis: a systematic review and meta-analysis. *Schizophr Bull* **45**:742–751.

Goh XX, Tang PY, Tee SF (2022) Effects of antipsychotics on antioxidant defense system in patients with schizophrenia: a meta-analysis. *Psychiatry Res* **309**:114429.

Gonzalez-Liencres C, Tas C, Brown EC, Erdin S, Onur E, Cubukcoglu Z, Aydemir O, Esen-Danaci A, Brüne M (2014) Oxidative stress in schizophrenia: a case-control study on the effects on social cognition and neurocognition. *BMC Psychiatry* **14**:268.

Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff?". *Schizophr Bull* **26**:119–136.

Grot S, Giguère C, Smine S, Mongeau-Pérusse V, Nguyen DD, Preda A, Potvin S, van Erp TGM, Fbirn Orban P (2021) Converting scores between the PANSS and SAPS/SANS beyond the positive/negative dichotomy. *Psychiatry Res* **305**:114199.

Gusti AMT, Qusti SY, Alshammari EM, Toraih EA, Fawzy MS (2021) Antioxidants-related superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: a preliminary case-control study. *Antioxidants* **10**:595.

Huo L, Lu X, Wu F, Chang C, Ning Y, Zhang XY (2021) Elevated activity of superoxide dismutase in male late-life schizophrenia and its correlation with clinical symptoms and cognitive deficits. *BMC Psychiatry* **21**:606.

Ighodaro OM, Akinloye OA (2018) First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. *Alexandria J Med* **54**:287–293.

Islam MT (2017) Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurol Res* **39**:73–82.

Jeganathan J, Breakspear M (2021) An active inference perspective on the negative symptoms of schizophrenia. *Lancet Psychiatry* **8**:732–738.

Juchnowicz D, Dzikowski M, Rog J, Waszkiewicz N, Zalewska A, Maciejczyk M, Karakuła-Juchnowicz H (2021) Oxidative stress biomarkers as a predictor of stage illness and clinical course of schizophrenia. *Front Psychiatry* **12**:728986.

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* **13**:261–276.

Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP (2002) Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophr Res* **58**:1–10.

Kumar J, Liddle EB, Fernandes CC, Palaniyappan L, Hall EL, Robson SE, Simmonite M, Fiesal J, Katshu MZ, Qureshi A, Skelton M, Christodoulou NG, Brookes MJ, Morris PG, Liddle PF (2020) Glutathione and glutamate in schizophrenia: a 7T MRS study. *Mol Psychiatry* **25**:873–882.

Lane HY, Wang SH, Lin CH (2023) Endogenous antioxidants predicted outcome and increased after treatment: a benzoate dose-finding, randomized, double-blind, placebo-controlled trial for Alzheimer's disease. *Psychiatry Clin Neurosci* **77**:102–109.

Lin CH, Huang CL, Chang YC, Chen PW, Lin CY, Tsai GE, Lane HY (2013) Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. *Schizophr Res* **146**:231–237.

Lin CH, Lane HY (2019) Early identification and intervention of schizophrenia: insight from hypotheses of glutamate dysfunction and oxidative stress. *Front Psychiatry* **10**:93.

Lin CH, Lane HY (2021) Plasma glutathione levels decreased with cognitive decline among people with mild cognitive impairment (MCI): a two-year prospective study. *Antioxidants* **10**:1839.

Lin CH, Lin CH, Chang YC, Huang YJ, Chen PW, Yang HT, Lane HY (2018) Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Biol Psychiatry* **84**:422–432.

Lin CH, Yang HT, Chen PK, Wang SH, Lane HY (2020) Precision medicine of sodium benzoate for the treatment of behavioral and psychological symptoms of dementia (BPSD). *Neuropsychiatr Dis Treat* **16**:509–518.

Lin E, Lin CH, Lane HY (2022) A bagging ensemble machine learning framework to predict overall cognitive function of schizophrenia patients with cognitive domains and tests. *Asian J Psychiatr* **69**:103008.

Liu F, Ng TB (2000) Effect of pineal indoles on activities of the antioxidant defense enzymes superoxide dismutase, catalase, and glutathione reductase, and levels of reduced and oxidized glutathione in rat tissues. *Biochem Cell Biol* **78**:447–453.

Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H, Iyo M, Hashimoto K (2008) Negative correlation between brain glutathione level and negative symptoms in schizophrenia: a 3T 1H-MRS study. *PLoS One* **3**:e1944.

Morris G, Anderson G, Dean O, Berk M, Galecki P, Martin-Subero M, Maes M (2014) The glutathione system: a new drug target in neuroimmune disorders. *Mol Neurobiol* **50**:1059–1084.

Murray AJ, Rogers JC, Katshu MZUH, Liddle PF, Upthegrove R (2021) Oxidative stress and the pathophysiology and symptom profile of schizophrenia spectrum disorders. *Front Psychiatry* **12**:703452.

Nam HJ, Kim N, Park T, Oh S, Jeon HO, Yoon SC, Lee YS, Lee WK, Ha K, Kim JH, Hong KS (2009) Cognitive profiles of healthy siblings of schizophrenia patients: application of the cognitive domains of the MATRICS consensus battery. *World J Biol Psychiatry* **10**:452–460.

Pigeolet E, Corbisier P, Houbion A, Lambert D, Michiels C, Raes M, Zachary MD, Remacle J (1990) Glutathione peroxidase, superoxide dismutase, and catalase inactivation by peroxides and oxygen derived free radicals. *Mech Ageing Dev* **51**:283–297.

Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A (2017) Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev* **2017**:8416763.

Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* **8**:271–276.

Sarandol A, Sarandol E, Acikgoz HE, Eker SS, Akkaya C, Dirican M (2015) First-episode psychosis is associated with oxidative stress: effects of short-term antipsychotic treatment. *Psychiatry Clin Neurosci* **69**:699–707.

Silver H, Feldman P, Bilker W, Gur RC (2003) Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *Am J Psychiatry* **160**:1809–1816.

Startup M, Jackson MC, Bendix S (2002) The concurrent validity of the Global Assessment of Functioning (GAF). *Br J Clin Psychol* **41**:417–422.

Suzuki T, Uchida H, Sakurai H, Ishizuki T, Tsunoda K, Takeuchi H, Mimura M (2015) Relationships between global assessment of functioning and other rating scales in clinical trials for schizophrenia. *Psychiatry Res* **227**:265–269.

Targum SD, Keefe RS (2008) Cognition and schizophrenia: is there a role for cognitive assessments in diagnosis and treatment? *Psychiatry* **5**:55–59.

Wang DM, Chen DC, Wang L, Zhang XY (2021) Sex differences in the association between symptoms and superoxide dismutase in patients with never-treated first-episode schizophrenia. *World J Biol Psychiatry* **22**:325–334.

Wechsler D (1991) *Wechsler intelligence scale for children*, 3rd ed. San Antonio, TX: Psychological Association.

Wechsler D (1997a) *Wechsler adult intelligence scale*, 3rd ed. San Antonio, TX: Psychological Association.

Wechsler D (1997b) *Wechsler memory scale*, 3rd ed. San Antonio, TX: Psychological Association.

Weydert CJ, Cullen JJ (2010) Measurement of superoxide dismutase, catalase and glutathione peroxidase in cultured cells and tissue. *Nat Protoc* **5**:51–66.

Wu Z, Zhang XY, Wang H, Tang W, Xia Y, Zhang F, Liu J, Fu Y, Hu J, Chen Y, Liu L, Chen DC, Xiu MH, Kosten TR, He J (2012) Elevated plasma superoxide dismutase in first-episode and drug naive patients with schizophrenia: inverse association with positive symptoms. *Prog Neuropsychopharmacol Biol Psychiatry* **36**:34–38.

Wu Z, Liu Q, Zhang Y, Guan X, Xiu M, Zhang X (2022) Superoxide dismutase, BDNF, and cognitive improvement in drug-naive first-episode patients with schizophrenia: a 12-week longitudinal study. *Int J Neuropsychopharmacol* **25**:128–135.

Yang H, Zhang J, Yang M, Xu L, Chen W, Sun Y, Zhang X (2023) Catalase and interleukin-6 serum elevation in a prediction of treatment-resistance in male schizophrenia patients. *Asian J Psychiatr* **79**:103400.

Yao JK, Reddy RD, van Kammen DP (1999) Human plasma glutathione peroxidase and symptom severity in schizophrenia. *Biol Psychiatry* **45**:1512–1515.

Zanelli J, Mollon J, Sandin S, Morgan C, Dazzan P, Pilecka I, Reis Marques T, David AS, Morgan K, Fearon P, Doody GA, Jones PB, Murray RM, Reichenberg A (2019) Cognitive change in schizophrenia and other psychoses in the decade following the first episode. *Am J Psychiatry* **176**:811–819.

Zhang XY, Zhou DF, Qi LY, Chen S, Cao LY, Chen DC, Xiu MH, Wang F, Wu GY, Lu L, Kosten TA, Kosten TR (2009) Superoxide dismutase and cytokines in chronic patients with schizophrenia: association with psychopathology and response to antipsychotics. *Psychopharmacology* **204**:177–184.