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Effects of oxidative stress and GDNF on patients with bipolar disorder: a prospective study

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Abstract

Background Bipolar disorder (BD) is a common mental disorder characterized by significant cognitive dysfunction, the mechanisms of which remain unclear. Oxidative stress and glial cell line-derived neurotrophic factor (GDNF) influence the pathophysiology of BD. Their specific roles, particularly concerning cognitive function during manic episodes, are unclear. The serum levels of superoxide dismutase (SOD) and malondialdehyde (MDA), and GDNF were biochemically assayed in patients with bipolar mania before and after treatment to explore their associations with cognitive function.

Methods A total of 75 patients in acute manic episodes of BD and 70 healthy controls were initially enrolled. During the 4-week intervention period with atypical antipsychotics and mood stabilizers, 5 patients discontinued follow-up, resulting in 70 completers included in the final analysis. The severity of manic symptoms were assessed using the Young Mania Rating Scale (YMRS). Cognitive function was assessed by the Digit Cancellation, Stroop Color and Word, and Trail Making Tests. Serum levels of SOD, MDA, and GDNF were measured using biochemical assays.

Results BD patients demonstrated higher serum SOD and MDA levels and lower GDNF levels compared to controls, following improvements after treatment. Pre-treatment YMRS scores and cognitive function assessments positively correlated with SOD and MDA levels, and negatively correlated with GDNF levels. Treatment significantly improved manic symptoms and cognitive function, although GDNF levels remained lower than in controls.

Conclusions The demonstrated associations with symptoms and cognitive functions during the manic phase substantially advance the understanding of the role of oxidative stress and GDNF in BD. Possible biomarkers for BD diagnosis and prognosis assessment are revealed. Further investigations into the complex pathophysiological mechanisms of BD are needed.

Clinical trial number Not applicable

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Keywords Bipolar disorder, Oxidative stress, Glial cell line-derived neurotrophic factor, Cognition

Background

Bipolar disorder (BD) refers to a group of chronic and complex mental illnesses with high prevalence and mortality rates [1]. Cognitive dysfunction is a significant characteristic of BD, in addition to affective symptoms. Cognitive dysfunction is prevalent throughout the early stages [2], acute episodes, and periods of remission of the illness [3]. This dysfunction significantly affects patients' social function and increases the risk of disease recurrence and progression [4, 5]. Therefore, addressing cognitive dysfunction in BD treatment has become a key focus [6]. However, the precise pathophysiological mechanisms of cognitive dysfunction in BD have not yet been elucidated.

Studies have explored the relationship between oxidative stress and BD [7]. Oxidative stress, characterized by an imbalance between oxidative processes and antioxidant defenses within the body, leads to an overproduction of free radicals when antioxidant functions are inadequate, damaging nucleic acids, proteins, and lipids [8]. Neurons are particularly susceptible to oxidative stress due to limited antioxidant defense mechanisms. During neurodevelopment, minor disturbances in redox balance affect the signaling pathways and processes of neurogenesis and neuronal differentiation, potentially leading to long-term behavioral and cognitive abnormalities in adulthood [9]. Findings from research into neurodegenerative diseases, such as Alzheimer's disease, support the notion that oxidative stress is directly involved in neurotransmitter transmission at neuronal synapses, leading to cognitive dysfunction [10]. Elevated levels of oxidative stress are observed in post-mortem brain tissue and peripheral blood of patients with BD [11, 12]. A possible link between oxidative stress and cognitive impairment in BD has been described [13, 14]. A study on adolescent BD associated lipid peroxidation with certain cognitive domains, such as executive function [15]. A separate study reported that patients with mental disorders and heightened oxidation tended to have reduced hippocampal volume, more severe clinical symptoms, and poorer cognitive function [16]. These findings underscore the significant role of oxidative stress in BD, which warrants further investigation.

Glial cell line-derived neurotrophic factor (GDNF) plays a significant role in the pathophysiology of BD [17–19]. GDNF and brain-derived neurotrophic factor are members of the neurotrophic factor family. Both are essential for neuronal growth, differentiation, survival, and support of mature neurons [20]. Preliminary research findings indicated that individuals with BD have a decreased level of serum GDNF compared to healthy individuals [21]. This finding was confirmed, particularly during the acute phases of mood episodes [22]. However, GDNF levels can vary under different emotional contexts [23–25]. Given these conflicting results, further research is urgently needed to clarify the role of GDNF in BD. Mice lacking the GDNF gene show impaired learning ability in the water maze test, highlighting the importance of GDNF in cognitive function [26]. Higher levels of serum GDNF in patients with schizophrenia have been correlated with better cognitive performance, suggesting a neuroprotective role for GDNF [27]. Both human and animal models have demonstrated that exercise enhances neuroplasticity and improves cognitive function by promoting GDNF production [28]. To date, research on the impact of GDNF on cognitive function in BD patients is limited.

Previous studies indicated a close association between oxidative stress and GDNF with cognitive function. However, research in BD is relatively limited. Considering the distinct pathological mechanisms of bipolar mania, this study specifically focused on bipolar mania. Two oxidative markers were selected: superoxide dismutase (SOD) as an antioxidant enzyme and malondialdehyde (MDA) as a lipid peroxidation product. Serum levels of SOD, MDA, and GDNF were compared in patients with bipolar mania before and after treatment. Furthermore, the relationship of these levels with cognitive function was assessed to provide a basis for BD diagnosis and prognosis assessment. The study hypothesis is that individuals with BD have higher serum levels of SOD and MDA, and lower levels of GDNF, and that serum levels of SOD, MDA, and GDNF correlate with cognitive dysfunction in these patients.

Methods

Participants

A total of 75 patients with BD who were admitted to Wu Tai Shan Hospital in Yangzhou City, Jiangsu Province, China, from February 2018 to February 2020 were selected for this study. Inclusion criteria were (1) meeting the clinical diagnostic criteria for BD according to ICD-10; (2) age of 18 to 65 years at enrollment; and (3) Young Mania Rating Scale (YMRS) score > 12. Exclusion criteria were (1) other mental disorders, confirmed through the Structured Clinical Interview of the Diagnostic and Statistical Manual-IV (SCID-I); (2) severe malignant tumors; (3) severe cognitive impairment preventing communication; (4) breastfeeding or pregnant women; (5) receipt of psychotropic medications within the past half month; (6) substance users, including smokers, alcoholics, and individuals with substance dependence; (7) use of modified

electroconvulsive therapy or transcranial magnetic stimulation within the past 6 months; (8) history of cardiovascular and cerebrovascular, organic brain, endocrine, and major liver, kidney, or lung diseases; (9) patients experiencing depressive episodes or mixed features, as the study focused on individuals in manic episodes to ensure a homogeneous study population; (10) failure to complete the minimum 4-week follow-up assessments and (11) failure to signed an informed consent to voluntarily participate in the study.

The healthy control group comprised health check-up volunteers at Wu Tai Shan Hospital in Yangzhou, Jiangsu Province. A total of 70 individuals were included. Their inclusion criteria were: (1) screening with the Chinese version of the Mini-International Neuropsychiatric Interview and not meeting the diagnostic criteria for any mental disorder; and (2) age of 18 to 65 years. The exclusion criteria were (1) cardiovascular and cerebrovascular, organic brain, endocrine, and major liver, kidney, or lung diseases; (2) smoking, alcohol, and/or substance dependence; (3) breastfeeding or pregnant women and (4) family history of mental disorders within two generations and three degrees of kinship.

Patients in the experimental group received atypical antipsychotic drugs, including quetiapine and olanzapine, combined with mood stabilizers that included lithium salts and valproic acid for 4 weeks. During the treatment period, patients did not receive antidepressant treatment; however, patients with agitation or anxiety might receive benzodiazepines.

All participants were provided with full information about the study before enrollment. The study obtained consent from participants and their legal guardians, with informed consent forms signed. The study was granted approval by the Medical Ethics Committee of Wu Tai Shan Hospital in Yangzhou City, Jiangsu Province.

Clinical and cognitive assessments

Two senior psychiatrists administered the YMRS to assess the severity of manic symptoms, with evaluations before treatment and at the 4-week follow-up. The inter-rater reliability correlation coefficients exceeded 0.8. Cognitive function was assessed by the Digit Cancellation Test (DCT), Stroop Color and Word Test (SCWT), and Trail Making Test (TMT). In the DCT, participants mark every digit in each row matching the first digit of that row as quickly as possible. This test assesses attention and information processing capabilities. The SCWT consists of three parts: the Stroop word-reading, Stroop color-naming, and Stroop color-word Test. Raw scores from the 45-s completion of the three tests assess the participant's information processing level, perceptual switching ability, and the ability to inhibit habitual behaviors. The TMT consists of TMT-A and TMT-B. In TMT-A, participants connect the numbers 1 to 25 in ascending order without skipping any numbers, continuing until number 25. For TMT-B, participants alternate between numbers and letters (1 to A, A to 2, 2 to B, B to 3, etc.), continuing until 13. Cognitive function was assessed at baseline and after 4 weeks of treatment in the experimental group, the control group did not undergo repeated cognitive assessments. In this study, cognitive function measurements are compared based on errors in the tests. All cognitive assessments were administered by two trained psychiatrists with inter-rater reliability > 0.8.

Fasting blood sampling and biochemical assays

Examinations for the experimental group of patients were performed before treatment and after 4 weeks, coinciding with assessments for the control group. Fasting venous blood (5 mL) was collected from both groups between 6:00 and 7:30 AM. Every sample was processed within 1 h of collection by centrifugation at 3500 r/min for 5 min to separate serum from blood cells. The serum was aliquoted into 1.5 mL tubes and stored at -80 °C for future analysis.

For detection of the oxidative stress indicators, SOD and MDA were measured with commercial assay kits (both from Nanjing Jiancheng Biological Engineering Co., Ltd., China) by the water-soluble tetrazolium salt method and thiobarbituric acid method, with intra-batch coefficient of variation (CV) at 5.05% and inter-batch CV at 3.32%. The detection limit for SOD and MDA was 0.5U/mL.

GDNF detection was by the GDNF ELISA Kit from Shanghai Youning Microbiology Technology Co., Ltd. (China), strictly following the ELISA method. The intra-assay CV was < 4%, the inter-assay CV was < 5%, the detection range was 31.2–2000.0 ng/L, and the sensitivity was < 2.0 ng/L.

Statistical analyses

All data tested for normality using the Shapiro-Wilk test. If data were normally distributed, continuous variables were expressed as mean ± standard deviation, and comparisons between the experimental and control groups performed using an independent samples t-test. Within-group comparisons of scores and indicators before and after treatment were performed using a paired samples t-test. If data were not normally distributed, non-parametric Mann-Whitney U and Wilcoxon tests were used. Qualitative data comparisons were made using the chi-square ($\chi 2$) test. Spearman's rank correlation assessed the correlation between oxidative stress indicators and GDNF with symptoms and various cognitive functions, respectively. All statistical analyses were performed using SPSS (IBM Corporation, USA). The sample size was calculated using G*Power 3.1 software, with effect size,

significance level (typically 0.05), and power (usually 0.80 or 0.90) to determine the required minimum sample size. $p < 0.05$ (two-tailed) indicated statistical significance.

Results

Comparison of general information between experimental and control groups

In this study, 5 of 75 enrolled patients (6.67% dropout rate) failed to complete the 4-week hospitalization protocol. Baseline blood samples from these 5 patients were not tested due to their early discharge, and the associated data were excluded from final statistical analysis to ensure methodological rigor. Among the 70 hospitalized patients who completed the 4-week follow-up, the mean duration of hospitalization was 35.3 ± 4.2 days. No statistically significant differences in gender ratio, age, average years of education, or other general information between the two groups ($p > 0.05$; Table 1). Further analysis revealed no significant gender differences in cognitive function, oxidative stress markers (SOD, MDA), or GDNF levels in the experimental group (all $p > 0.05$).

Comparison of peripheral serum levels of SOD, MDA, and GDNF between experimental and control groups

YMRS scores in the experimental group decreased significantly after 4 weeks of treatment compared to before treatment ($t = 37.674$, $p < 0.01$). Before treatment, the experimental group showed significantly longer completion times, more incorrect marks, and higher TMT-A and TMT-B scores compared to the control group, while the SCWT word-reading, color-naming, and color-word interference were significantly lower ($p < 0.05$ or $p < 0.01$). After 4 weeks of treatment, the experimental group's completion time and errors in the DCT, and TMT-A and TMT-B scores decreased significantly. Additionally, the experimental group showed a significant increase in the SCWT (word-reading, color-naming, and color-word interference) ($p < 0.05$ or $p < 0.01$). After 4 weeks of treatment, the experimental group's DCT completion times and TMT-A and TMT-B scores were significantly higher than the control group. The SCWT (word-reading, color-naming, and color-word interference) scores were significantly lower than the control group ($p < 0.05$ or $p < 0.01$). The experimental group's DCT incorrect marks were higher than the control group, but not statistically significant ($t = 0.26$, $p > 0.05$).

Before treatment, serum SOD and MDA levels in the experimental group were significantly higher than in the control group (SOD: $t = 90.603$, $p < 0.05$; MDA: $t = 36.277$, $p < 0.05$), and GDNF level was significantly lower ($t = 88.799$, $p < 0.05$). After 4 weeks of treatment, serum SOD and MDA levels in the experimental group decreased significantly compared to before treatment (SOD: $t = 74.773$, $p < 0.05$; MDA: $t = 36.952$, $p < 0.05$), and GDNF level significantly increased ($t = 82.314$, $p < 0.05$). After treatment, no significant difference in SOD and MDA levels was found between the experimental and control groups, but GDNF level remained significantly lower in the experimental group ($t = 7.883$, $p < 0.05$), as shown in Table 2.

Correlation analysis between serum SOD, MDA, GDNF levels and YMRS scores, and cognitive function in the experimental group

Correlation analysis showed positive correlation between pre-treatment SOD levels and YMRS scores ($r = 0.436$, $p < 0.01$). Pre-treatment MDA levels also correlated positively with YMRS scores ($r = 0.648$, $p < 0.01$). Pre-treatment GDNF levels correlated negatively with YMRS scores (r=-0.520, $p < 0.01$). Pre-treatment SOD levels correlated positively with DCT completion time ($r = 0.593$, $p < 0.01$), incorrect marks ($r = 0.865$, $p < 0.01$), TMT-A completion time ($r = 0.875$, $p < 0.01$), and TMT-B completion time ($r = 0.893$, $p < 0.01$), and correlated negatively with SCWT word-reading (r=-0.846, $p < 0.01$), color-naming (r=-0.807, $p < 0.01$), and color-word interference (r=-0.817, $p < 0.01$). MDA levels correlated positively with DCT completion time ($r = 0.640$, $p < 0.01$), incorrect marks ($r = 0.923$, $p < 0.01$), TMT-A completion time ($r = 0.924$, $p < 0.01$), and TMT-B completion time ($r = 0.928$, $p < 0.01$), and correlated negatively with SCWT word-reading (r=-0.873, $p < 0.01$), color-naming (r=-0.854, $p < 0.01$), and color-word interference (r=-0.845, $p < 0.01$). GDNF levels correlated negatively with DCT completion time (r=-0.615, $p < 0.01$), incorrect marks (r=-0.845, $p < 0.01$), TMT-A completion time (r=-0.926, $p < 0.01$), and TMT-B completion time (r=-0.919, $p < 0.01$), and correlated positively with SCWT word-reading ($r = 0.875$, $p < 0.01$), color-naming ($r = 0.848$, $p < 0.01$), and color-word interference ($r = 0.853$, $p < 0.01$). Details are provided in Table 3. No significant correlations were observed between changes in serum SOD, MDA, and GDNF levels and changes in cognitive

Table 1 Demographic of patients with BD and healthy controls

	Patients ($n = 70$)	Controls ($n = 70$)	χ^2/t	p
Gender (male/female)	31/39	39/31	1.828	0.176
Age (years)	37.77 ± 6.87	38.80 ± 7.90	0.823	0.411
Educations (years)	12.41 ± 2.19	12.04 ± 2.21	0.995	0.321
Duration of illness (months)	76.24 ± 12.68	-	-	-

Table 2 Variations in clinical symptoms, cognitive function, oxidative stress indicators, and GDNF levels

	Patients ($n=70$)		Controls ($n=70$)	t_a	t_b	t_c
	Before treatment	After treatment				
YMRS scores	34.89 ± 6.04	6.64 ± 2.63	-	37.674**	-	-
DCT						
completion times	221.60 ± 50.72	184.53 ± 20.67	172.33 ± 14.75	43.10**	4.12**	5.66*
incorrect marks	0.97 ± 2.01	0.42 ± 0.84	0.39 ± 1.07	2.08*	2.15*	0.26
SCWT						
word-reading	84.16 ± 5.96	87.31 ± 2.37	103.08 ± 4.36	4.11**	-21.44**	26.59*
color-naming	56.26 ± 5.03	62.64 ± 4.63	71.25 ± 4.15	7.81**	-19.27**	11.59*
color-word	32.17 ± 3.71	39.92 ± 3.96	44.80 ± 3.95	11.95**	-19.51**	7.30*
TMT						
TMT-A	80.16 ± 4.94	64.79 ± 6.90	47.56 ± 5.15	15.15**	38.23**	16.74*
TMT-B	187.10 ± 12.03	143.43 ± 17.31	119.43 ± 5.30	17.33**	43.07**	11.09*
SOD(U/L)	943.83 ± 28.13	512.97 ± 30.45	506.21 ± 28.43	74.773*	90.603*	1.359
MDA(nmol/ml)	6.22 ± 0.35	4.28 ± 0.28	4.19 ± 0.31	36.952*	36.277*	1.688
GDNF(ng/ml)	108.39 ± 26.13	490.46 ± 26.42	527.88 ± 29.65	82.314*	88.799*	7.883*

*$p<0.05$, **$p<0.01$; t_a: Before treatment VS After treatment; t_b: Before treatment VS Controls; t_c: After treatment VS Controls; YMRS: Young Mania Rating Scale; DCT: Digit Cancellation Test; SCWT: Stroop Color and Word Test; TMT: Trail Making Test; SOD: superoxide dismutase; MDA: malondialdehyde; GDNF: glial cell line-derived neurotrophic factor

Table 3 Correlation among SOD, MDA, and GDNF with clinical symptoms and cognitive function in patients with bipolar disorder

	SOD		MDA		GDNF	
	r	*p*	*r*	*p*	*r*	*p*
YMRS	0.436	< 0.01	0.648	< 0.01	-0.520	< 0.01
DCT						
completion times	0.593	< 0.01	0.640	< 0.01	-0.615	< 0.01
incorrect marks	0.865	< 0.01	0.923	< 0.01	-0.845	< 0.01
SCWT						
word-reading	-0.846	< 0.01	-0.873	< 0.01	0.875	< 0.01
color-naming	-0.807	< 0.01	-0.854	< 0.01	0.848	< 0.01
color-word	-0.817	< 0.01	-0.845	< 0.01	0.853	< 0.01
TMT						
TMT-A	0.875	< 0.01	0.924	< 0.01	-0.926	< 0.01
TMT-B	0.893	< 0.01	0.928	< 0.01	-0.919	< 0.01

YMRS: Young Mania Rating Scale; DCT: Digit Cancellation Test; SCWT: Stroop Color and Word Test; TMT: Trail Making Test; SOD: superoxide dismutase; MDA: malondialdehyde; GDNF: glial cell line-derived neurotrophic factor

function after treatment, even after controlling for the severity of mood symptoms ($p>0.05$).

Discussion

There are three main findings of this study. First, patients with BD displayed significant cognitive deficits. Second, patients with BD displayed higher serum SOD and MDA levels and lower GDNF levels compared to the normal control group. After treatment, the experimental group's serum SOD and MDA levels decreased significantly while GDNF levels increased, but GDNF levels were still lower than those of the control group. Third, pre-treatment YMRS scores and cognitive function assessments positively correlated with serum SOD and MDA levels, and negatively with GDNF levels. These findings demonstrate associations between serum SOD, MDA, and GDNF concentrations in patients with BD and their symptoms and cognitive dysfunction.

Patients with BD mania exhibited increased oxidative stress parameters and decreased GDNF levels compared to the healthy control group, further supporting the potential role of oxidative stress imbalance and GDNF in BD pathophysiology. Previous clinical studies on BD showed considerable variation in oxidative stress parameters and GDNF levels [29–32], possibly due to different disease states, sample types, and drug treatment. Indeed, research findings support our observations regarding changes in oxidative stress parameters and GDNF levels in individuals with BD. Specifically, free radical secretion in the brains of BD patients with mania has been associated with catecholamines and dopamine. Furthermore, dopamine hyperfunction in BD patients results in increased free radical secretion, triggering changes in oxidative stress parameters [33]. Individuals with BD show abnormal oxidative phosphorylation and lipid metabolism across different affective states, leading to

DNA and RNA damage. Concurrently, there is a significant increase in oxidative stress markers and a marked decrease in antioxidant enzyme activity [34]. Patients with mood disorders have reduced serum GDNF levels, possibly linked to astrocyte loss and blood-brain barrier dysfunction. The collective findings support the dysregulation of oxidative stress and GDNF changes in BD patients and further support the neurodevelopmental hypothesis of BD.

In this study, we observed a reduction in oxidative stress indicators and an increase in GDNF levels as symptoms improved in BD patients during manic episodes. The potential role of mood stabilizers and antipsychotics in this process warrants attention. Lithium, known for its neuroprotective properties, enhances neurotrophic factors such as GDNF, which promotes neuronal survival and function by activating the Ret pathway in the hippocampus [35]. Animal studies have shown that lithium and valproic acid protect against amphetamine-induced oxidative stress [36], while integrative analyses indicate that lithium influences brain structural changes linked to GDNF receptor pathways [37]. Additionally, lithium enhances neural stem cell proliferation, supporting neurogenesis and synaptic plasticity [38]. Valproate, another mood stabilizer, mitigates oxidative stress by inhibiting glycogen synthase kinase 3 (GSK3) and histone deacetylases (HDAC), which are involved in inflammatory and oxidative pathways [39]. Clinical data further suggest that antipsychotics and mood stabilizers elevate serum GDNF levels [22], consistent with in vitro findings that antipsychotics stimulate GDNF secretion [40]. However, no significant associations were found between changes in oxidative stress parameters or GDNF levels and the types or dosages of medications used, leaving it unclear whether these changes are medication-related or reflect BD pathophysiology. Future studies should focus on larger, medication-naïve first-episode BD cohorts to clarify these mechanisms.

The present study revealed no significant association between alterations in serum SOD, MDA or GDNF levels during treatment and improvements in cognitive function. However, evidence suggests that baseline levels of these biomarkers may hold greater relevance to cognitive performance compared to their dynamic fluctuations. A study demonstrated that elevated baseline GDNF levels in healthy individuals were associated with enhanced working memory, whereas changes in GDNF levels failed to predict cognitive improvements in patients with schizophrenia [41]. Similarly, another research indicated that, despite significant abnormalities in oxidative stress markers among individuals with bipolar disorder, variations in these markers were not correlated with cognitive outcomes [42]. Furthermore, a review highlighted that therapeutic efficacy may be more closely tied to baseline oxidative stress and inflammatory states rather than their temporal changes during intervention [43]. These observations suggest that baseline biomarker levels may more accurately reflect the underlying biological mechanisms of cognitive dysfunction, whereas dynamic changes could be confounded by factors such as pharmacological effects and interindividual heterogeneity. Future investigations should prioritize extended follow-up periods, larger and more diverse cohorts, and sophisticated analytical approaches to elucidate the complex interplay between baseline levels, temporal biomarker changes, and cognitive function.

Interestingly, we observed that after effective treatment, BD patients in a manic state had oxidative stress indicators that were not significantly different from those of the normal control group. Although the concentration of GDNF increased, it was still below that of the normal control group, and this difference was statistically significant. GDNF, primarily secreted by glial cells, is an important neurotrophic factor related to neuronal plasticity, affecting neuronal development, survival, differentiation, and increasing the density and length of neural synapses [40]. Post-mortem brain analyses have revealed abnormalities in the gray matter regions of the prefrontal cortex and cingulate gyrus in BD patients, primarily characterized by a reduction in the number, density, and size of glial cells [44]. This finding suggests that the reduction of GDNF in BD patients may be persistent. In this study, after treatment with mood stabilizers and antipsychotic drugs, BD patients in a manic state exhibited increased serum GDNF levels, indicating that the therapeutic interventions have likely facilitated the synthesis and release of neurotrophic factors, thereby contributing to the improvement of patients' symptoms. However, the GDNF levels remained lower than those of the normal control group, suggesting that even though the treatment is effective, the neuroprotective mechanisms in patients have not fully returned to healthy levels. This further suggests that the complex pathophysiological mechanisms of BD may not be fully addressed by a single treatment approach, and thus all impaired neural mechanisms may not be comprehensively repaired. Furthermore, the duration of treatment, choice and dosage of medication, and individual differences can all affect the therapeutic outcome. Future studies should extend the follow-up period and combine comprehensive treatment methods to verify the changes in GDNF levels.

Extensive prior research has concentrated on the role of oxidative stress and GDNF in the pathophysiology of cognitive impairments [27, 45], with the majority of the research examining Alzheimer's disease, Parkinson's disease, schizophrenia, and other such conditions. Fewer studies have addressed the relationship between these factors in patients with BD. In the present investigation,

we evaluated the correlation between oxidative stress indicators and GDNF with cognitive functions in patients with BD. The findings positively correlate oxidative stress indicators with the completion time of the DCT, number of incorrect markings, and completion time of TMT-A and TMT-B. The findings also negatively correlate the indicators with the total number of word-reading, color-naming, and color-word interference in the SCWT. Conversely, GDNF concentrations were inversely correlated with the completion time of the DCT, number of incorrect markings, and completion time of TMT-A and TMT-B, and positively correlated with the total number of word-reading, color-naming, and color-word interference in the SCWT. These results imply that oxidative stress indicators and GDNF levels may be associated with attention and executive functions in patients with BD mania, consistent with previous findings [46]. A recent Mendelian randomization study [47] probed the impact of oxidative stress on cognitive function. The results indicated that a deficiency in antioxidant enzymes might be a significant mechanism for impaired cognitive function. Other research has further suggested that free radicals may accumulate in the prefrontal cortex, leading to neuronal damage and ultimately resulting in cognitive symptoms [48]. Variations in neurotrophic factors, such as GDNF, may also lead to brain atrophy and progressive cognitive impairment in BD patients [49, 50]. The underlying pathophysiological mechanisms linking oxidative stress and GDNF to cognitive function remain elusive and require further exploration.

In this investigation, we assessed attention functions using the DCT, TMT-A, and SCWT, and executive functions using the TMT-B, providing a comprehensive evaluation of cognitive functions in BD patients during mania. The results revealed that BD patients in a manic state performed significantly worse than healthy controls on the DCT (completion time and error count), SCWT, and TMT, indicating widespread cognitive dysfunction, consistent with previous reports [51]. After 4 weeks of pharmacological intervention, the experimental group showed improvements in YMRS scores and all cognitive assessments compared to baseline. However, only the DCT error count returned to a level comparable to healthy controls, while DCT completion time, SCWT scores, and TMT performance remained significantly impaired.

Learning effects constitute a critical consideration in longitudinal cognitive function research, particularly when implementing repeated testing within short intervals. Recent investigations in healthy populations have demonstrated minimal learning effects in cognitive assessments(such as SCWT) administered over brief retest periods. Within clinical populations exhibiting cognitive impairments, the magnitude of learning effects tends to be substantially attenuated [52]. Our findings revealed that the improvement amplitude in the patient cohort significantly exceeded the anticipated threshold for learning effects, indicating that their influence on outcome measures remains constrained and unlikely to substantially confound therapeutic efficacy evaluations. To mitigate potential confounding from learning effects, the implementation of parallel test versions or regression-based adjustment of baseline scores [52] is recommended. While learning effects are frequently regarded as measurement artifacts, they may under specific circumstances yield valuable insights regarding cognitive trajectory alterations [53]. Consequently, future research should incorporate systematic consideration of learning effect mechanisms during study design phases, coupled with advanced statistical approaches to enhance result validity.

Prior longitudinal studies have reported mixed findings on long-term cognitive outcomes in BD. For instance, a 6-year study found persistent cognitive deficits in BD patients even after symptom remission [54], while a meta-analysis reported no significant differences in long-term cognitive outcomes between BD patients and healthy controls [55]. These discrepancies may stem from variations in follow-up duration, illness severity, and cognitive domain heterogeneity. Additionally, the impact of medication cannot be overlooked. For example, mood stabilizers have been shown to modulate postsynaptic protein signaling, potentially improving cognitive functions [56], whereas antipsychotics have been associated with gray matter loss and cognitive impairments [57, 58]. Therefore, future studies should conduct long-term follow-ups to explore the effects of different psychopharmacological treatments on cognitive outcomes.

This study is a small-scale clinical trial, where patients' cognitive functions are influenced by various factors, such as the number of episodes and past treatment history. Several limitations should be addressed in future research. First, larger sample sizes and long-term patient follow-ups are necessary to enhance the robustness of findings. Second, the present study did not systematically document concomitant medication use or quantify potential pharmacodynamic interactions between therapeutic agents and laboratory biomarkers. Third, regarding methodological considerations, the potential influence of learning effects on cognitive function assessments warrants attention. Fourth, this study exclusively included patients in the manic phase of BD, which limits the generalizability of findings to the broader spectrum of this complex disease. Future studies should expand sample sizes, investigate specific medications, include depressive and mixed states, incorporate post-treatment measurements in control groups, and implement repeated cognitive assessments in both experimental and

control groups. These steps will enhance the understanding of BD pathophysiology, clarify the specificity of findings, and improve the validity and generalizability of the results.

Conclusions

In summary, this study demonstrates that during the manic phase of BD, patients exhibit increased serum oxidative stress indicators (SOD, MDA) and decreased GDNF concentrations, which improve as symptoms remit. The findings suggest that oxidative stress and GDNF may be involved in the pathophysiological processes of BD manic episodes. This study further establishes that oxidative stress indicators (SOD, MDA) and GDNF levels during the manic phase in BD patients are associated with symptoms and cognitive functions. Determining the specific pathophysiological mechanisms necessitates additional investigation.

Abbreviations

BD	Bipolar disorder
GDNF	Glial cell line-derived neurotrophic factor
SOD	Superoxide dismutase
MDA	Malondialdehyde
YMRS	Young mania rating scale
DCT	Digit cancellation test
SCWT	Stroop color and word test
TMT	Trail making test
GSK3	Glycogen synthase kinase 3
HDAC	Histone deacetylases

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Author contributions

Conception and design: YQ, ZXB. Development of methodology: TQ, YHD. Analysis and interpretation of data: JF, QJC. Writing of the manuscript: YQ, LCW. Study supervision: TQ, ZXB. All authors reviewed the manuscript.

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Data availability

Data AvailabilityThe data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

We declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki and that all procedures were carried out with the adequate understanding and written consent of the subjects. We also certify that formal approval to conduct the experiments described has been obtained from the human subject review board of our institution. All experimental protocols were approved by the Medical Ethics Committee of Wu Tai Shan Hospital in Yangzhou City, Jiangsu Province. Informed consent was obtained from all subjects or their guardian. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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