

World Journal of *Psychiatry*

World J Psychiatry 2023 December 19; 13(12): 973-1144



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ABOUT COVER

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The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJP* as 3.1; IF without journal self cites: 2.9; 5-year IF: 4.2; Journal Citation Indicator: 0.52; Ranking: 91 among 155 journals in psychiatry; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ting-Shao Zhu

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

December 19, 2023

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INSTRUCTIONS TO AUTHORS

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Case Control Study

Brain-derived neurotrophic factor, sex hormones and cognitive decline in male patients with schizophrenia receiving continuous antipsychotic therapy

Jin Li, Wen-Huan Xiao, Fei Ye, Xiao-Wei Tang, Qiu-Fang Jia, Xiao-Bin Zhang

Specialty type: Psychiatry**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Glumac S, Croatia;
Hosak L, Czech Republic**Received:** August 26, 2023**Peer-review started:** August 26, 2023**First decision:** September 5, 2023**Revised:** October 4, 2023**Accepted:** November 9, 2023**Article in press:** November 9, 2023**Published online:** December 19, 2023**Jin Li, Qiu-Fang Jia, Xiao-Bin Zhang**, Department of Psychiatry, The Affiliated Guangji Hospital of Soochow University, Suzhou 215137, Jiangsu Province, China**Wen-Huan Xiao, Fei Ye, Xiao-Wei Tang**, Department of Psychiatry, Affiliated Wutaishan Hospital of Medical College of Yangzhou University, Yangzhou 225000, Jiangsu Province, China**Corresponding author:** Xiao-Bin Zhang, MD, PhD, Chief Physician, Department of Psychiatry, The Affiliated Guangji Hospital of Soochow University, No. 11 Guangqian Road, Suzhou 215137, Jiangsu Province, China. zhangxiaobim@163.com**Abstract****BACKGROUND**

There are systematic differences in clinical features between women and men with schizophrenia (SCZ). The regulation of sex hormones may play a potential role in abnormal neurodevelopment in SCZ. Brain-derived neurotrophic factor (BDNF) and sex hormones have complex interacting actions that contribute to the etiology of SCZ.

AIM

To investigate the influence of BDNF and sex hormones on cognition and clinical symptomatology in chronic antipsychotic-treated male SCZ patients.

METHODS

The serum levels of follicle-stimulating hormone, luteinizing hormone (LH), estradiol (E2), progesterone, testosterone (T), prolactin (PRL) and BDNF were compared between chronic antipsychotic-treated male (CATM) patients with SCZ ($n = 120$) and healthy controls ($n = 120$). The Positive and Negative Syndrome Scale was used to quantify SCZ symptoms, while neuropsychological tests were used to assess cognition. Neuropsychological tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess executive functions (BDT), attention (DCT, TMT-A), memory (SS, PASAT), and verbal proficiency (SVF).

RESULTS

Although E2 levels were significantly lower in the patient group compared to the

healthy controls, T, PRL, and LH levels were all significantly higher. Additionally, the analysis revealed that across the entire sample, there were positive correlations between E2 Levels and BDNF levels as well as BDNF levels and the digital cancellation time. In CATM patients with SCZ, a significant correlation between the negative symptoms score and PRL levels was observed.

CONCLUSION

Sex hormones and BDNF levels may also be linked to cognitive function in patients with chronic SCZ.

Key Words: Brain-derived neurotrophic factor; Clinical symptoms; Cognitive function; Schizophrenia; Sex hormones

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Core Tip: Brain-derived neurotrophic factor (BDNF) and sex hormones are known to be involved to the psychopathology of schizophrenia (SCZ). However, the influence of BDNF and sex hormones on cognition and symptoms in chronic antipsychotic-treated male (CATM) SCZ patients have yet to be investigated. Testosterone, prolactin (PRL) and luteinizing hormone were significantly higher in the patient group than in the healthy controls while estradiol (E2) levels were significantly lower. Analysis also identified positive correlations between E2 levels and BDNF levels, and BDNF levels and the digital cancellation time, in the whole sample. we found significant correlations between PRL levels and negative symptoms score in CATM patients with SCZ.

Citation: Li J, Xiao WH, Ye F, Tang XW, Jia QF, Zhang XB. Brain-derived neurotrophic factor, sex hormones and cognitive decline in male patients with schizophrenia receiving continuous antipsychotic therapy. *World J Psychiatry* 2023; 13(12): 995-1004

URL: <https://www.wjgnet.com/2220-3206/full/v13/i12/995.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v13.i12.995>

INTRODUCTION

It has been proved that there are differences in schizophrenia (SCZ) clinical side effects between females and males[1]. In SCZ, gender differences may play a significant role in the factors that mediate schizophrenic expression[2]. The current study hypothesizes that sex hormones alter the manifestation of symptoms, either directly or indirectly, and account for many of the observed gender differences[3]. The organizational and activation effects of sex hormones on SCZ have received a lot of critical attention[4]. During a crucial period in the fetus's life, organizational effects have a permanent impact on the developing brain. Evidence recommends that adjustments to sex hormones might be related to the neurodevelopmental etiology of SCZ[5]. The activating impacts are the immediate impact of circulating chemicals. When hormone levels rise, the impact will appear, and when hormone levels fall, the impact will become weaker. Both luteinizing hormone (LH) and testosterone (T) play a role in puberty by promoting the expansion of white matter in the frontal and temporal connections[6]. It is important to note that the regions of the brain that are most affected by adolescent gonadal hormones are also the regions of the brain that are most relevant to the pathophysiology of SCZ[7]. Recent research indicates that T and masculinity predict hippocampus or cerebellum volumes that are typically larger in men[8], whereas estradiol (E2) levels were associated with bilateral insula resting-state functional connectivity in girls[9]. Adolescent hormonal changes may activate genes that regulate normal neurodevelopment, leading to an increase in connectivity and a decrease in gray matter[10].

T has genomic and non-genomic impacts on the cerebrum through androgen receptors, and is involved in hippocampal CA1 neuron morphology[11]. It has been established that estrogen plays a role in cognitive processes such as memory, learning, and mood regulation[12]. Studies in rats have shown that progesterone (P), a neurosteroid, has numerous impacts on cognition, for example, upgrading learning and memory, advancing nerve development and myelination[13].

Sex hormones and brain-derived neurotrophic factor (BDNF) have been linked to cognitive function in an increasing number of studies. For example, a new investigation on ovariectomized rodents showed that E2 essentially expanded spatial learning and memory by increasing 17 β -E2 and BDNF levels in the hippocampus[14]. The BDNF pathway plays a role in the protective effects of estrogen. Additionally, P interferes with estrogen's protective effect under certain conditions[15]. In grown-up male rodents, treatment with T and BDNF intuitively affected androgen receptor articulation [16] as well as dendritic length[17]. According to our previous research, patients with chronic SCZ who suffer from attention and spatial memory impairments have elevated serum T levels[18]. However, there are currently insufficient systematic studies on the interplay between BDNF and follicle-stimulating hormone (FSH), LH, E2, P, T, and prolactin (PRL) in chronic antipsychotic-treated male (CATM) patients.

We hypothesize that neurotrophic factors mediate cognitive decline in male patients with chronic SCZ *via* hormones. This article focuses on the following issues: (1) Whether patients with chronic SCZ have altered levels of BDNF and sex hormones (including FSH, LH, E2, P, T, and PRL); (2) Whether there is a connection between BDNF and sex hormone levels; and (3) Whether the communication between BDNF and sex hormones is involved in the clinical symptoms and

cognition of SCZ patients.

MATERIALS AND METHODS

Participants

This was a case-control study, and the sample size calculation method was as follows: $\alpha = 0.05$, $\beta = 0.20$, $Meant = 0.25$, and $Meanc = 0.21$; the sample size calculation was input into the Biostatistics website (www.cnstat.org/samplesize/12/), and the difference between the two sets of means was compared, $n = 200$ (cases). If the maximum number of lost cases was considered to be 20%, then the total number of cases in both groups should be: $200 + 200 \cdot 0.2 \approx 240$ (cases), $nt = 120$ (cases), $nc = 120$ (cases) and power = 0.8036.

A total of 120 CATM patients with SCZ from the Affiliated WuTaiShan Hospital of the Medical College of Yangzhou University (Yangzhou, China) were recruited between February 2018 and July 2019. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, these patients fulfilled the criteria for SCZ. In addition, 120 healthy males were included as control subjects. The controls were matched by age and education with the SCZ group. All the controls were in good physical health and had no mental illness. [Table 1](#) depicts the demographic characteristics of the patient group and the healthy control group. Participants in this study must have taken antipsychotic medication for at least a year. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Subjects were excluded if they had a history of substance abuse or dependence, neurological diseases, or serious psychiatric comorbidities.

The WuTaiShan Hospital Ethics Committee approved the study (approval No. 2018-011), and written informed consent was provided by each participant.

Hormone assay

Serum samples were centrifuged (3000 rpm for 10 min) and then stored at -80°C . Sex hormone levels (FSH, LH, E2, P, T, PRL) were estimated using an Entrance immunoassay analyzer and the manufacturer's reagents (Beckman Coulter Inc., Brea, CA, United States). After that, an enzyme-linked immunosorbent assay (Emax Immunoassay System kit) was used to measure the concentration of BDNF (Promega, Madison, WI, United States) according to the instructions of the manufacturer.

Neurocognitive assessments

A neuropsychological battery of cognitive tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess cognitive performance.

The followings were evaluated by the neurocognitive battery: Executive functions: Executive functions were evaluated using the BDT. Maintaining focus and attention: Attention was evaluated using the DCT and TMT-A. Memory: The SS and PASAT were used to measure memory. Verbal proficiency: Verbal fluency was assessed by the SVF test.

Statistical analysis

SPSS 17.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, United States). We first compared the qualities and mental execution between the controls and patients, and then compared the BDNF and sex hormone levels of patients and controls using the independent samples *t*-test. The next step was to investigate the connections between BDNF levels and cognitive function in the entire sample ($n = 240$) and between sex hormone levels and BDNF levels. Pearson's product moment correlation was used to investigate the connections between the patient group's PANSS scores and sex hormone levels. After taking into account any potential confounders, the relationship between sex hormone levels and PANSS scores, BDNF levels, and cognitive function was modeled using multiple linear regression. The Bonferroni correction was used to adjust for multiple comparisons. The significance level was set at $P < 0.05$.

RESULTS

Demographic data, sex hormones, BDNF, and cognitive performances in patients and healthy controls

The characteristics and clinical data of 120 CATM patients with SCZ and 120 controls are presented in [Table 1](#). There were significant differences in body mass index (BMI) between patients and controls ($P < 0.001$). The patient group had significantly higher levels of LH ($P < 0.05$), T ($P < 0.05$), and PRL ($P < 0.001$) than the controls (both $P < 0.001$), and significantly lower levels of BDNF and E2 than the controls (both $P < 0.001$). The patients performed worse in all mental subscales (all $P < 0.001$). These data are shown in [Table 2](#).

Interrelationships of sex hormones and BDNF in all subjects

In all subjects ($n = 240$), LH, E2, T, and PRL ($P < 0.05$) were all fundamentally connected to BDNF levels before adjustment of confounding factors (age, schooling, smoking, BMI). Only the relationships between BDNF levels and LH, E2, and PRL remained significant ($P < 0.05$) after confounding factors were removed. The relationship between E2 and BDNF remained statistically significant after Bonferroni correction ($P < 0.01$). These data are shown in [Table 3](#).

Table 1 Demographic characteristics, clinical data, brain-derived neurotrophic factor, and sex hormones in chronic antipsychotic-treated male patients with schizophrenia and healthy controls (mean ± SD)

Variable	CATM patients (n = 120)	Healthy controls (n = 120)	F or χ^2 (P value)
Age (yr)	51.0 ± 10.3	52.2 ± 6.4	27.4 (0.28)
Education (years)	9.2 ± 3.0	9.1 ± 2.8	0.8 (0.62)
Smokers (%)	60.8	65.9	0.6 (0.4)
BMI (kg/m ²)	25.7 ± 3.4	24.0 ± 2.2	33.5 (< 0.001)
BDNF (ng/mL)	2.5 ± 1.6	9.7 ± 3.2	35.5 (0.00)
FSH (ng/mL)	8.6 ± 6.7	9.0 ± 6.6	0.1 (0.67)
LH (ng/mL)	6.7 ± 3.3	4.9 ± 2.6	1.6 (0.00)
E2 (ng/mL)	40.5 ± 17.1	56.2 ± 24.3	4.5 (0.00)
P (ng/mL)	0.8 ± 0.3	0.8 ± 0.4	0.2 (0.84)
T (ng/mL)	4.8 ± 1.8	4.0 ± 1.2	2.4 (0.01)
PRL (ng/mL)	25.4 ± 22.4	10.6 ± 5.5	24.1 (0.00)
Age of onset (yr)	22.9 ± 5.8		
Duration of illness (yr)	28.0 ± 9.3		
PANSS score			
Positive symptoms	11.3 ± 4.9		
Negative symptoms	20.1 ± 10.0		
General psychopathology	31.2 ± 9.0		
Total score	62.6 ± 20.2		

BDNF: Brain-derived neurotrophic factor; CATM: Chronic antipsychotic-treated male; BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin; PANSS: Positive and Negative Syndrome Scale.

Table 2 Comparison of cognitive scores between chronic antipsychotic-treated male schizophrenia patients and healthy controls

Cognitive index	CATM patients	Controls	F (P value)	MD (95%CI)
DCT	304.1 ± 215.0	130.8 ± 43.3	50.8 (< 0.001)	173.2 (124.0 to 222.4)
SVF	16.0 ± 7.8	27.6 ± 7.9	0.0 (< 0.001)	-11.6 (-8.7 to -14.5)
SS	11.6 ± 4.2	16.4 ± 4.2	0.1 (< 0.001)	-4.7 (-3.4 to -6.1)
TMT-A	101.3 ± 57.9	50.0 ± 21.7	26.5 (< 0.001)	51.3 (35.6 to 67.0)
BDT	17.1 ± 9.0	31.8 ± 8.8	0.2 (< 0.001)	-14.7 (-11.6 to -17.8)
PASAT correct	19.8 ± 10.5	34.0 ± 10.2	0.0 (< 0.001)	-14.1 (-9.5 to -18.7)
PASAT try	23.9 ± 11.0	36.9 ± 10.7	0.4 (< 0.001)	13.0 (-8.2 to 17.8)

95%CI: 95% confidence interval; DCT: Digit Cancellation Test; SVF: Semantic Verbal Fluency; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task; BDT: Block Design Test.

Relationships between BDNF and cognitive functions in all subjects

In all subjects, the DCT, class familiarity, SS, TMT-A, block design, and PASAT were all fundamentally connected to BDNF levels prior to adjustment of confounding factors (all $P < 0.001$). Only the relationships between BDNF levels and the DCT, category fluency, TMT-A, and block design remained significant ($P < 0.05$) after confounding factors were taken into account. The relationship between DCT and BDNF levels remained significant after Bonferroni correction ($P < 0.0023$). These data are shown in Table 4.

Relationships between PRL levels and psychotic symptoms in CATM patients

In CATM patients with SCZ, significant association between PRL levels and the negative side effects score ($r = 0.196$, $P <$

Table 3 Correlations between sex hormones and brain-derived neurotrophic factor levels in all subjects¹

	BDNF			
	<i>r</i>	<i>P</i> value ²	<i>P</i> value ³	<i>P</i> value ⁴
FSH (ng/mL)	0.068	0.467	0.638	NS
LH (ng/mL)	-0.256	0.007	0.011	NS
E2 (ng/mL)	0.343	< 0.001	0.001	S.
P (ng/mL)	0.074	0.459	0.173	NS
T (ng/mL)	-0.215	0.032	0.055	NS
PRL (ng/mL)	-0.267	0.004	0.04	NS

¹Pearson product moment.

²Before adjusting for confounding factors.

³After adjusting for confounding factors (body mass index).

⁴Bonferroni correction was applied ($\alpha_{\text{new}} = 0.05/5 = 0.01$).

NS: Not significant; S.: Significant; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin.

Table 4 Correlations between brain-derived neurotrophic factor levels and cognitive function in all subjects¹

	BDNF			
	<i>r</i>	<i>P</i> value ²	<i>P</i> value ³	<i>P</i> value ⁴
DCT	-0.376	< 0.001	0.0019	NS
Category fluency	0.539	< 0.001	0.022	NS
SS	0.307	< 0.001	0.398	NS
TMT-A	-0.516	< 0.001	0.010	NS
Block design	0.557	< 0.001	0.015	NS
PASAT correct	0.442	< 0.001	0.404	NS
PASAT try	0.405	< 0.001	0.201	NS

¹Pearson product moment.

²Before adjusting for confounding factors.

³After adjusting for confounding factors (body mass index).

⁴Bonferroni correction was applied ($\alpha_{\text{new}} = 0.05/7 = 0.007$).

NS: Not significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

0.05) and the score for general psychopathology was found ($r = 0.181$, $P < 0.05$). The relationship between PRL levels and general psychopathology or negative factors remained significant ($P < 0.05$) after adjusting for confounding factors. As shown in Table 5, only the relationship between PRL levels and the negative factors remained significant after the Bonferroni correction ($P < 0.017$).

DISCUSSION

The CATM group's elevated levels of LH, PRL, and T, in addition to their decreased levels of E2, were examined in depth for the first time in this study in comparison to the controls. One of the major findings in this study was that E2 Levels and BDNF levels, as well as BDNF levels and the DCT, were correlated in all subjects. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant.

Previous studies have shown that in men, LH and T seem to have a role in advancing the development of white matter [6,10]. As gender differences play a significant role in SCZ, hormones may play a role in the pathophysiology of SCZ. In the initial period of SCZ in men, higher T levels in puberty and youth, show that T might be related to the initiation of psychosis in patients [19]. Recently, an ever-increasing number of studies have focused on dehydroepiandrosterone (DHEA)/T in addition to standard antipsychotic treatment in relation to the side effects of SCZ [20]. These studies demonstrated that patients with SCZ experiencing negative, depressive, and anxiety symptoms could benefit from DHEA augmentation as a treatment. However, we found that CATM patients with SCZ had T levels higher than those in the

Table 5 Relationships between prolactin levels and psychotic symptoms in patients¹

	Positive symptoms score				Negative symptoms score				General psychopathology score			
	<i>r</i>	<i>P</i> value ²	<i>P</i> value ³	<i>P</i> value ⁴	<i>r</i>	<i>P</i> value ²	<i>P</i> value ³	<i>P</i> value ⁴	<i>r</i>	<i>P</i> value ²	<i>P</i> value ³	<i>P</i> value ⁴
PRL	0.152	0.098	0.254	NS	0.196	0.032	0.011	S.	0.181	0.048	0.030	NS

¹Pearson product moment.

²Before adjusting for confounding factors.

³After adjusting for confounding factors (body mass index).

⁴Bonferroni correction was applied (a new $\alpha = 0.05/3 = 0.017$).

NS: Not significant; S.: Significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

controls, but that there was no correlation between this increase and psychopathology. It was demonstrated that decreasing levels of LH reduced short-term episodic memory loss in an SCZ model treated with phencyclidine[21]. We found that the LH levels in the CATM patients with SCZ were higher than those in controls, even though there was no relationship between this increment and mental capability.

It has been hypothesized for a considerable amount of time that the blocking effect of antipsychotic medications on dopamine D2 receptors is the cause of the elevated PRL levels associated with psychotic symptoms. PRL levels were found to be elevated in CATM patients with SCZ in the current study. However, unlike a previous study that investigated patients with chronic SCZ, we found no link between elevated PRL and impaired cognitive function[22]. Hyperprolactinemia was most significantly associated with executive function, working memory, and processing speed in a previous study of prolactinoma patients[23]. In addition, it was discovered that a decrease in the volume of gray matter in the frontal cortex and hippocampus was correlated with PRL concentration. In the future, the connection between PRL levels and cortical thickness and hippocampal base volume in patients with ongoing SCZ should be examined to determine the connection between hyperprolactinemia and diminished mental capability.

Research focusing on the connection between PRL levels and the side effects of SCZ has been primarily conducted in male patients; however, no consistent conclusion has been reached. Positive symptoms, delusions, and speech incoherence are all negatively correlated with PRL levels, according to some researchers[24]. On the other hand, one study found a correlation between positive symptoms in schizophrenic patients and elevated PRL levels[25]. Another review showed that PRL levels were significantly connected with negative side effects[26]. One study found no link between psychopathology and PRL levels[27]. In previous studies[25,28], we found that higher PRL levels and negative side effects were connected.

The “estrogen hypothesis” has been used for more than three decades to explain how estrogen protects the brain. E2 and selective estrogen receptor modulators are helpful adjunctive treatments for patients with SCZ[29]. Our study found that CATM patients with SCZ had lower levels of the protective hormone E2 than normal male controls. This finding is consistent with the preceding hypotheses. It was found that BDNF gene expression can be controlled by estrogen[30]. Indeed, even after two measurement revisions, this study found a huge direct connection between E2 and BDNF, which is consistent with previous investigations.

The higher incidence of SCZ in men and the earlier age of onset may be partially explained by T[31]. Our current findings were consistent with those of another study[32] in which SCZ cases had significantly higher T levels and significantly lower BDNF levels compared to controls. A previous study with a small sample size found a significant

correlation between low T levels and penile-related symptoms in men taking antipsychotics and a trend in hyperprolactinemia was associated with low T[33]. Antipsychotics frequently result in hyperprolactinemia, which can affect the measurement of other gonadal hormone levels[34]. It should be noted that antipsychotics such as clozapine and aripiprazole are less likely to cause hyperprolactinemia.

Even though these conclusions are not consistent, more and more researchers are focusing on the connection between SCZ with impaired cognitive function and abnormal serum BDNF levels[35,36]. However, a recent study found that first-episode and drug-naïve SCZ patients had significantly higher BDNF serum levels and better Repeatable Battery for the Assessment of Neuropsychological Status scores[37]. In a previous study, we found that the improvement in clinical symptoms was linked to higher BDNF levels in schizophrenic patients[38]. Similarly, we observed that the level of BDNF in SCZ patients was lower than that in controls and that there was a positive relationship between BDNF levels and mental capability. We also found critical and positive relationships between E2 and BDNF levels, and between BDNF levels and the DCT. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant. Rashidy-Pour *et al*[14] in 2019 demonstrated that E2 significantly increased spatial learning and memory by increasing 17-E2 and BDNF levels in the hippocampus of ovariectomized rats. The BDNF pathway is responsible for estrogen's neuroprotective effects[16]. However, we found no correlation between BDNF levels and clinical symptoms. This necessitates further investigation into the reasons for this finding.

The limitations of this study require consideration. The lack of confirmation regarding the consistency of the markers in the central nervous system and peripheral blood is the primary limitation of this study. As the biomarkers were only measured once in this case-control study, the study was constrained by the lack of longitudinal comparisons. Thirdly, the study did not determine how antipsychotic medication affected BDNF and gonadal hormone levels.

CONCLUSION

In conclusion, CATM patients with SCZ showed lower levels of BDNF and E2 and elevated levels of LH, T, and PRL compared to controls. In all cognitive subscales, we found that CATM patients with SCZ performed significantly worse. In CATM patients with SCZ, we also found a marked relationship between PRL levels and the negative side effects score. Sex hormones and BDNF levels may also be linked to cognitive function. With the exception of PRL and negative symptoms, this case-control study only found positive correlations across the entire sample. As a result, our findings ought to be regarded as preliminary.

ARTICLE HIGHLIGHTS

Research background

Due to gender differences in the clinical manifestations of schizophrenia (SCZ), this study assumes that sex hormones directly or indirectly alter the clinical manifestations of SCZ.

Research motivation

An increasing number of studies have shown that sex hormones act through brain derived neurotrophic factors (BDNF), which can also affect the expression of sex hormone receptors.

Research objectives

The purpose of this study is to explore the significant impact of the interaction between BDNF and sex hormones on the clinical manifestations and cognitive function of chronic antipsychotic-treated male (CATM) SCZ patients.

Research methods

We used a cross-sectional case-control study method to collect blood from both normal control and CATM SCZ patients for testing BDNF and sex hormone levels, as well as cognitive function in both groups.

Research results

We found a significant decrease in estradiol (E2) levels in the patient group, and a significant correlation between prolactin levels and negative symptom scores. In the entire sample, there is a positive correlation between E2 level, BDNF level, and the Digit Cancellation Test (reflecting attention function).

Research conclusions

Compared with the normal control group, there were changes in the levels of BDNF and sex hormones in the patient group. The levels of sex hormones in the patient group are related to negative symptoms.

Research perspectives

The interaction between BDNF and sex hormones may be involved in negative symptom expression and cognitive impairment in chronic male SCZ patients.

FOOTNOTES

Co-corresponding authors: Qiu-Fang Jia and Xiao-Bin Zhang.

Author contributions: Li J and Zhang XB designed the study and manuscript preparation; Li J and Xiao WH recruited subjects, collected clinical data, laboratory samples, and cognitive assessment and did preliminary data analysis; Ye F and Tang XW assisted in the symptoms of schizophrenia assessment and data analysis; Jia QF did literature search, final analysis of the data, and prepared the final manuscript; All authors contributed to manuscript preparation and approved its final version. Qiu-Fang Jia and Xiao-Bin Zhang contributed equally to this work as co-corresponding authors. The reasons for designating Qiu-Fang Jia and Xiao-Bin Zhang as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Qiu-Fang Jia and Xiao-Bin Zhang contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Qiu-Fang Jia and Xiao-Bin Zhang as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Supported by This study was supported by the Suzhou Municipal Sci-Tech Bureau Program, No. SS202070; Scientific and Technological Program of Suzhou, No. SS202069; Suzhou clinical Medical Center for mood disorders, No. Szlcyxzx202109; Suzhou Clinical Key Disciplines for Geriatric Psychiatry, No. SZXK202116; Suzhou Key Technologies Program, No. SKY2021063; Jiangsu Province social development project, No. BE2020764; Research Project of Jiangsu Commission of Health, No. M2020031; Elderly Health Research Project of Jiangsu Commission of Health, No. LR2022015 and No. LKZ2023020.

Institutional review board statement: The WuTaiShan Hospital Ethics Committee approved the study (approval No. 2018-011).

Informed consent statement: The written informed consent was provided by each participant.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

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S-Editor: Lin C

L-Editor: A

P-Editor: Zhang XD

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