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Impact of antipsychotics on prolactin and its associations with neurocognition in patients with schizophrenia

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ABSTRACT

Background and objectives: Cognitive impairment is a core feature of schizophrenia (SCZ). Previous studies suggest a close relationship between prolactin and neurocognition. However, antipsychotics have a great impact on prolactin dysregulation. This study investigates how antipsychotics modulate prolactin and its associations with neurocognition in SCZ patients.

Methods: A total of 425 SCZ patients were recruited from psychiatric hospitals. Neurocognition was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status. Blood samples were collected after an overnight fast to measure prolactin levels. Analyses were conducted using moderated regression models with two moderators: prolactin-raising antipsychotics and hyperprolactinemia.

Results: The prolactin-raising group showed significantly higher prolactin levels than the prolactin-sparing group. Prolactin levels showed significant negative associations with immediate memory and delayed memory. Moreover, the association between prolactin levels and immediate memory was modulated by prolactin-raising antipsychotics and the interaction between prolactin-raising antipsychotics and hyperprolactinemia. Specifically, the negative association was significant only in patients taking prolactin-raising antipsychotics, especially when their prolactin levels exceeded the threshold of hyperprolactinemia.

Conclusions: These findings underscore the need for regular serum prolactin monitoring in patients receiving prolactin-raising antipsychotics, particularly those with confirmed hyperprolactinemia. Clinicians should exercise particular caution when prescribing such agents to patients with memory impairment and consider prolactin-sparing alternatives where clinically appropriate.

1. Introduction

Schizophrenia (SCZ) is a complex and severe mental disorder with a lifetime prevalence of approximately 1 % worldwide (Owen et al., 2016; Saha et al., 2005). Typically appearing in early adulthood, SCZ is characterized by a chronic course of illness (McCutcheon et al., 2020). SCZ manifests a wide range of dysfunctions (Jauhar et al., 2022) and imposes a heavy healthcare burden on both patients and society (Cloutier et al., 2016). According to a review, approximately 80–90 % of patients are unemployed, and their life expectancy is shortened by 10–20 years (Chesney et al., 2014).

Cognitive impairments are one of the core features of SCZ, affecting as many as 98 % of patients with SCZ (Gebreegziabhere et al., 2022; Keefe et al., 2005). These impairments are manifested in multiple cognitive domains in patients with SCZ (Schaefer et al., 2013). According to the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, patients with SCZ typically exhibit deficits in seven cognitive domains: processing speed, attention, memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition (Gebreegziabhere et al., 2022; Marder and Fenton, 2004; Nuechterlein et al., 2004). The first six domains are neurocognitive and are considered to be more relevant to patients with SCZ (Green et al., 2004).

Hormones play an important role in cognitive function. A review suggested that prolactin may be one of the potential targets for improving cognitive function in patients with SCZ (Tost et al., 2020). Prolactin, primarily synthesized by lactotroph cells in the anterior pituitary gland, plays a crucial role in lactation (Bernard et al., 2019).

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Emerging evidence links elevated prolactin levels to cognitive impairment across populations. In older men, elevated prolactin levels are associated with cognitive decline (Castanho et al., 2014). In patients with prolactinoma, a disorder characterized by prolactin hypersecretion, elevated prolactin levels are associated with prefrontal cortex dysfunction, which may lead to cognitive impairment (Chen et al., 2022). Sex-specific effects appear in patients with first-episode psychosis, where elevated prolactin levels associate with reduced language expressivity in males and impaired working memory in females (Jordà-Baleri et al., 2024). In patients with SCZ, prolactin levels are frequently abnormal relative to healthy controls. Previous studies have confirmed elevated prolactin levels in SCZ patients (Jones et al., 2021; Vuk Pisk et al., 2019), including those with drug-naïve SCZ (Pan et al., 2025; Wasnik et al., 2019). Furthermore, prolactin dysregulation has been linked to cognitive impairment in SCZ patients, including deficits in processing speed and working memory (Montalvo et al., 2014; Moore et al., 2013).

Antipsychotics can significantly disrupt prolactin regulation, leading to elevated prolactin levels (Wada et al., 2025). However, the effects of antipsychotics on prolactin vary by pharmacodynamic profile. A review indicates that antipsychotics with potent dopamine antagonism increase prolactin secretion, whereas those with weaker antagonism exert minimal effects, which are often negligible (Peuskens et al., 2014). Interestingly, aripiprazole can even counteract the impact of prolactin-raising antipsychotics (Labad et al., 2020). Elevated prolactin levels contribute to many adverse outcomes, such as sexual dysfunction and cognitive impairment (Peuskens et al., 2014; Xu et al., 2024). Recent evidence further indicates that prolactin-raising antipsychotics can affect the associations between prolactin and gonadal hormones (Hamers et al., 2024). Sex hormones are associated with cognitive function (Guan et al., 2021; Szoeke et al., 2021) and may serve as potential mediators between prolactin levels and cognitive function (Brand et al., 2024; Hamers et al., 2024). These findings prompt consideration of whether prolactin-raising antipsychotics affect associations between prolactin and neurocognition. The results from a previous study support this hypothesis, which showed the association between prolactin levels and processing speed seems only significant in SCZ patients taking prolactin-raising antipsychotics, while not in those taking prolactin-sparing antipsychotics (Brand et al., 2024).

Moreover, prolactin typically fluctuates within a normal physiological range. Persistent elevation beyond the normal range is defined as hyperprolactinemia (Peuskens et al., 2014). The detrimental effects of hyperprolactinemia on cognitive function have been reported (Chen et al., 2022; Montalvo et al., 2014; Yao et al., 2017). Given prolactin's physiological variability, hyperprolactinemia may also modulate the relationship between prolactin and cognition. Specifically, significant prolactin-cognition associations may manifest only when prolactin levels exceed the threshold for hyperprolactinemia.

Therefore, this study aimed to explore the impact of antipsychotics on prolactin and its associations with neurocognition in patients with SCZ. Three hypotheses were proposed: (1) SCZ patients taking prolactin-raising antipsychotics would exhibit higher prolactin levels and a higher prevalence of hyperprolactinemia compared to those taking prolactin-sparing antipsychotics; (2) The elevated prolactin levels would associate with worse neurocognition; (3) The association between prolactin and neurocognition would be modulated by prolactin-raising antipsychotics and hyperprolactinemia. To better illustrate the potential causal pathway linking prolactin-raising antipsychotics to worse neurocognitive performance, a directed acyclic graph was constructed to clarify and visualize the assumed causal relationship (see Fig. 1).

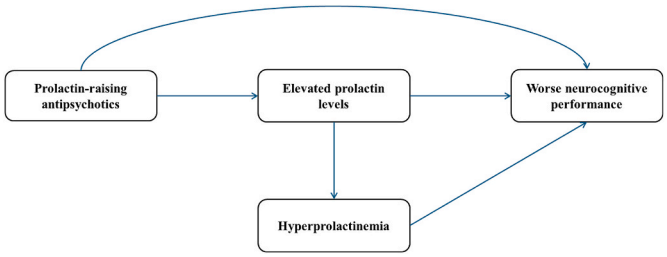

Fig. 1. Directed acyclic graph for prolactin-raising antipsychotics to worse neurocognitive performance. (1) Direct effect: Prolactin-raising antipsychotics may be directly associated with worse neurocognitive performance; (2) Indirect effect: Prolactin-raising antipsychotics may elevate prolactin levels, which, in turn, may contribute to worse neurocognitive performance; (3) Threshold-dependent indirect effect: Prolactin-raising antipsychotics may elevate prolactin levels; however, only when these levels reach the threshold of hyperprolactinemia might they subsequently lead to worse neurocognitive performance.

2. Methods

2.1. Study design and study population

This cross-sectional study was conducted from 2018 to 2020 in China. The study protocol was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences (H18031). Totally, 425 participants were recruited from psychiatric hospitals. Inclusion criteria required participants to: (1) be aged between 18 and 65 years; (2) have a diagnosis of SCZ confirmed by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID); (3) keep a stable dose of antipsychotics for two months; (4) have the decisional capacity to provide written informed consent. Exclusion criteria included: (1) current pregnancy or lactation; (2) organic brain diseases or severe physical illnesses; and (3) substance abuse, excluding tobacco.

2.2. Antipsychotics assessment

The dosage of all antipsychotics used by each patient was recorded and then converted to the chlorpromazine equivalents using the defined daily dose method from the World Health Organization (http://www.whocc.no/). According to the classification method in a previous study (Hamers et al., 2024): (1) Patients who used aripiprazole (regardless of other antipsychotics) were assigned to the prolactin-sparing group; (2) Patients who did not use aripiprazole but receiving prolactin-raising antipsychotics (paliperidone, risperidone, haloperidol, olanzapine, zuclopenthixol, pimozide and amisulpride) were assigned to the prolactin-raising group; (3) Patients who used neither aripiprazole nor any prolactin-raising antipsychotics but other prolactin-sparing antipsychotics (clozapine, asenapine, quetiapine, and flupentixol) were assigned to the prolactin-sparing group. The proportion of specific antipsychotics within each group is detailed in Supplementary Table 1.

2.3. Clinical assessment

The severity of clinical symptoms in SCZ patients was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), which consists of three subscales: positive symptoms, negative symptoms, and general psychopathology symptoms. The higher the PANSS score, the more severe the psychiatric symptoms.

2.4. Neurocognitive assessment

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess neurocognitive function in five domains: immediate memory, visuospatial/constructional ability, language, attention, and delayed memory (Randolph et al., 1998). Higher RBANS scores indicate better cognitive functioning. The Chinese version of the RBANS has demonstrated good reliability and validity (Cheng

et al., 2011).

2.5. Hormone assessment

After an overnight fast, blood samples were drawn promptly after venipuncture by nurses between 6:00 and 8:00 a.m. Prolactin levels were measured using an electro-chemiluminescent immunoassay analyzer (Roche C6000, Roche Diagnostics, Indianapolis, IN, USA). Hyperprolactinemia thresholds were sex-specific: >0.42 IU/L (20 ng/mL) for men and >0.53 IU/L (25 ng/mL) for women (Peuskens et al., 2014). Patients exceeding these thresholds were assigned to the hyperprolactinemia group.

2.6. Statistical analysis

Normality was assessed using the Shapiro-Wilk test. Between-group comparisons employed independent t-tests for continuous normally-distributed variables, Mann-Whitney U tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. Multiple linear regression models were used to examine associations between prolactin levels and each neurocognitive domain. Initial candidate covariates for the regression models were identified through correlation analyses, utilizing Pearson correlation for continuous variables and Spearman's rank correlation for non-continuous variables. Variables showing significant ($p < 0.05$) correlations with a neurocognitive domain were included as candidate covariates, with the final covariates determined via stepwise selection procedure. To evaluate moderating effects, Model 3 of Hayes' PROCESS macro (v4.2) was applied, specifying prolactin levels as the predictor, each neurocognitive domain as the dependent variable, with antipsychotic types and hyperprolactinemia status as moderators. Regression coefficients quantified main effects (prolactin, moderators) and prolactin × moderator interaction terms. Simple slope analyses were subsequently performed for any statistically significant moderating effects.

Considering the potential mediating role of sex hormones between prolactin and neurocognition (Brand et al., 2024; Hamers et al., 2024), sex-specific analyses were conducted by re-running primary statistical analyses separately for male and female patients. All statistical analyses were performed using SPSS v25.0, with a significance threshold defined as p-value <0.05 (two-tailed).

3. Results

3.1. Comparisons between the prolactin-sparing and the prolactin-raising groups

Among the patients, 47.06 % ($n = 200$) were assigned to the prolactin-sparing group, and 52.94 % ($n = 225$) were assigned to the prolactin-raising group. No significant group differences were observed in BMI and illness duration (all $p > 0.05$). Significant group differences were observed in gender, age, years of education, age of onset, and antipsychotic dose (all $p < 0.05$). For clinical scales, no significant group differences were found in PANSS scores and RBANS scores (all $p > 0.05$). A significant group difference was found in prolactin levels: prolactin levels were significantly higher in the prolactin-raising group compared to the prolactin-sparing group ($z = 4.714$, $p < 0.001$, Fig. 2). The prevalence of hyperprolactinemia was significantly higher in the prolactin-raising group ($\chi^2 = 15.208$, $p < 0.001$). Detailed statistics are shown in Table 1.

3.2. Comparisons between the non-hyperprolactinemia and hyperprolactinemia groups

Among the patients, 44.47 % ($n = 189$) had hyperprolactinemia, while 55.53 % ($n = 236$) did not. No significant group differences were observed in years of education, age of onset, and antipsychotic dose (all $p > 0.05$). There were significant group differences in gender, age, BMI, and illness duration (all $p < 0.05$). For clinical scales, no significant group differences were found in PANSS scores and RBANS scores (all $p > 0.05$). A significant group difference was found in prolactin levels: prolactin levels were significantly higher in the hyperprolactinemia group compared to the non-hyperprolactinemia group ($z = 17.619$, $p < 0.001$). Detailed statistics are presented in Table 1.

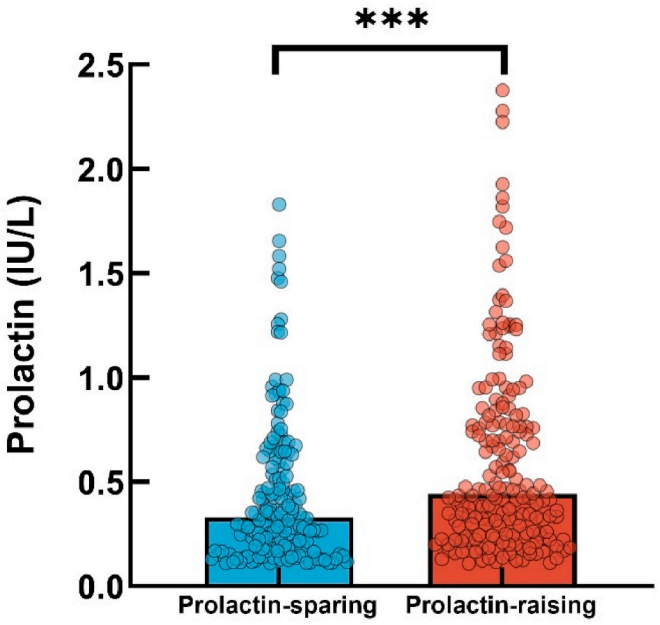

Fig. 2. Comparison in prolactin levels between the prolactin-sparing group and the prolactin-raising group. *** = $p < 0.001$.

3.3. Associations between prolactin levels and neurocognition

Supplementary Table 2 presents the correlation matrix between neurocognitive domains and other variables. Variables showing significant correlation were identified as initial candidate covariates for regression models, including gender, age, years of education, age of onset, illness duration, positive symptoms, negative symptoms, and general psychopathology symptoms that showed significant correlations with neurocognitive domains. Candidate covariates were entered into stepwise regression models to optimize covariate selection. Regression models revealed significant negative associations between prolactin levels and immediate memory ($\beta = -3.545$, $t = -2.277$, $p = 0.023$), as well as between prolactin levels and delayed memory ($\beta = -4.390$, $t = -2.480$, $p = 0.014$), but no significant associations with other neurocognitive domains. Complete regression results are provided in Table 2.

3.4. Moderating effects of prolactin-raising antipsychotics and hyperprolactinemia

The moderating analyses revealed specific patterns regarding the impact of prolactin levels on immediate memory, influenced by antipsychotic type and hyperprolactinemia status (Table 3). The significant "Prolactin levels × Antipsychotic type" interaction ($\beta = 46.108$, $t = 2.347$, $p = 0.019$) demonstrated that the association between prolactin levels and immediate memory differed significantly depending on antipsychotic type. The significant "Prolactin levels × Antipsychotic type × Hyperprolactinemia status" interaction ($\beta = -20.698$, $t = -2.978$, $p = 0.003$) indicated that the moderating effect of antipsychotic type depended on the presence or absence of hyperprolactinemia. The non-significant "Prolactin levels × Hyperprolactinemia status" interaction ($\beta = 11.933$, $t = 0.852$, $p = 0.395$) indicated that

Table 1
Comparisons between the subgroups.

median [min, max]/mean (SD)	Prolactin-sparing ($n = 200$)	Prolactin-raising ($n = 225$)	$t/Z/\chi^2$	p-value	Non-hyperprolactinemia ($n = 236$)	Hyperprolactinemia ($n = 189$)	$t/Z/\chi^2$	p-value
Gender (M/F)	120/80	158/67	4.890	**0.027**	143/93	135/54	5.446	**0.020**
Age	43 [18, 64]	45 [18, 65]	2.089	**0.037**	42 [18, 65]	46 [18, 65]	2.252	**0.024**
Years of education	8 [2, 17]	9 [2, 17]	2.150	**0.032**	8 [2, 17]	9 [2, 17]	0.952	0.241
BMI	24.19 [15.55, 35.71]	23.74 [15.31, 36.30]	−0.802	0.423	23.46 [15.37, 35.71]	24.21 [15.31, 36.30]	2.096	**0.036**
Age of onset	22 [11, 39]	23 [11, 43]	2.418	**0.016**	23 [11, 43]	23 [11, 41]	−0.176	0.860
Illness duration (year)	19 [0, 47]	19 [0, 46]	0.442	0.659	17 [0, 45]	22 [0, 47]	2.532	**0.011**
Antipsychotic dose (mg/d)	350 [20, 1200]	440 [16, 1200]	3.303	**0.001**	385 [17, 1200]	400 [20, 1100]	1.108	0.268
PANSS	85 [30, 136]	84 [33, 139]	−0.201	0.841	84 [30, 136]	84 [40, 139]	−0.540	0.589
Positive symptoms	17 [7, 40]	18 [7, 38]	0.283	0.777	18 [7, 40]	17 [7, 36]	−0.783	0.433
Negative symptoms	24.40 (7.28)	24.00 (7.38)	1.149	0.251	23.78 (7.71)	24.21 (6.86)	0.382	0.703
General psychopathology symptoms	41 [16, 70]	42 [18, 73]	0.414	0.672	42 [16, 70]	41 [18, 73]	−0.469	0.639
RBANS	345 [214, 515]	343 [230, 519]	−0.635	0.514	345 [220, 519]	343 [214, 514]	−1.236	0.217
Immediate memory	53 [31, 114]	49 [40, 114]	−0.635	0.525	53 [31, 114]	53 [40, 114]	−1.109	0.267
Visuospatial/ constructional	69 [50, 121]	72 [50, 126]	1.106	0.269	69 [50, 121]	69 [50, 126]	0.173	0.862
Language	80 [40, 130]	79 [40, 114]	−1.137	0.255	79 [40, 117]	79 [40, 130]	−0.356	0.722
Attention	79 [40, 142]	79 [46, 142]	−0.412	0.680	79 [40, 142]	79 [40, 142]	−1.264	0.206
Delayed memory	60 [40, 107]	56 [40, 107]	−0.718	0.473	60 [40, 107]	60 [40, 107]	−0.589	0.556
Prolactin (IU/L)	0.33 [0.11, 2.19]	0.47 [0.11, 2.46]	4.714	**<0.001**	0.25 [0.11, 0.49]	0.78 [0.42, 2.46]	17.619	**<0.001**
Hyperprolactinemia [n (%)]	69 (34.50 %)	120 (53.33 %)	15.208	**<0.001**				

Note: BMI=Body Mass Index; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. Bold font indicates statistical significance.

Table 2
Regression models between neurocognition and prolactin levels.

	Variables	Unstandardized β	t	p
Immediate memory	Years of education	1.410	5.320	<0.001
	Negative symptoms	−0.385	−3.829	<0.001
	Prolactin levels	−3.545	−2.277	0.023
Visuospatial/ constructional	Years of education	1.391	5.228	<0.001
	Negative symptoms	−0.289	−2.846	0.005
Language	Gender	−4.358	−3.076	0.002
	Age	0.184	3.284	0.001
	Years of education	1.111	4.491	<0.001
	Negative symptoms	−0.511	−5.477	<0.001
Attention	Gender	3.265	1.978	0.049
	Years of education	1.598	5.599	<0.001
	Negative symptoms	−0.429	−3.940	<0.001
Delayed memory	Years of education	1.583	5.253	<0.001
	Negative symptoms	−0.487	−4.261	<0.001
	Prolactin levels	−4.390	−2.480	0.014

Note: Parameters of regression models: (1) $F = 17.988$, $p < 0.001$, $R^2 = 0.114$ for immediate memory; (2) $F = 21.185$, $p < 0.001$, $R^2 = 0.091$ for visuospatial/ constructional; (3) $F = 19.216$, $p < 0.001$, $R^2 = 0.155$ for language; (4) $F = 20.500$, $p < 0.001$, $R^2 = 0.127$ for attention; (5) $F = 19.386$, $p < 0.001$, $R^2 = 0.121$ for delayed memory.

hyperprolactinemia status did not significantly alter the association between prolactin levels and immediate memory. No significant moderating effects were found for delayed memory (Table 3).

Table 3
Regression models for moderating effects of prolactin-raising antipsychotics and hyperprolactinemia on neurocognition.

	Variables	Unstandardized β	t	p
Immediate memory	Years of education	1.454	5.475	**<0.001**
	Negative symptoms	−0.371	−3.686	**<0.001**
	Prolactin levels	−17.161	−1.295	0.196
	Antipsychotic type	15.357	6.322	**0.016**
	Prolactin levels × Antipsychotic type	46.108	2.347	**0.019**
	Hyperprolactinemia status	8.496	1.703	0.089
	Prolactin levels × Hyperprolactinemia status	11.933	0.852	0.395
	Antipsychotic type × Hyperprolactinemia status	−20.698	−2.978	**0.003**
	Prolactin levels × Antipsychotic type × Hyperprolactinemia status	−43.816	−2.153	**0.032**
Delayed memory	Years of education	1.635	5.410	**<0.001**
	Negative symptoms	−0.490	−4.275	**<0.001**
	Prolactin levels	−10.468	−0.694	0.488
	Antipsychotic type	12.048	1.674	0.095
	Prolactin levels × Antipsychotic type	40.673	1.819	0.070
	Hyperprolactinemia status	7.898	1.391	0.165
	Prolactin levels × Hyperprolactinemia status	0.646	0.041	0.967
	Antipsychotic type × Hyperprolactinemia status	−17.930	−2.266	**0.024**
	Prolactin levels × Antipsychotic type × Hyperprolactinemia status	−36.580	−1.579	0.115

Note: Parameters of regression models: (1) $F = 7.284$, $p < 0.001$, $R^2 = 0.136$ for immediate memory; (2) $F = 7.628$, $p < 0.001$, $R^2 = 0.142$ for delayed memory. Bold font indicates statistical significance.

3.4.1. Simple slope analysis for the moderating effect of prolactin-raising antipsychotics on immediate memory

When stratifying by antipsychotic type, the association between prolactin levels and immediate memory was significant only in the prolactin-raising group ($\beta = -4.505$, $t = -2.270$, $p = 0.024$), while not in the prolactin-sparing group ($\beta = -1.336$, $t = -0.490$, $p = 0.625$). Complete regression results are provided in Supplementary Table 3.

3.4.2. Simple slope analysis for the moderating effect of the prolactin-raising antipsychotics and hyperprolactinemia interaction on immediate memory

Patients were stratified by both antipsychotic type and hyperprolactinemia status. In patients taking prolactin-sparing antipsychotics, prolactin levels showed no significant association with immediate memory, regardless of hyperprolactinemia status. Interestingly, among patients taking prolactin-raising antipsychotics, prolactin levels showed a marginally significant negative association with immediate memory in those with hyperprolactinemia ($\beta = -3.889$, $t = -1.713$, $p = 0.089$), while exhibiting a marginally significant positive association in those without hyperprolactinemia ($\beta = 30.449$, $t = 1.743$, $p = 0.084$). Complete regression results are provided in Supplementary Table 4. In summary, the negative association approached significance only in patients with both prolactin-raising antipsychotics and hyperprolactinemia.

3.5. Sex-specific analyses

As shown in Supplementary Fig. 1, both male and female patients showed significant differences in prolactin levels between the prolactin-sparing and prolactin-raising groups (both $p < 0.001$). Analysis of moderating effects revealed distinct sex differences. As shown in Supplementary Table 5, no moderating effects were found on immediate memory in male patients. However, significant moderating effects on immediate memory were observed in female patients (Supplementary Table 6). Specifically for the terms: "Prolactin levels × Antipsychotic type" ($\beta = 30.056$, $t = 2.352$, $p = 0.020$) and "Prolactin levels × Antipsychotic type × Hyperprolactinemia status" ($\beta = -94.912$, $t = -2.512$, $p = 0.013$). Moreover, significant moderating effects on delayed memory were also observed in female patients. Specifically for the term: "Prolactin levels × Antipsychotic type × Hyperprolactinemia status" ($\beta = -88.110$, $t = -2.061$, $p = 0.042$) (Supplementary Table 6).

4. Discussion

This study explored the impact of prolactin-raising antipsychotics on prolactin and its associations with neurocognition in patients with SCZ. Three key findings emerge: (1) Patients taking prolactin-raising antipsychotics exhibited higher prolactin levels than those taking prolactin-sparing antipsychotics; (2) Prolactin levels showed significant negative associations with memory domains (immediate memory and delayed memory). (3) The association between prolactin and immediate memory was modulated by prolactin-raising antipsychotics, as well as by the interaction between prolactin-raising antipsychotics and hyperprolactinemia.

Consistent with our hypothesis, patients taking prolactin-raising antipsychotics showed elevated prolactin levels compared to those taking prolactin-sparing antipsychotics. This finding was consistent with a previous study (Hamers et al., 2024), which also identified higher prolactin levels in patients taking prolactin-raising antipsychotics. Prolactin release is regulated via the inhibitory effect of dopamine (Lyons and Broberger, 2014). Dopamine is secreted by neurons in the arcuate nucleus of the hypothalamus and acts on dopamine receptors (D2) in the anterior lobe of the pituitary gland, inhibiting the synthesis and secretion of prolactin (Kirsch et al., 2022). Prolactin-raising antipsychotics include high-potency D2 receptor antagonists, which may remove inhibition from lactotroph cells in the anterior pituitary, thereby increasing prolactin secretion. It should be noted that increased prolactin levels induced by prolactin-raising antipsychotics are associated with some side effects. These may include sexual dysfunction (Redman et al., 2021), menstrual irregularities (Kulshreshtha et al., 2017), infertility (Kutlesic et al., 2024), and reduced bone mineral density (Lally et al., 2019). Therefore, prolactin levels require close monitoring during antipsychotic treatment, particularly with prolactin-raising antipsychotics.

In this study, prolactin levels showed associations only with memory domains, highlighting its close relationship with memory function. This close relationship may be attributed to the interaction between prolactin and the hippocampus. Prolactin receptors are widely distributed throughout the brain (Penadés et al., 2015). The hippocampus, a crucial brain structure for memory, exhibits a close interaction with prolactin (Torner, 2016). Notably, prolactin may enhance memory by promoting synaptogenesis and neuronal plasticity within the hippocampus (Carretero et al., 2019). Evidence from an animal study confirmed that prolactin levels are associated with the number of hippocampal neural precursors in mice (Walker et al., 2012). Additionally, prolactin is not only synthesized by lactotroph cells but also locally produced in the hippocampus, suggesting a direct modulatory role in memory-related neural circuits (Carretero et al., 2019).

This study revealed that the association between prolactin and immediate memory was modulated by prolactin-raising antipsychotics. Specifically, the significant association was found only in patients taking prolactin-raising antipsychotics, while not in those taking prolactin-sparing antipsychotics. A previous study found that prolactin was associated with working memory in patients with chronic SCZ (Moore et al., 2013), whereas another study reported no significant associations between prolactin and neurocognition in patients with drug-naive SCZ (Luo et al., 2024). This inconsistency may be attributed to the impact of prolactin-raising antipsychotics, which are commonly used long-term in chronic SCZ.

Moreover, this study revealed that the association between prolactin and immediate memory was also modulated by the interaction between prolactin-raising antipsychotics and hyperprolactinemia. Specifically, among patients taking prolactin-raising antipsychotics, the association exhibited a negative trend (although not significant) only when elevated prolactin levels exceeded the hyperprolactinemia threshold. These findings suggest a potential threshold effect modulating the prolactin-neurocognition association, with the critical threshold possibly exceeding conventional clinical hyperprolactinemia criteria. While this study used the clinical hyperprolactinemia threshold as a predefined cutoff, its precision for this specific cognitive association may be limited. Future research should determine the exact prolactin threshold that modulates the prolactin-immediate memory relationship. Nevertheless, the established clinical threshold for hyperprolactinemia retains practical relevance. Additionally, considering the close relationship between prolactin and hippocampal function (Carretero et al., 2019), we speculate that the impact of prolactin on hippocampal function may be physiologically significant only when prolactin levels are high, which may offer a potential mechanistic explanation for our results. Notably, in patients taking prolactin-raising antipsychotics without exceeding the hyperprolactinemia threshold, this study found that the association with immediate memory exhibited a positive trend (although not significant). This unexpected contrast suggests that the prolactin-memory relationship in SCZ is more complex than previously recognized. It is plausible that these patients possess additional protective factors preserving their cognition. Specifically, despite also exposure to prolactin-raising antipsychotics, they did not develop hyperprolactinemia, which may reflect the existence of these protective factors. Further research is warranted to explain this phenomenon.

In summary, these findings highlight the critical importance of proactive clinical management strategies when prescribing prolactin-raising antipsychotics. Specifically, implementing routine biochemical monitoring of serum prolactin concentrations is strongly suggested for

patients receiving such medications, with particular attention to those developing hyperprolactinemia. Furthermore, clinicians should exercise heightened clinical risk-benefit assessments when considering the use of prolactin-raising antipsychotics for patients presenting with significant memory impairment. When clinically appropriate, alternative agents less likely to elevate prolactin, such as aripiprazole, should be considered.

Several limitations should be considered in this study. First, our cohort comprised exclusively hospitalized patients, who typically present with more severe symptoms and cognitive impairment. This may limit the generalizability of our findings to the broader SCZ population. Second, the cross-sectional design employed in this study limits causal inference; future longitudinal studies are needed to better elucidate causal pathways. Third, future studies should investigate hypoprolactinemia's cognitive impact, given its potential clinical relevance (Duru et al., 2025). This study included only 19 hypoprolactinemic patients (diagnostic thresholds: <0.106 IU/L [5 ng/mL] for men and <0.148 IU/L [7 ng/mL] for women) (Urhan and Karaca, 2024), with 13 in the prolactin-sparing group and 6 in the prolactin-raising group. Fourth, while sex-stratified analyses were performed, future studies should account for menopausal status, a potential confounder in females (Metcalf et al., 2023). Fifth, regression models explained limited variance despite significance, indicating robust associations but substantial unexplained heterogeneity, potentially from unmeasured confounders or biological complexity beyond the current design scope, particularly the potential mediating role of sex hormones in the prolactin-cognition pathway (Brand et al., 2024; Hamers et al., 2024). Sixth, venipuncture stress may affect the accuracy of prolactin measurements. In this study, prolactin levels were measured from blood drawn immediately after venipuncture. Serial sampling via an indwelled cannula provides more reliable results by minimizing acute stress effects (Wilkinson et al., 2024).

5. Conclusions

In conclusion, this study provides novel insights into the impact of antipsychotics on prolactin and its associations with neurocognition in patients with SCZ. This study supports the robust relationship between prolactin-raising antipsychotics and elevated prolactin levels. Critically, the negative association between prolactin and immediate memory is significant only in patients taking prolactin-raising antipsychotics. These findings have potential implications for clinical practice: proactive monitoring of prolactin is strongly suggested in patients taking prolactin-raising antipsychotics (especially those with hyperprolactinemia), and careful consideration is advised when treating patients with memory impairment.

CRediT authorship contribution statement

Qihui Guo: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Rongrong Zhu:** Data curation, Conceptualization. **Yang Tian:** Data curation. **Dongmei Wang:** Writing – review & editing, Project administration. **Xiangyang Zhang:** Writing – review & editing, Project administration, Funding acquisition.

Availability of data and materials

The data that support the findings of this study are publicly available. The corresponding author can be contacted upon reasonable request.

Ethical statement

The authors declare that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Declaration of competing interest

The authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.12.022.

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