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The impact of childhood trauma exposure on social functioning in schizophrenia: the moderated mediation role of oxytocin and oxytocin receptor gene polymorphisms

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Abstract

Background. Childhood trauma has been linked to increased risk of schizophrenia and social dysfunction, and oxytocin and its receptor gene have been implicated in regulating social behavior. This study investigated the potential role of oxytocin and oxytocin receptor gene (OXTR) in mediating the effects of childhood trauma on social functioning in schizophrenia.
Methods. The study consisted of 382 patients with schizophrenia and 178 healthy controls who were assessed using the Taiwanese version of the Childhood Trauma Questionnaire (CTQ-SF), the Social Functioning Scale (SFS), and plasma oxytocin levels. DNA was extracted to genotype the OXTR and ten single-nucleotide polymorphisms (SNPs; rs2254298, rs237885, rs237887, rs237899, rs53576, rs9840864, rs13316193, rs7632287, rs1042778, and rs237895) were selected.
Results. Patients with schizophrenia showed higher CTQ-SF scores ($t = 12.549$, $p < 0.001$), lower SFS scores ($t = -46.951$, $p < 0.001$), and lower plasma oxytocin levels ($t = -5.448$, $p < 0.001$) compared to healthy controls. The study also found significant differences in OXTR SNPs between both groups, with risk alleles being more prevalent in patients with schizophrenia ($t = 2.734$, $p = 0.006$). Results indicated a significant moderated mediation effect, with oxytocin and the OXTR SNPs partially mediating the relationship between childhood trauma exposure and social functioning in patients with schizophrenia (index of mediation = 0.038, 95% CI [0.033–0.044]).
Conclusions. The findings suggest that oxytocin and its receptor gene may be promising targets for interventions aimed at improving social functioning in patients with a history of childhood trauma and schizophrenia. However, further research is needed to fully understand these effects and the potential of oxytocin-based interventions in this population.

Introduction

Exposure to childhood trauma is prevalent in patients with mental disorders and increases risk of later psychopathology (Hogg et al., 2023). Studies have shown that such exposure can lead to higher risk of psychotic symptoms and disorders, with the risk increasing for those who experience multiple types of trauma (Croft et al., 2019). This is consistent with a meta-analysis that found a dose–response relationship between childhood adversity and psychosis, emphasizing that risk increases with multi-victimization or more severe exposures (Varese et al., 2012). Childhood trauma is also connected to higher rates of schizophrenia compared to healthy controls (Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013), with an odds ratio of 2.87 (Radua et al., 2018). Broadly defined adversity and different forms of abuse, including neglect during childhood, have been shown to affect various dimensions of symptom severity in patients with psychotic disorders. Most forms are linked to increased severity not only in hallucinations and delusions but also in other aspects such as negative, depressive, disorganized, and manic dimensions of patients with psychotic disorders. However, neglect seems to be specifically related to negative and depressive dimensions (Alameda et al., 2021; Bailey et al., 2018). This partially supports the idea that psychotic symptoms arise from childhood trauma, as they are more severe symptoms and slower improvement rates (Aas et al., 2016). Childhood trauma also affects social cognition in these patients, leading to poorer emotional recognition (Penney, Pruessner, Malla, Joober, & Lepage, 2023) and theory of mind (Vaskinn, Engelstad, Torgalsbøen, & Rund, 2021). Cumulative exposure to childhood trauma among

patients with mental disorders has been linked to negative outcomes across various domains, including health, criminal, financial, educational, and social functioning (Copeland et al., 2018). This is further supported by a negative association between general childhood adversity and both general and social functioning outcomes in patients with psychotic disorders (Christy et al., 2023). Specifically, in patients with schizophrenia, lower social functioning has been observed regardless of whether they are in an active illness phase or in remission (Hjelseng et al., 2022).

Childhood trauma can affect individuals' social functioning by causing permanent changes in brain development. Patients with schizophrenia who experienced childhood trauma exhibit reduced volumes in the hippocampus (Teicher, Samson, Anderson, & Ohashi, 2016), decreased cortical thickness of frontal and temporal gyri (Rapado-Castro et al., 2020), increased activation of posterior cingulate gyrus, precuneus, and dorsomedial prefrontal cortex (Quidé et al., 2017), and decreased connectivity between the posterior cingulate gyrus and amygdala (Cancel et al., 2017). Childhood trauma affects individuals' interactions with their social status, integration, and interpersonal stress, and increases the risk of mental disorders, where supportive relationships are diminished, due to social thinning and stress generation, according to the neurocognitive social transactional model (McCrory, Foulkes, & Viding, 2022). It has been noticed that patients with schizophrenia who experienced more severe childhood trauma experience greater stress during social activities (Dokuz, Kani, Uysal, & Kuşcu, 2022). Neurocognitive domains like threat processing (McCrory et al., 2022), reward processing (Armbruster-Genç et al., 2022; McCrory et al., 2022), and emotional regulation (McCrory, Ogle, Gerin, & Viding, 2019) are impacted. Childhood trauma also predicts impaired social cognition, which accounts for significant variance in real-world social functioning in patients with schizophrenia (Kilian et al., 2018). An affective pathway with depression, paranoia, and anxious attachment as connecting components, mediates the effect of childhood trauma on social functioning in patients with schizophrenia (Palmier-Claus et al., 2016). Other pathways, such as poor impulse control and motor retardation can also worsen social dysfunction in these individuals (Isvoranu et al., 2017).

Disruptions in oxytocin regulation have been linked to childhood trauma. Individuals with a history of childhood trauma exhibit lower plasma oxytocin levels (Opacka-Juffry & Mohiyeddini, 2012; Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2014), which have been linked to structural changes in the brain (Mielke et al., 2018), and are a predictor of severe clinical symptoms (Rubin et al., 2018) and poor social cognition (Balikci, Aydin, Tas, & Esen Danaci, 2018) in patients with schizophrenia (Ferreira & Osório, 2022). Our previous study found a positive correlation between plasma oxytocin levels, social cognition, and social functioning in patients with schizophrenia (Goh & Lu, 2022). Given its involvement in theory of mind and other domains such as trust, attachment, and social memory (Kirsch, 2015), lower oxytocin levels may also contribute to an abnormal attributional style in which patients attribute negative events excessively to external causes, leading to psychotic symptoms and poor social functioning (Mercedes Perez-Rodriguez, Mahon, Russo, Ungar, & Burdick, 2015). The interpretation of oxytocin levels may depend on the presence of oxytocin receptors (OXTR), and variations in the OXTR gene have been linked to schizophrenia risk (Montag et al., 2013; Watanabe et al., 2012), clinical symptoms (Giralt-López et al., 2020; Haram et al., 2015), social cognition (Nakata et al., 2021), and treatment response (Souza, de Luca, Meltzer, Lieberman, & Kennedy, 2010). A case series found that rare missense coding of OXTR single nucleotide polymorphisms (SNPs) was associated with impaired cognitive function and severe childhood trauma (Veras et al., 2018). Gene–environment interactions may alter OXTR expression and produce different phenotypes in schizophrenia due to childhood trauma (Rosenfield, Jiang, & Pauselli, 2022).

Childhood trauma affects schizophrenia patients negatively, impacting neurocognitive domains, altering neuroendocrine regulation, and leading to epigenetic changes that can result in poor social functioning. While disruptions in the oxytocinergic system linked to childhood trauma have been studied as potential contributors to schizophrenia's pathophysiology, there is a critical gap in understanding the specific mechanisms involved. In particular, the theoretical frameworks explaining how childhood trauma might translate into social dysfunction in schizophrenia patients through oxytocinergic pathways. The novelty of this study lies in its aim to investigate the impact of oxytocin and OXTR SNPs in linking childhood trauma to social functioning in patients with schizophrenia, considering moderated mediation role of OXTR in increasing vulnerability to schizophrenia. This unique focus on the oxytocin and OXTR may open new perspectives for understanding the complex interplay between childhood trauma, genetic factors, and social dysfunction in schizophrenia.

Materials and methods

Participants and procedures

This study consisted of 382 patients with schizophrenia and 178 healthy controls, all between 20 and 65 years of age. Approval was obtained from the Joint Institutional Review Board of Taipei Medical University and all participants signed written informed consent. Patients with schizophrenia were recruited from a psychiatric outpatient clinic, while healthy controls were recruited through online advertisements. Trained psychiatrists conducted a structured interview using the *Structured Clinical Interview for the DSM-5, Clinician Version* (SCID-5-CV) (First, Williams, Karg, & Spitzer, 2016) to screen for mental disorders in all participants. Patients had to meet DSM-5 diagnostic criteria for schizophrenia, have no other current or lifetime mental disorders, and be on a stable antipsychotics dosage for at least 4 weeks. Healthy controls were participants without any history or family history of mental disorders. Participants were excluded if they had epilepsy, intellectual disability, neurocognitive disorder, severe neurological disorder, substance use disorder, severe renal disease, or any other severe medical conditions. Participants were excluded if pregnant, breastfeeding, or undergoing hormonal therapy. No treatment was provided for any participants and patients with schizophrenia continued with regular treatment.

Measures

Childhood trauma exposure

The childhood trauma exposure was assessed using the Taiwanese version of the Childhood Trauma Questionnaire – Short Form (CTQ-SF), a 28-item self-report tool consisting of 25 clinical items and three validity items, measuring five types of childhood adversities (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) (Bernstein et al., 2003; Cheng, Chen, Chou, Kuo, & Huang, 2018). Participants rated each of the 25 clinical items on a five-point Likert scale (1 =

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never true, 5 = very often true), with the total score for the clinical items ranging from 25 to 125. The three validity items were not included in the total score calculation, as they serve a different purpose in assessing the questionnaire's reliability. Participants were interviewed to clarify their childhood trauma exposure for cross-validation.

Social functioning

The social functioning was measured using the Social Functioning Scale (SFS), covering seven domains (social withdrawal, interpersonal behavior, social activities, recreation, independence-performance, independence-competence, employment) (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). The SFS identifies strengths/weaknesses, presence/absence of social skills, and competence/performance. The questionnaire consisted of 79 items with varying response formats and all items were assigned to the seven domains. A higher score indicated more competence in the corresponding social behavior or higher frequency of the social behavior.

Plasma oxytocin levels

To improve accuracy of oxytocin measurement, steps were taken to standardize and validate the process (Tabak et al., 2023). Given the difficulties in measuring central oxytocin levels, plasma oxytocin levels were used as a proxy for oxytocin function (Valstad et al., 2017). Blood samples were collected in the morning and participants were required to provide two samples on different days. Participants were instructed to avoid tobacco, caffeine, and analgesics the day before blood was collected. Blood was collected within days 21–25 of the menstrual cycle of female participants to reduce within-group variation (Engel, Klusmann, Ditzen, Knaevelsrud, & Schumacher, 2019). In total, 20 ml of venous blood was collected, centrifuged at 3000 rpm for 15 min at 4 °C, and cold plasma was stored at −80 °C in multiple 1 ml aliquots. Solid-phase extraction was performed on each plasma sample using Sep-Pak C18 columns before analysis. Plasma oxytocin levels were determined using a commercial enzyme immunosorbent assay (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA). The mean of two plasma oxytocin levels collected on two different days was used for analysis with inter- and intra-assay coefficients of variation less than 10%. No significant cross-reactivity or interference between oxytocin and analogs was observed.

Oxytocin receptor polymorphism

DNA was extracted from peripheral blood mononuclear cells using the Easy Blood Genomic DNA Purification Kit (GeneMark, Atlanta, GA, USA). Genotyping was done using iPLEX Gold chemistry (Agena Biosciences, San Diego, CA, USA) on the MassARRAY Analyzer 4 system. Genotype calls were made using Typer 4.0 (Agena Biosciences), and quality was evaluated by testing Hardy–Weinberg equilibrium proportions and Mendelian inheritance consistency. SNPs were selected based on their minor allele frequency (MAF) greater than 5% in the Chinese population according to the 1000 Genomes Project and the Ensembl project, as well as their involvement in psychiatric phenotypes and childhood trauma. Among all the tag SNPs in the OXTR gene, located on human chromosome 3p25.3, ten SNPs were selected for this study, including those associated with schizophrenia (rs2254298 [Cristóbal-Narváez et al., 2017; Montag et al., 2012], rs237885 [Montag et al., 2013], rs237887 [Souza et al., 2010], rs237899 [Souza et al., 2010], rs53576 [Giralt-López et al., 2020; Nakata et al., 2021], rs9840864 [Watanabe et al., 2012]); prosocial behavior (rs13316193 [Liu, Shang, Pei, & Su, 2021], rs7632287 [Walum et al., 2012]); and childhood trauma (rs1042778 [Julian et al., 2019], rs237895 [Toepfer et al., 2019]). Detailed information, including alleles, chromosome position, functional consequence, MAF, and clinical significance for each selected SNP, is summarized in online Supplementary material 1. The Additive Genetic Risk Scores (AGRS) were calculated by summing the risk alleles, with scores ranging from 0 to 20 (refer to online Supplementary material 2). Pairwise linkage disequilibrium (LD) was analyzed using Haploview version 4.2 (Barrett, Fry, Maller, & Daly, 2005).

Covariates

The present study analyzed demographic factors, lifestyle and health factors, and psychopathology as covariates. Included were demographic factors such as gender, age, and education, and baseline psychopathology was measured using the Positive and Negative Syndrome Scale (PANSS) administered by trained psychiatrists (Kay, Fiszbein, & Opler, 1987). The daily doses of antipsychotics were calculated as chlorpromazine equivalent (Leucht et al., 2015) for analysis.

Statistical analyses

Data were analyzed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA). The normality of distributions was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since the distribution of plasma oxytocin levels was not normally distributed, we performed a logarithmic transformation to achieve a normal distribution for subsequent analyses. Demographic data and clinical measures were compared between groups using the t test or χ^2 test as appropriate. Pearson's χ^2 test was used to examine the odds ratios (OR) between groups for allelic and genotypic distributions. Interaction between the gene and environment was tested using ANOVA. Pearson's correlation coefficients were used to calculate the effect of childhood trauma, plasma oxytocin levels, and AGRS of OXTR SNPs on social functioning for each group. Hierarchical regression analysis was used to investigate unique variance in social functioning explained by childhood trauma, plasma oxytocin levels, and AGRS of OXTR SNPs, beyond that explained by covariates such as sex, age, years of education, psychopathology, and antipsychotic dose. The potential effects of plasma oxytocin levels as a mediator were determined using moderated mediation models (model 7) (see online Supplementary material 3). In this model, childhood trauma served as the independent variable, social functioning as the dependent variable, and plasma oxytocin levels as the mediator. The AGRS of OXTR SNPs acted as a moderator in the relationship between childhood trauma and plasma oxytocin levels. The analysis also controlled for covariates such as sex, age, years of education, psychopathology, and antipsychotic dose. The model was validated using the PROCESS macro v4.1 (Hayes, 2022) in SPSS, and was corrected for bias with 5000 resampled data sets. All reported probability values are based on a two-tailed test, with statistical significance set at $p < 0.05$. As the issue of multiple comparisons was present in this study, Bonferroni correction was applied to adjust the significance level.

Results

Participant characteristics

Table 1 shows the demographic characteristics of 382 patients with schizophrenia and 178 healthy controls. Patients with

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Table 1. Demographic characteristics of patients with schizophrenia and healthy controls

	Schizophrenia $n = 382$		Healthy controls $n = 178$		Significance	
	M	S.D.	*M*	S.D.	t/χ^2	*P*
Age	43.87	9.51	42.84	10.07	1.171	0.242
Sex (male/female)	220/162		92/86		1.716	0.191
Education years	10.31	2.93	11.21	3.30	−3.109	0.002
Family history of schizophrenia	57	(14.92%)				–
Family history of any mental disorder	132	(34.55%)				–
PANSS						
Total scores	75.98	17.17				–
Positive symptoms	17.95	6.85				–
Negative symptoms	19.96	8.07				–
General psychopathology	33.85	7.56				–
Antipsychotic dose (CPZ equiv. in mg)	389.18	302.30				–
Childhood Trauma Questionnaire						
Total scores	64.75	24.40	44.63	13.42	12.549	<0.001
Physical abuse	14.35	4.98	10.59	3.38	10.470	<0.001
Emotional abuse	13.81	7.54	7.91	3.66	12.463	<0.001
Sexual abuse	7.23	3.55	6.00	1.01	6.217	<0.001
Physical neglect	13.15	5.10	10.00	3.99	7.945	<0.001
Emotional neglect	16.22	6.72	10.16	4.75	12.253	<0.001
Social Functioning Scale						
Total scores	104.43	18.20	178.89	15.81	−46.951	<0.001
Social withdrawal	10.00	1.80	14.27	0.80	−38.859	<0.001
Interpersonal behavior	5.44	1.27	7.99	1.00	−25.693	<0.001
Social activities	12.93	3.63	41.12	7.87	−45.618	<0.001
Recreational activities	16.34	3.04	30.49	4.34	−39.224	<0.001
Independence (performance)	24.33	3.75	37.98	1.01	−66.124	<0.001
Independence (competence)	32.42	4.23	38.12	0.99	−24.899	<0.001
Employment	2.97	1.98	8.92	1.14	−44.876	<0.001
Plasma oxytocin levels (ng/ml)	11.60	3.58	13.48	3.90	−5.448	<0.001
Additive genetic risk scores	5.25	3.91	4.34	3.08	2.734	0.006

schizophrenia had fewer years of education than healthy controls ($t[558] = -3.109$, $p = 0.002$), but there were no significant differences in age and gender between the two groups.

Childhood trauma and social functioning

Patients with schizophrenia had higher scores on the CTQ-SF than healthy controls ($t[558] = 12.549$, $p < 0.001$). All CTQ-SF subscales showed significant differences with higher scores for physical, emotional, and sexual abuse and physical and emotional neglect for patients with schizophrenia. Patients with schizophrenia had worse social functioning in all domains compared to healthy controls according to the SFS, with a significant difference ($t[558] = -46.951$, $p < 0.001$).

Plasma oxytocin and OXTR gene polymorphisms

The plasma oxytocin levels of patients with schizophrenia were lower than healthy controls ($t[558] = -5.448$, $p < 0.001$). Significant differences were observed in genotype frequencies between patients with schizophrenia and healthy controls for seven OXTR SNPs (rs1042778, rs2254298, rs237885, rs237887, rs237895, rs237899, and rs53576), with more rare homozygotes (risk alleles) found in patients (see online Supplementary material 4 for more details on genotype frequencies between the two groups). The AGRS of the OXTR SNPs were higher in patients with schizophrenia than in healthy controls ($t[558] = 2.734$, $p = 0.006$). Binary logistic regression showed that OXTR SNP AGRS significantly predicted status as either schizophrenia or control ($\beta = 0.111$, S.E. = 0.030, Wald = 13.610, df = 1, $p < 0.001$),

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indicating that individuals were 1.118 (95% CI [1.054–1.186]) times more likely to develop schizophrenia per unit increase in AGRS (unstandardized β weight for the constant $\beta = 1.270$, S.E. = 0.628, Wald = 4.086, df = 1, $p = 0.043$). The model explained 6.4% (Nagelkerke R^2) of the total variance and the model correctly classified 69.8% of cases.

Gene–environment correlation

The ANOVA results showed significant differences in childhood trauma levels based on OXTR SNPs genotypes, except for rs7632287, among all participants and in patients with schizophrenia (see Table 2). When looking at healthy controls, differences were only found in OXTR rs1042778, rs13316193, rs237885, rs237895, rs237899, and rs53576. In patients with schizophrenia, an increasing gradient in CTQ-SF scores was observed across genotypes of homozygotes of major alleles, heterozygotes alleles, to homozygotes of minor alleles (risk alleles). These findings suggest evidence for a gene–environment correlation with OXTR SNPs and a history of childhood trauma.

Childhood trauma, social functioning, and oxytocin

Hierarchical regression analysis of predictors of social functioning

Childhood trauma was significantly associated with social functioning in patients with schizophrenia but not in healthy controls. Higher CTQ-SF scores in patients with schizophrenia were linked to lower social functioning (refer to online Supplementary material 5).

A hierarchical regression analysis was conducted to predict social functioning of patients with schizophrenia using four sets of predictor variables in successive steps: childhood trauma (CTQ-SF), plasma oxytocin, AGRS of OXTR SNPs, and demographic variables (sex, age, years of education, antipsychotic dose, and PANSS). The results of the hierarchical regression analysis are presented in Table 3. The results showed that childhood trauma as measured by CTQ-SF scores was a significant predictor of social functioning ($B = -0.661$, $p < 0.001$) accounting for 74.8% of the variation ($R^2 = 0.748$, $p < 0.001$). Plasma oxytocin levels ($B = 2.983$, $p < 0.001$) and AGRS of OXTR SNPs ($B = -5.337$, $p < 0.001$) were also significant predictors, contributing an additional 7.7% ($\Delta R^2 = 0.077$, $p < 0.001$) and 7.3% ($\Delta R^2 = 0.073$, $p < 0.001$) of the explanation of social functioning, respectively. Demographic variables did not contribute to predicting social functioning ($\Delta R^2 = 0.001$, $p = 0.307$).

The mediating effect of plasma oxytocin

The study found that childhood trauma had a significant impact on both plasma oxytocin ($\beta = -0.130$, S.E. = 0.004, $t = -36.923$, $p < 0.001$) and social functioning ($\beta = -0.269$, S.E. = 0.031, $t = -8.724$, $p < 0.001$) in patients with schizophrenia, after controlling for covariates (sex, age, years of education, psychopathology, and antipsychotic dose). Plasma oxytocin levels were also found to have a significant effect on social functioning ($\beta = 3.020$, S.E. = 0.211, $t = 14.334$, $p < 0.001$). The bootstrapped unstandardized indirect effect was significant ($\beta = -0.391$, S.E. = 0.028, 95% CIs [−0.329 to −0.208]) and shown in online Supplementary material 6. The present study showed that the mediation effect of plasma oxytocin accounted for 59.24% of the total effect between childhood trauma and social functioning.

The moderating effect of the OXTR gene polymorphisms

As shown in Fig. 1a, childhood trauma had a significant impact on plasma oxytocin ($\beta = -0.031$, S.E. = 0.007, $t = -4.107$, $p < 0.001$) and the interaction between childhood trauma and AGRS of OXTR SNPs (CTQ-SF × AGRS) also significantly affects plasma oxytocin ($\beta = 0.013$, $t = 16.055$, $p < 0.001$). Figure 1b shows that the gradient for average and high scores of AGRS is steeper, indicating stronger impact of childhood trauma on plasma oxytocin. At lower AGRS scores, the line tends to straighten, diminishing the impact of childhood trauma on plasma oxytocin. However, at higher AGRS scores, the impact increases, with larger decreases in plasma oxytocin with increasing CTQ-SF. Higher risk allele scores amplify the impact of childhood trauma on plasma oxytocin. The conditional indirect effect of childhood trauma on social functioning of patients with schizophrenia was highest at high AGRS scores, reduced at average scores, and further diminished at lower scores. The indirect effect in the presence of the moderator (at the mean level) was 0.098 and within the confidence interval at $p < 0.05$. Results support the hypothesis that AGRS of OXTR SNPs moderate the indirect effect of childhood trauma on social functioning of schizophrenia patients through plasma oxytocin, with an index of 0.038 (95% CI [0.033–0.044]). Moderating effects were observed for all individual OXTR SNP genotypes, except for rs13316193, rs7632287, and rs9840864 (refer to online Supplementary material 7).

Discussion

The present study examines the impact of childhood trauma on social functioning in patients with schizophrenia. In line with the previous study (Hjelseng et al., 2022), patients with schizophrenia who experienced more severe childhood trauma have worse social functioning compared to those with less trauma. However, this relationship was not found in the healthy control group in this study. Hjelseng et al. (2022) also found that both patients in active phase and remission who had experienced childhood trauma had poorer social functioning, indicating that the relationship between childhood trauma and social functioning is more of a trait than a state. While poor social functioning is a diagnostic criterion, not all patients with schizophrenia have childhood trauma, and other factors such as depression, paranoia, and anxious attachment can also affect social functioning (Palmier-Claus et al., 2016). Results suggest a connection between childhood trauma and social functioning, linked by oxytocin. The hierarchical regression analysis showed that plasma oxytocin and OXTR SNPs were contributing factors to changes in social functioning in patients with schizophrenia. The association between childhood trauma and social dysfunction in patients with schizophrenia, but not in healthy controls, suggests unique mechanisms specific to schizophrenia involving brain development, genetics, and neuroendocrine functioning.

Oxytocin is proposed as a candidate neuroendocrine for schizophrenia. The present study found that plasma oxytocin levels were lower in patients with schizophrenia compared to healthy controls. OXTR genotypic distributions and allele frequencies for the targeted SNPs were significant different among patients with schizophrenia and healthy controls. It also found that rare homozygotes of OXTR SNPs (rs1042778, rs2254298, rs237885, rs237887, rs237895, rs237899, and rs53576) were more common in patients with schizophrenia and that the AGRS of OXTR SNPs was higher in patients with schizophrenia. It is also found that AGRS of OXTR SNPs significantly predicted

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Table 2. Effects of interaction between childhood trauma and OXTR SNPs in patients with schizophrenia and healthy controls

	CTQ									Post-hoc Bonferroni		
	(A)		(B)		(C)					(A) *v.* (B)	(A) *v.* (C)	(B) *v.* (C)
OXTR SNPs	*M*	S.D.	*M*	S.D.	*M*	S.D.	*F*	df	*p*	*p*	*p*	*p*
rs1042778	GG		GT		TT							
	(*n* = 220)		(*n* = 128)		(*n* = 34)							
SCZ	59.50	22.30	88.71	19.95	75.48	23.06	44.061	2, 379	<0.001	<0.001	0.002	0.040
	(*n* = 123)		(*n* = 50)		(*n* = 5)							
HC	45.45	13.57	37.92	8.22	31.75	7.50	3.761	2, 175	0.025	0.175	0.126	1.000
	(*n* = 343)		(*n* = 178)		(*n* = 39)							
All	54.59	20.79	79.61	26.87	69.45	26.41	42.089	2, 557	< 0.001	< 0.001	0.001	0.112
rs13316193	TT		TC		CC							
	(*n* = 282)		(*n* = 86)		(*n* = 14)							
SCZ	55.99	20.78	88.23	15.10	97.07	13.29	110.906	2, 379	<0.001	<0.001	<0.001	0.346
	(*n* = 133)		(*n* = 40)		(*n* = 5)							
HC	45.95	14.03	39.57	8.73	38.00	10.12	3.642	2, 175	0.028	0.062	0.367	1.000
	(*n* = 415)		(*n* = 126)		(*n* = 19)							
All	52.61	19.36	76.28	25.14	77.38	30.98	65.039	2, 557	<0.001	<0.001	<0.001	1.000
rs2254298	GG		GA		AA							
	(*n* = 130)		(*n* = 168)		(*n* = 84)							
SCZ	49.15	17.84	64.47	20.86	89.49	17.63	122.815	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 76)		(*n* = 84)		(*n* = 18)							
HC	44.94	13.88	44.22	12.81	44.73	13.96	0.054	2, 175	0.947	1.000	1.000	1.000
	(*n* = 206)		(*n* = 252)		(*n* = 102)							
All	47.57	16.56	58.21	20.93	79.46	25.19	94.074	2, 557	<0.001	<0.001	<0.001	<0.001
rs237885	TT		TG		GG							
	(*n* = 197)		(*n* = 155)		(*n* = 30)							
SCZ	49.26	18.02	78.28	18.39	96.53	13.21	166.190	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 116)		(*n* = 56)		(*n* = 6)							
HC	44.40	12.34	46.64	15.22	30.50	6.12	4.113	2, 175	0.018	0.890	0.038	0.015
	(*n* = 313)		(*n* = 211)		(*n* = 36)							
All	47.46	16.30	68.89	22.47	85.53	27.80	118.372	2, 557	<0.001	<0.001	<0.001	<0.001

(*Continued*)

Table 2. (*Continued.*)

	CTQ									Post-hoc Bonferroni		
	(A)		(B)		(C)					(A) *v.* (B)	(A) *v.* (C)	(B) *v.* (C)
OXTR SNPs	*M*	S.D.	*M*	S.D.	*M*	S.D.	*F*	df	*p*	*p*	*p*	*p*
rs237887	GG		GA		AA							
	(*n* = 127)		(*n* = 186)		(*n* = 69)							
SCZ	49.17	20.50	68.07	22.48	84.48	17.39	67.758	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 89)		(*n* = 71)		(*n* = 18)							
HC	46.10	13.63	43.94	13.55	40.11	11.11	1.660	2, 175	0.193	0.936	0.254	0.837
	(*n* = 216)		(*n* = 257)		(*n* = 87)							
All	47.91	18.01	61.40	23.07	75.30	24.30	55.248	2, 557	<0.001	<0.001	<0.001	<0.001
rs237895	TT		TC		CC							
	(*n* = 189)		(*n* = 160)		(*n* = 33)							
SCZ	49.28	18.87	76.41	17.94	96.88	15.35	152.388	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 116)		(*n* = 49)		(*n* = 13)							
HC	46.86	14.31	40.31	8.88	41.08	15.49	4.801	2, 175	0.009	0.012	0.402	1.000
	(*n* = 305)		(*n* = 209)		(*n* = 46)							
All	48.36	17.30	67.94	22.34	81.11	29.61	87.404	2, 557	<0.001	<0.001	<0.001	<0.001
rs237899	GG		GA		AA							
	(*n* = 187)		(*n* = 151)		(*n* = 44)							
SCZ	48.95	18.25	75.62	18.23	94.61	16.14	159.830	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 111)		(*n* = 56)		(*n* = 11)							
HC	46.92	13.47	40.50	11.84	42.64	16.23	4.565	2, 175	0.012	0.010	0.914	1.000
	(*n* = 298)		(*n* = 207)		(*n* = 55)							
All	48.19	16.64	66.12	22.89	84.22	26.39	97.861	2, 557	<0.001	<0.001	<0.001	<0.001
rs53576	AA		AG		GG							
	(*n* = 160)		(*n* = 155)		(*n* = 67)							
SCZ	49.19	17.65	76.68	12.18	94.84	17.31	238.807	2, 379	<0.001	<0.001	<0.001	<0.001
	(*n* = 90)		(*n* = 75)		(*n* = 13)							
HC	47.25	14.66	40.39	7.94	37.11	6.45	8.674	2, 175	<0.001	0.035	0.001	1.000
	(*n* = 250)		(*n* = 230)		(*n* = 80)							
All	48.47	16.61	69.04	18.71	78.26	30.23	106.123	2, 557	<0.001	<0.001	<0.001	0.002
rs7632287	GG		GA		AA							
	(*n* = 346)		(*n* = 33)		(*n* = 3)							

SCZ	64.53	24.33	77.50	4.95	84.33	36.20	1.257	2, 379	0.286	1.000	0.486	1.000
	(n = 150)		(n = 27)		(n = 1)							
HC	44.84	13.48	36.00	0.00	35.50	10.61	0.896	2, 175	0.410	1.000	0.988	1.000
	(n = 496)		(n = 60)		(n = 4)							
All	58.31	23.36	56.75	24.13	64.80	37.40	0.198	2, 557	0.820	1.000	1.000	1.000
rs9840864	CC		CG		GG							
	(n = 213)		(n = 141)		(n = 28)							
SCZ	51.31	18.42	78.96	19.29	95.50	18.56	132.834	2, 379	<0.001	<0.001	<0.001	<0.001
	(n = 108)		(n = 56)		(n = 14)							
HC	45.42	13.67	43.34	12.50	43.79	15.51	0.469	2, 175	0.626	1.000	1.000	1.000
	(n = 321)		(n = 197)		(n = 42)							
All	49.32	17.17	68.83	23.86	78.26	30.20	73.775	2, 557	<0.001	<0.001	<0.001	0.025

status as patients with schizophrenia or healthy controls after controlled for age, sex, and years of education. The results suggest that there is oxytocinergic dysfunction in schizophrenia, both at the genomic (OXTR SNPs) and molecular (plasma oxytocin) levels. These findings are preliminary but provide evidence for further research.

The present study goes beyond prior theoretical discussions by examining the implications of genetic variants in the OXTR gene on linking childhood trauma to social functioning in schizophrenia. In line with Woolway et al. (2022), who examined the polygenic risk of schizophrenia and childhood adversities, we found evidence of a gene–environment correlation between OXTR SNPs and childhood trauma in schizophrenia. This was indicated by significant differences in CTQ-SF scores across all OXTR SNPs genotypes, except for rs7632287, with an increasing gradient of childhood trauma across genotypes of homozygotes of major alleles to homozygotes of risk alleles. This suggests that childhood trauma is another factor contributing to oxytocin homeostasis in patients with schizophrenia. It is also important to consider the possible LD among the studied SNPs. Although our online Supplementary materials do not show significant LD relationships among them, it is possible that other unidentified SNPs on the OXTR gene could have crucial roles in the association between childhood trauma and social functioning in schizophrenia.

The present study found that the effect of childhood trauma on social functioning in schizophrenia was mediated by plasma oxytocin and moderated by OXTR SNPs. A higher number of OXTR risk alleles increases the impact of childhood trauma on plasma oxytocin, except for SNPs rs13316193, rs7632287, and rs9840864, which have no significant frequency differences between schizophrenia patients and healthy controls. It is believed that childhood trauma may alter the genetic distributions in schizophrenia and interfere with the oxytocin system, causing social dysfunction. The molecular mechanisms underlying OXTR transcription and regulation of protein expression are also worth considering in this context. OXTR gene transcription is a complex process governed by the interplay of multiple transcription factors that bind to specific regulatory elements in the gene's promoter region (Gimpl & Fahrenholz, 2001). These transcription factors modulate gene expression by recruiting co-activators and co-repressors, which, in turn, can influence chromatin remodeling and accessibility to the transcriptional machinery. Additionally, studies have shown that epigenetic modifications, such as DNA methylation and histone acetylation, can influence OXTR expression and function. For instance, hypermethylation of the OXTR promoter region has been associated with reduced OXTR expression (Gregory et al., 2009). Furthermore, post-transcriptional regulation of OXTR includes processes such as alternative splicing, mRNA stability, and translation efficiency (Mizumoto, Kimura, & Ivell, 1997). Certain OXTR SNPs have been found to affect receptor expression and function, such as the volume of the amygdala (Furman, Chen, & Gotlib, 2011; Inoue et al., 2010), potentially contributing to the observed differences in oxytocin levels and social functioning in schizophrenia.

Childhood trauma may interact with OXTR gene polymorphisms, potentially leading to alterations in oxytocin regulation, reduced social skills, and increased risk of schizophrenia and social dysfunction. These changes might occur through mechanisms such as modification in brain development, alterations in stress response, and changes in social cognition and social skills. Importantly, these interactions between childhood trauma and

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Table 3. Hierarchical regression analysis of predictors of social functioning in patients with schizophrenia

	R	R^2	ΔR^2	p	B	S.E. B	β	t	p
Model 1	0.886	0.748		<0.001					
CTQ-SF					−0.661	0.018	−0.886	−37.188	<0.001
Model 2	0.928	0.861	0.077	<0.001					
CTQ-SF					−0.275	0.030	−0.368	−9.083	<0.001
Plasma oxytocin					2.983	0.206	0.587	14.494	<0.001
Model 3	0.967	0.935	0.073	<0.001					
CTQ-SF					0.206	0.031	0.277	6.590	<0.001
Plasma oxytocin					1.366	0.162	0.269	8.425	<0.001
Additive genetic risk scores					−5.337	0.260	−0.976	−20.541	<0.001
Model 4	0.967	0.936	0.001	0.307					
CTQ-SF					0.206	0.031	0.277	6.580	<0.001
Plasma oxytocin					1.358	0.166	0.267	8.190	<0.001
Additive genetic risk scores					−5.336	0.260	−0.976	−20.503	<0.001
Sex					−0.835	0.485	−0.023	−1.721	0.086
Age					−0.035	0.025	−0.018	−1.392	0.165
Education years					−0.015	0.082	−0.002	−0.183	0.855
Antipsychotic dose					0.001	0.001	0.011	0.856	0.392
PANSS					−0.007	0.014	−0.006	−0.470	0.638

genetic factors can lead to changes in gene function, potentially through epigenetic modifications, that can influence the regulation of oxytocin and contribute to the observed outcomes. For instance, it has been reported that experiences of trauma can lead to epigenetic changes, such as DNA methylation, which can affect the expression of genes like OXTR. The present study found associations between childhood trauma and OXTR genetic variations in both patients with schizophrenia and healthy individuals. However, the associations of childhood trauma with low plasma oxytocin levels and social dysfunction were only observed in patients with schizophrenia. This disparity may be explained by the difference in the average number of risk alleles, with healthy controls having fewer risk alleles than patients with schizophrenia. The impact of trauma on plasma oxytocin was lower with fewer risk alleles (1.64 risk alleles), explaining why not everyone with childhood trauma has low plasma oxytocin and poor social functioning. To the best of our knowledge, studies specifically examining the correlations of childhood trauma with OXTR gene in social functioning of patients with schizophrenia are limited. The present study advances our understanding of schizophrenia, the influence of childhood trauma, and the implications of oxytocinergic dysfunction.

Limitations

The present study should be interpreted in the consideration of several limitations. While the CTQ-SF is a well-established and reliable tool for measuring childhood trauma, including among patients with schizophrenia (Cay, Chouinard, Hall, & Shinn, 2022), the retrospective nature of the questionnaire has its limitations in terms of recall bias and underreporting (Baldwin, Reuben, Newbury, & Danese, 2019). It's worth noting that there's a discrepancy in the literature regarding the agreement between retrospective and prospective reports of childhood trauma experiences. Some studies indicate moderate agreement between these types reports of childhood trauma experiences (Reuben et al., 2016), while others suggest that retrospective and prospective measures of childhood trauma may identify different groups of individuals, potentially leading to different risk pathways to mental illness (Baldwin et al., 2019). These differences underscore the importance of recognizing these measurement differences when conducting research into childhood trauma and developing interventions. Therefore, caution should be exercised when interpreting the findings from our study that used a retrospective measure. Future studies could benefit from using a prospective design and multiple informants to mitigate these concerns.

Previous studies have identified a dose–response relationship between the number and severity of trauma exposures and functional outcomes. In an effort to address these complexities, we conducted additional analyses examining the association between the number of types of childhood trauma and OXTR SNPs, as well as their moderated mediation effect on social functioning in schizophrenia. In this analysis, any scores exceeding the moderate exposure cut-off point on each subscale of the CTQ-SF (physical abuse: ⩾10; emotional abuse: ⩾13; sexual abuse: ⩾8; physical neglect: ⩾10; emotional neglect: ⩾15) were classified as indicative of exposure to childhood trauma (Bernstein & Fink, 1998). The results reveal intricate relationships between the number of trauma types, OXTR genetic variations, plasma oxytocin levels, and social functioning. The majority of the risk alleles of OXTR SNPs tested in our study were indeed positively associated with a history of specific childhood trauma, as detailed in online Supplementary material 8. Interestingly, the direct effect of the number of trauma types on social functioning was not significant in the moderated mediation model, as detailed in online Supplementary material 9. This suggests that the relationship between the number of types of

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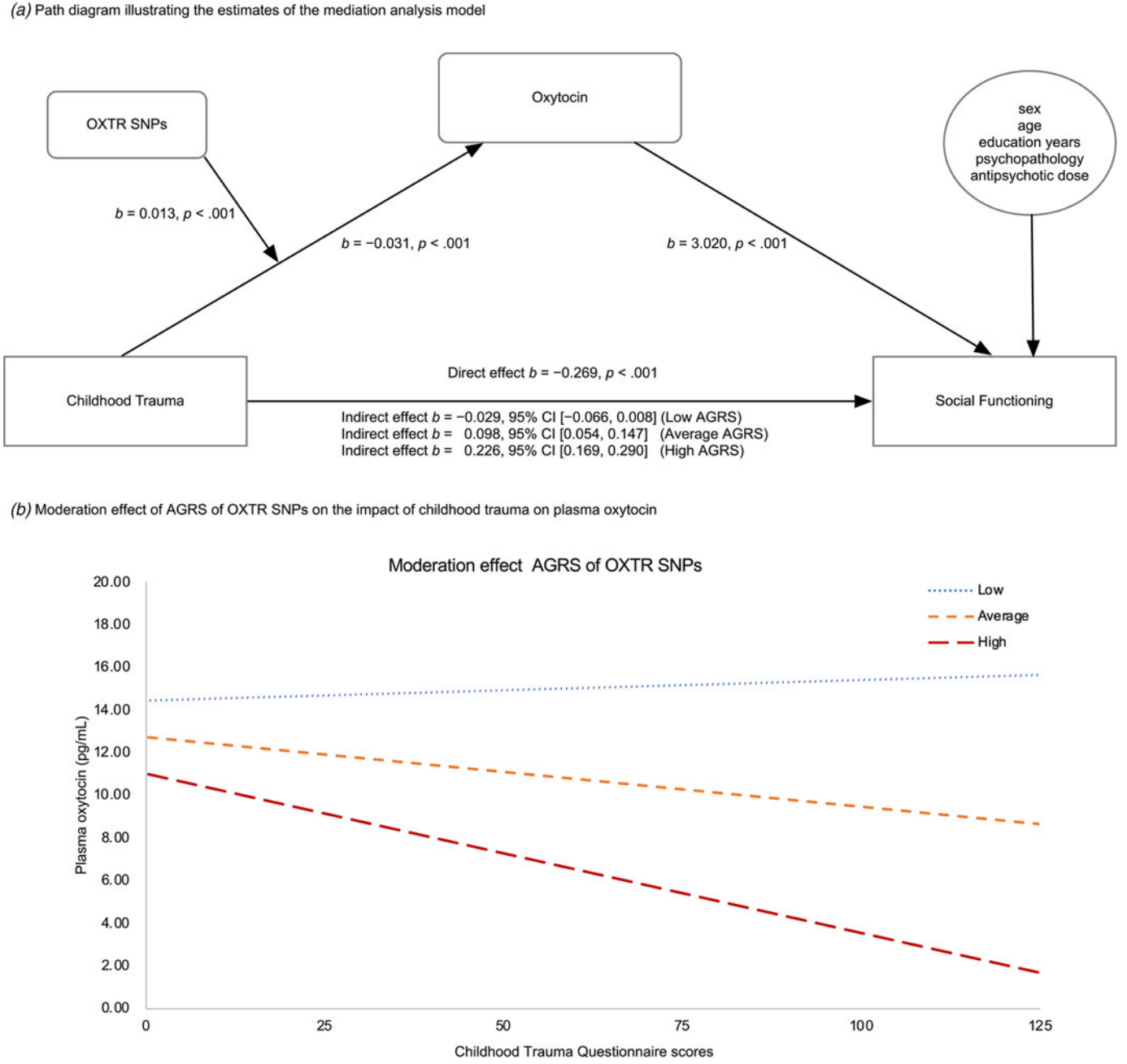

Figure 1. Moderated mediation effect of plasma oxytocin and OXTR SNPs on the relationship between childhood trauma and social functioning in patients with schizophrenia: (a) path diagram illustrating the estimates of the mediation analysis model and (b) moderation effect of AGRS of OXTR SNPs.

childhood trauma and social functioning may be more complex. Our study failed to provide the exact number of the childhood trauma experiences, and the way we quantified the number of trauma types as having the same weight might not have adequately captured the full impact of these experiences. This highlights the potential value of adopting more nuanced measures for cumulative childhood trauma that can capture the severity and frequency of different types of trauma.

Using plasma oxytocin as a proxy for central oxytocinergic function is not ideal, but obtaining cerebrospinal fluid for oxytocin measurement is impractical. The present study attempted to control for confounding factors in plasma oxytocin measurement, including minimizing potential substance use influences by excluding participants with a substance use disorder and instructing participants to avoid tobacco, caffeine, and analgesics prior to blood collection. However, without direct measures of substance use (e.g. urine or blood tests), the potential influence of substance use cannot be completely ruled out. Moreover, there may be other unmeasured factors, such as stress and inflammation, that could affect the results.

The cross-sectional design limits the conclusions about the causality between childhood trauma, OXTR SNPs, plasma oxytocin, and social functioning. It is not possible to determine if OXTR SNPs and lower plasma oxytocin are a result of illness or play a causal role in the development of schizophrenia. The present study found differences in the interactions between childhood trauma and genotypic distribution of OXTR between schizophrenia patients and healthy controls, such as interactions between childhood trauma and OXTR SNPs rs2254298, rs237887, rs9840864, which were only present in schizophrenia patients and not in healthy controls. However, it is not possible to conclude whether these differences are due to genetic variations in schizophrenia, the impact of childhood trauma, or a shared genetics pathway in schizophrenia and childhood trauma. Another limitation to consider is the relatively small sample size for certain OXTR SNPs with low minor allele frequencies. This might introduce increased statistical uncertainty, which could affect the robustness of our findings. Future studies with larger sample sizes would provide greater power to detect associations, especially for variants with low minor allele frequencies, and would help to further validate these preliminary findings. In our study, we have identified several SNPs in OXTR that may have significant roles in the observed associations. It is important to further investigate the functional consequences of these SNPs, including their potential impact on gene expression, protein structure, or receptor function. For example, some OXTR SNPs may alter the affinity of transcription factors to the promoter region, thus influencing the gene expression. Others in exon regions that were not examined in the present study, may lead to changes in the amino acid sequence of the oxytocin receptor, affecting its structure and function, or alter the efficiency of receptor signaling pathways. Additionally, examining the possible LD among the SNPs could provide insights into the underlying genetic architecture of OXTR and its role in the disease. Longitudinal cohort studies with baseline OXTR genotyping and plasma oxytocin levels that predate exposure to childhood trauma would be ideal for determining causal relationships, but this type of study was not feasible in the present study due to logistical difficulties.

Conclusions

Childhood trauma exposure has been linked to poor social functioning in patients with schizophrenia, and that oxytocin and its receptor gene may play a role in mediating this relationship. The present study indicated that there was a significant moderated mediation effect, with plasma oxytocin and the OXTR SNPs partially mediating the impact of childhood trauma on social functioning in patients with schizophrenia. These results indicate that oxytocin and its receptor gene may be promising targets for interventions aimed at improving social functioning in patients with a history of childhood trauma and schizophrenia. Further research is needed to fully understand the mechanisms underlying these effects and to determine the potential of oxytocin-based interventions for this population.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172300274X

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