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The *OXT rs6133010* variant modulates susceptibility to psychiatric symptoms during withdrawal in patients with alcohol dependence

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Abstract

Background Alcohol dependence (AD) confers susceptibility to distressing withdrawal symptoms that often lead to relapse. While neuroadaptation during withdrawal influences symptoms, the genetic factors behind it have not been thoroughly investigated. We utilized propensity score matching and investigated connections between AD, *OXT rs6133010*, and withdrawal symptoms to address confounding variables. By elucidating the *OXT rs6133010*-AD interaction, we aim to gain insights into alcohol withdrawal variability and contribute to personalized treatment approaches.

Methods A cross-sectional study design was employed involving a total of 389 AD patients and 184 healthy controls who were genotyped for the *OXT rs6133010* polymorphism. Psychiatric symptoms were evaluated using standardized scales during early withdrawal. Propensity score matching mitigated age and education differences.

Results A two-way ANOVA demonstrated a significant AD x *OXT rs6133010* interaction effect on hostility and anxiety. Further analysis revealed that the regulatory impact of *OXT rs6133010* was exclusively in AD patients. Specifically, AD patients with the AA homozygote showed robust protection against hostility and anxiety. Path analysis unveiled the underlying mechanism of OXT symptom regulation.

Conclusion This study presents novel evidence that *OXT rs6133010* specifically modulates psychiatric symptoms in AD. The G allele may heighten hostility and anxiety vulnerability during alcohol withdrawal. These findings emphasize

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considering environmental factors when studying and utilizing oxytocin therapeutically. Additionally, OXT may not directly act as an anxiolytic but instead regulates anxiety by modulating hostility.

Keywords Alcohol dependence, Oxytocin, Withdrawal symptoms

Introduction

Alcohol misuse and dependence are significant contributors to the global disease burden and leading causes of preventable death worldwide. According to Substance Abuse and Mental Health Services Administration's (SAMHSA) 2020 data, approximately 24.0% of adults in the United Kingdom reported participating in binge drinking in the previous month. Alcohol Dependence (AD) is a chronic and relapsing brain disorder attributed to excessive drinking, exacerbating various medical and psychiatric issues and ultimately reducing the lifespan of those affected [1]. The World Health Organization reports that AD is globally prevalent in 29.1% of the population during their lifetime, with notable health, social, and economic effects [2]. One noteworthy feature of alcohol use disorder (AD) is its elevated relapse rate, which can reach up to 60% within a year of abstinence [3]. The available literature proposes that the development of psychological and psychiatric symptoms during alcohol withdrawal and early abstinence plays a role in the increased relapse rates [4, 5]. Patients often turn to drinking again to relieve or avoid these distressing symptoms, thus perpetuating a cycle of dependence [6]. However, there is considerable individual variation in the type, severity and duration of withdrawal symptoms. Only a limited number of studies have investigated the genetic factors that affect neural adaptation processes during withdrawal, which could explain the differences in symptom profiles and the risk of relapse [7]. In the realm of substance addiction research, Volkow and colleagues underscored the difficulties associated with withdrawal from substance addiction owing to genetic predisposition [6, 8]. It is probable that genetic factors interact with the neurobiological effects of alcohol in shaping a person's susceptibility to particular withdrawal symptoms [9, 10]. Variations in symptom profiles may result from polymorphisms that moderate the effect of alcohol on neurological systems associated with emotion, stress response, and reward processing [11, 12]. Knowledge of these factors could aid in devising customized treatment plans that cater to the individual symptom experiences of patients, thereby boosting long-term remission rates.

Oxytocin (OXT) is a crucial neuropeptide that exerts its effects through binding to its unique G protein-coupled receptor, the oxytocin receptor (OXTR). The OXTR is widely distributed throughout the brain, particularly in regions associated with social behavior, emotional regulation, and reward processing, including the nucleus acumens, amygdala, and prefrontal cortex [13]. When oxytocin binds to OXTR, it initiates various intracellular signaling cascades, primarily through Gq/11 proteins, leading to the activation of phospholipase C and subsequent calcium mobilization. This signaling pathway modulates neuronal excitability, synaptic plasticity, and neurotransmitter release, ultimately influencing behavior and emotional responses [14, 15]. Notably, dysfunction in the oxytocinergic system has been linked to psychiatric disorders, including depression, anxiety, and substance use disorders, with increasing evidence supporting its influence on motivation and addiction risk [16, 17]. For instance, the *OXTR rs53576* variant has been linked to altered stress sensitivity and social processing in alcohol-dependent individuals, while the *OXTR rs2254298* has been implicated in anxiety and depression within the context of substance use disorders [18, 19]. Recently, the OXT variant *rs6133010* has been identified as a promising candidate for investigating susceptibility to alcohol dependence. Yang et al.. (2017a) highlighted the role of the *OXT rs6133010* polymorphism in addictive disorders [19]. Studies investigating the relationship between *OXT rs6133010* and emotion recognition propose possible modulation of the severity of withdrawal symptoms, as it interacts with alcohol's impact on neural systems involved in emotion processing. The *OXT rs6133010* genotype significantly impacts emotion cognition, with G carriers demonstrating better accuracy in recognizing angry expressions than AA carriers [20]. Hence, exploring the correlation between the *OXT rs6133010* polymorphism and withdrawal-related psychiatric symptoms may provide valuable insights for the development of new biologically targeted treatments aimed at alleviating AD symptoms.

However, earlier genetic studies on psychiatric disorders related to alcoholism have reported unreliable results, indicating either high variability or weak correlation [21, 22]. This disparity can be attributed to the modest effects of general genetic variance [23] and the intricate nature of psychiatric disorders, which are shaped by both genetic and environmental factors [24]. Genetic factors are complicated by other influences, such as individual characteristics (for example, age and sex) and environmental factors such as culture and education. Thus, accurately determining the genetic impact on psychiatric symptoms is challenging. For example, possessing a higher education level correlates with reduced aggression levels [25], a lower tendency toward emotional distress [26], and enhanced executive function [27]. These factors potentially function as protective

barriers against psychiatric symptoms [28]. To counteract selection bias, genome-wide association studies (GWAS) employ large sample sizes. Nevertheless, GWASs suffer from limited ability to control for potential confounding factors. The nature of GWAS, which is hypothesis-free, presents a challenge in efficiently identifying the most significant confounding factors and how best to address them [29]. Furthermore, the availability of nongenetic data in voluminous datasets limits the scope of GWAS. To overcome these limitations, this study utilized propensity score matching (PSM) to balance the confounding variables between AD patients and healthy controls [30, 31]. In contrast to GWAS, PSM calculates propensity scores for multiple preselected confounders simultaneously and matches groups to minimize the influences of individual characteristics and environmental factors that can interfere with genetic research [32]. This approach targets specific confounders known to obscure genetic effects, thereby enabling the exploration of pure genetic factors' effects on withdrawal symptoms.

Overall, this study investigated the relationship between AD and *OXT rs6133010* in influencing susceptibility to psychological distress during withdrawal. Initially, we mitigated the impact of confounding factors using PSM to more accurately assess the effects of the gene. Subsequently, we examined both the individual effects and the interaction between AD and *OXT rs6133010* on various psychiatric symptoms. Finally, we explored whether the effects of *OXT rs6133010* on different psychiatric symptoms were interconnected or separate and, based on these findings, proposed a potential regulatory mechanism of OXT.

Materials and methods

Participants

This study recruited a total of 400 Chinese male participants from several psychiatric hospitals in northern China. Eleven subjects were excluded due to incomplete data, resulting in a final sample size of 389 male patients. The main inclusion criteria for individuals with AD were as follows: (1) diagnosis of AD by at least two psychiatrists according to DSM-IV criteria, who hold valid psychiatric occupational license; (2) age between 18 and 65 years; and (3) Chinese Han ethnicity and male sex. The exclusion criteria for AD participants were as follows: (1) history of other drug abuse or addiction and (2) presence of severe mental illness in the patient or their first-degree relatives. Prior to admission, all AD patients underwent evaluation by a psychiatrist to ensure the absence of significant depression or anxiety symptoms. All assessments, including the evaluation of withdrawal symptoms, were conducted on the third day after admission during the mandatory withdrawal period.

Two hundred male healthy controls (HCs) were recruited from the same region. The inclusion and exclusion criteria for the healthy control group were identical to those of the AD group, with the exception that individuals in the HCs group had no history of alcohol or other drug dependence. Informed written consent was obtained from all participants, and the study staff received appropriate training. The estimated sample size was calculated using G*Power (V3.1.7). Based on previous research findings, the effect size was set at 0.40 [33]. Other parameters were set as follows: statistical power $(1\text{-}\beta) = 0.95$ and significance level $\alpha = 0.05$. The calculated result indicated that the sample size needed was equal to or greater than 162 participants.

This study was approved by the Institutional Review Board of Inner Mongolian Medical University (YKD2015003). The participants completed questionnaires and submitted blood samples, which were preserved at − 80 °C for DNA extraction. All patients provided written informed consent upon being informed that their blood samples would be subjected to a gene assay.

Experimental procedures

General information

General information was collected through simple questions, which included age, educational years, marital status, and living status. Age and educational years were recorded as numerical values in years. Marital status was converted into a binary variable, with unmarried coded as 0 and married coded as 1. Living status was also converted into a binary variable, with living without family coded as 0 and living with family coded as 1.

Aggression

Aggression was assessed using the Chinese version of the Buss-Perry Aggression Questionnaire (BPAQ). The BPAQ consists of 30 items and measures five different forms of aggression, namely, physical aggression, verbal aggression, anger, hostility, and indirect aggression. Participants rated their agreement with each item on a five-point Likert scale, with higher scores indicating greater levels of aggression. The BPAQ is a widely utilized tool for assessing aggression and has demonstrated high internal consistency reliability, with a Cronbach's α coefficient of 0.80 [34].

Anxiety

Anxiety was assessed using the Zung Self-Rating Anxiety Scale (SAS) [35], a self-report measure consisting of 20 items that evaluate the severity of anxiety symptoms experienced during the past week. Participants rated each item on a 4-point Likert scale, ranging from 1 (none or little of the time) to 4 (most or all of the time). Total

scores on the SAS range from 20 to 80, with higher scores indicating greater severity of anxiety symptoms [36]. The SAS demonstrates high internal consistency reliability, with a Cronbach's α coefficient of 0.82 [37]. In the current study, the SDS showed good internal consistency, with a Cronbach's α = 0.83.

Depression

Depression symptom severity was assessed using the Zung Self-Rating Depression Scale (SDS) [38], a self-report measure consisting of 20 items that evaluate affective and somatic depressive symptoms experienced during the past week. Participants rated each item on a 4-point Likert scale, ranging from 1 (none or little of the time) to 4 (most or all of the time). Total scores on the SDS range from 20 to 80, with higher scores indicating greater severity of depression symptoms [39]. The SDS demonstrates high internal consistency reliability, with a Cronbach's α coefficient of 0.70 [40]. In the current study, the SDS showed good internal consistency, with a Cronbach's α = 0.79.

Genotyping

Peripheral blood samples (5 ml) were collected from all participants, and genomic DNA was extracted using the salting-out method. Genotyping of *OXT rs6133010* was performed using the scalable MassARRAY@ System, which utilizes MALDI-TOF technology. Genotypes were determined using a 5'nuclease fluorescent TaqMan™ primer obtained from Applied Biosystems (Foster City, CA) [19].

Statistical analysis

Statistical analyses were conducted to examine the effects of alcohol dependence diagnosis and *OXT rs6133010* genotype on withdrawal-related psychiatric symptoms. All analyses were conducted using R version 4.2.1. First, Pearson's correlation analysis was performed to identify potential confounding variables that could influence psychiatric symptoms ($p < 0.05$). Propensity score matching (PSM) was then employed to address confounding effects. Logistic regression was used to estimate propensity scores for AD patients and matched healthy controls (HCs), employing 1:1 nearest neighbor matching with a caliper of 0.1 to optimize balance. Matching successfully reduced differences across groups for all confounds (age, education), with nonsignificant t tests confirming group equivalence ($p > 0.05$). Before conducting the main analyses, we tested the Hardy-Weinberg equilibrium for *OXT rs6133010* genotype distribution using chi-square tests.

To minimize Type I error inflation in subsequent analyses, we first conducted a multivariate analysis of variance (MANOVA) with AD and *OXT rs6133010* as independent variables and all psychiatric symptoms (physical aggression, verbal aggression, anger, hostility, anxiety, and depression) as dependent variables. Next, two-way analysis of variance (2 × 2 ANOVA) was conducted to examine the main and interaction effects of AD and *OXT rs6133010* on multiple psychiatric symptoms. Subsequently, a series of multiple regression analyses were performed to investigate specific and interactional effects of AD and *OXT rs6133010* on psychiatric symptoms. AD, *OXT rs6133010*, and the interaction of AD × *OXT rs6133010* were entered as predictors for different psychiatric symptoms. Simple main effects analyses and multiple comparison tests were employed to explore significant interactions and clarify the nature of the effects on symptoms.

Finally, pathway analysis was utilized to explore potential biological mechanisms underlying the effects of the *OXT rs6133010* genotype on psychiatric symptoms during alcohol withdrawal.

Results

Preliminary analysis

First, we conducted a correlation analysis to identify potential confounding variables related to psychiatric symptoms. Table 1 presents the results, showing that age, educational years, marital status, and living status were potential factors influencing psychiatric symptoms.

Table 1 Correlation analysis among demographic variables and psychiatric symptoms

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1.Age	1									
2.Educational Year	-0.33***	1								
3.Marital Status	0.25***	-0.11**	1							
4.Living Status	0.12**	-0.09*	0.36***	1						
5.Physical Aggression	0.04	-0.22***	-0.10*	0.02	1					
6.Verbal Aggression	0.16***	-0.24***	-0.01	0.04	0.65***	1				
7.Anger	0.20***	-0.25***	-0.04	0.11*	0.65***	0.75***	1			
8.Hostility	0.17***	-0.20***	-0.03	0.02	0.60***	0.68***	0.66***	1		
9.Anxiety	0.15***	-0.20***	-0.02	0.02	0.29***	0.32***	0.42***	0.44***	1	
10.Depression	0.02	-0.06	-0.05	-0.03	0.17***	0.14**	0.23***	0.18***	0.17***	1

Note: *$p < 0.05$;**$p < 0.01$;***$p < 0.001$

Specifically, educational years emerged as a significant sociological variable, showing significant correlations with multiple forms of aggression and anxiety ($|r| > 0.20$, $p < 0.001$). Age exhibited significant positive correlations with verbal aggression, anger, hostility, and anxiety ($r > 0.15$, $p < 0.001$). Marital status demonstrated a significant negative correlation with physical aggression (r = -0.10, $p < 0.05$). Furthermore, living status displayed a significant positive correlation with anger ($r = 0.11$, $p < 0.05$). These findings suggest that age, educational years, marital status, and living status should be considered influential factors in the data analysis, given their significant associations with the specific factors assessed in this research study.

Propensity score matching

As presented in Table 2, our study conducted descriptive analyses for two different sample types and examined the differences between the two groups (independent sample t test for continuous variables, chi-square test for categorical variables). The descriptive analyses revealed significant differences between the AD and HCs groups in terms of age ($t = 9.57$, $p < 0.001$) and education level ($t = 6.33$, $p < 0.001$), with the AD group being older and having fewer years of education. To address these confounding factors and isolate the effects of AD and the *OXT rs6133010* genotype, propensity score matching (PSM) was employed. PSM was used to eliminate sample selection bias by matching AD and HCs subjects based on similar demographic characteristics. Following PSM, a total of 312 matched subjects were retained. The matched groups did not exhibit significant differences in terms of age ($t = 0.70$, $p = 0.49$), education ($t = 0.13$, $p = 0.90$), marital status ($\chi^2 = 0.24$, $p = 0.71$), or living status ($\chi^2 = 0.45$, $p = 0.59$; see Table 2).

Descriptive statistics

Out of the 312 participants, 156 were HCs and 156 were AD. The average age of the participants was 37.83 ± 9.36 years, and the average number of educational years was 12.01 ± 2.69 years. Marital status indicated that 96 participants were unmarried (30.77%) and 216 were married (69.23%). Regarding living status, 73 participants were living without family (23.40%), while 239 participants were living with family (76.6%). In the HCs group, the genotype distribution for *OXT rs6133010* was as follows: 124 AA genotypes (79.5%), 29 AG genotypes (18.6%), and 3 GG genotypes (1.9%). These distributions were found to be consistent with Hardy-Weinberg equilibrium ($\chi^2 = 0.70$, $p > 0.05$), indicating that *OXT rs6133010* adhered to Mendel's laws of heredity. Additionally, the minor allele frequency (MAF) of this SNP was determined to be 11.2%, which aligns with the frequencies observed in HapMap and 1000Genomes (HapMap: MAF = 0.04 ~ 0.12). Based on previous research, the AG and GG homozygotes were combined into the G allele and coded as 1, while the AA homozygote was coded as 0. Figure 1 displays the aggression, anxiety, and depression scores (standard normal scores) for the different genotype groups. The MANOVA with two between-subject factors, AD and *OXT rs6133010*, revealed a significant interaction effect on aggression ($F = 2.27$, $p = 0.047$). Based on this result, subsequent 2 × 2 analysis of variance (ANOVA) tests were conducted to explore specific dimensions of aggression in detail.

Aggression

We initially examined the aggression scores for each group. A 2 × 2 analysis of variance (ANOVA) was conducted, with two between-subject factors of AD (AD/HCs) and *OXT rs6133010* (AA/G). Compared to HCs (physical aggression: M_{HCs}= 25.05, SD_{HCs} = 19.30; verbal aggression: M_{HCs} = 25.48, SD_{HCs} = 18.30; Anger: M_{HCs} = 21.77, SD_{HCs} = 18.95; hostility: M_{HCs} = 17.86, SD_{HCs} = 16.17), the AD group exhibited significant main effects on various dimensions of aggression, including physical aggression ($F_{(1,308)} = 20.48$, $p < 0.001$, $\eta^2 p = 0.06$), verbal aggression ($F_{(1,308)} = 14.33$, $p < 0.001$, $\eta^2 p = 0.04$), anger ($F_{(1,308)} = 36.97$, $p < 0.001$, $\eta^2 p = 0.11$) and hostility ($F_{(1,308)} = 30.97$, $p < 0.001$, $\eta^2 p = 0.09$) (Table 3). Notably,

Table 2 Comparison of demographic variables before and after propensity score matching

Covariates	Before PSM			After PSM		
	HCs (*n* = 184)	AD (*n* = 389)	χ^2 / t	HCs (*n* = 156)	AD (*n* = 156)	χ^2 / t
Age	35.63 ± 9.87	43.72 ± 9.24	-9.57***	37.46 ± 9.58	38.20 ± 9.15	0.70
Educational Year	12.35 ± 2.52	10.80 ± 2.85	6.33***	11.99 ± 2.49	12.03 ± 2.89	0.13
Marital Status			3.41			0.24
unmarried	63(34.2%)	104(26.7%)		46(29.5%)	50(32.1%)	
married	121(65.8%)	285(73.3%)		110(70.5%)	106(67.9%)	
Living Status			2.90			0.45
Living without family	48(26.1%)	77(19.8%)		34(21.8%)	39(25.0%)	
Living with family	136(73.9%)	312(80.2%)		122(78.2%)	117(75.0%)	

Note: HCs: healthy controls; AD: alcohol dependence; *$p < 0.05$;**$p < 0.01$;***$p < 0.001$

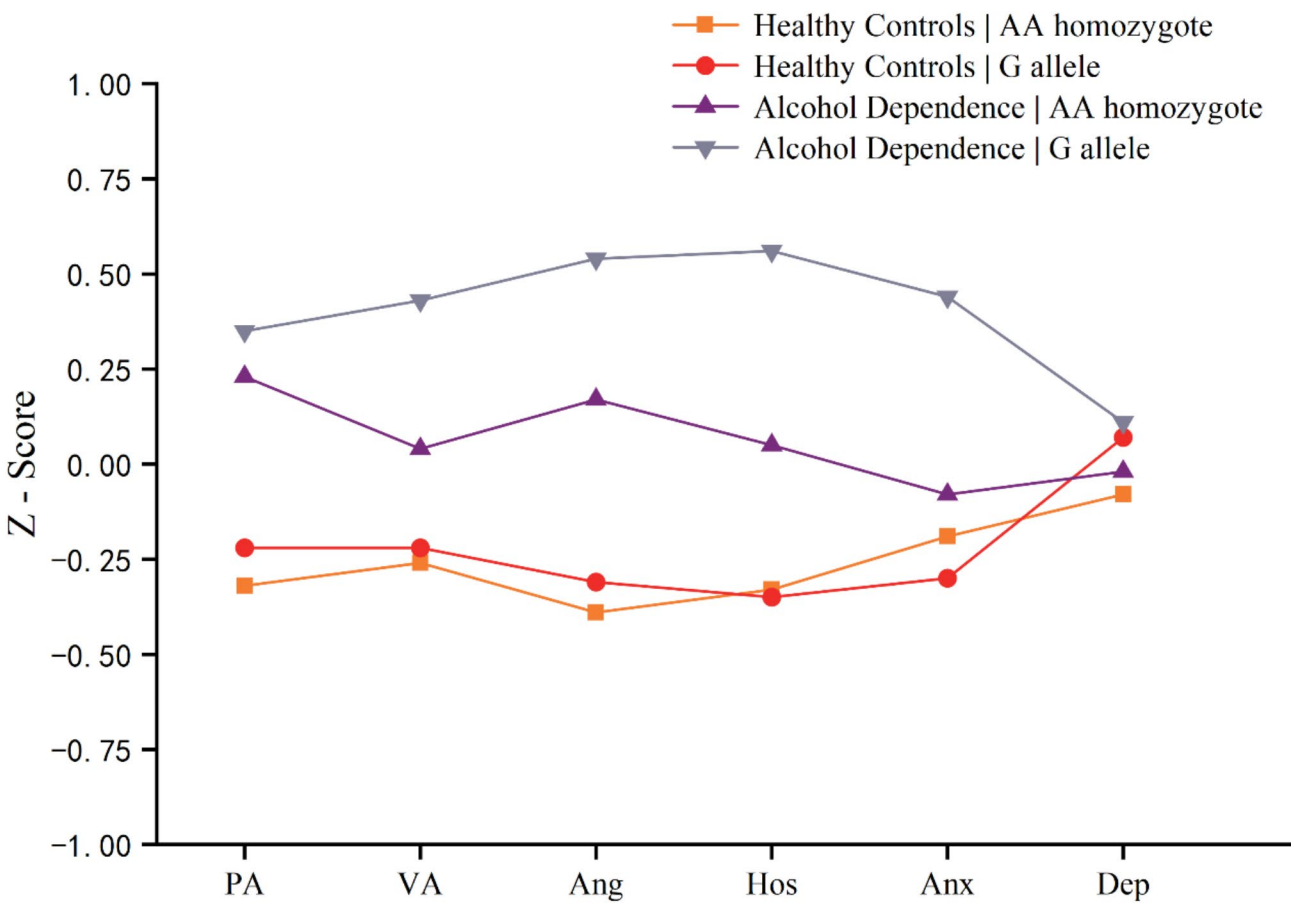

Fig. 1 Aggression ratings and mood scores across groups categorized by AD and *OXT* rs6133010 genotype
Note: Z-scores for physical aggression (PA), verbal aggression (VA), anger (Ang), hostility (Hos), anxiety (Anx), and depression (Dep) for the four subgroups. Higher Z-scores indicate greater severity of symptoms

Table 3 Two-way ANOVA results for aggression dimensions by alcohol dependence and *OXT rs6133010* genotype

Parameter	Factor	SS	df	MS	F	*p*	η^2p
Physical Aggression	AD	18.79	1	18.79	20.48	< 0.001	0.06
	Rs6133010	0.87	1	0.87	0.95	0.33	0.003
	Interaction	0.002	1	0.002	0.01	0.96	< 0.001
	Residual	282.51	308	0.92			
Verbal Aggression	AD	13.26	1	13.26	14.33	< 0.001	0.04
	Rs6133010	3.19	1	3.19	3.44	0.06	0.01
	Interaction	1.55	1	1.55	1.67	0.20	0.005
	Residual	284.99	308	0.93			
Anger	AD	31.33	1	31.33	36.97	< 0.001	0.11
	Rs6133010	2.93	1	2.93	3.46	0.06	0.01
	Interaction	1.34	1	1.34	1.59	0.21	0.005
	Residual	260.98	308	0.85			
Hostility	AD	26.70	1	26.70	30.97	< 0.001	0.09
	Rs6133010	3.16	1	3.16	3.67	0.06	0.01
	Interaction	5.11	1	5.11	5.93	0.02	0.02
	Residual	265.46	308	0.86			

Note: AD: alcohol dependence; Interaction: AD × *rs6133010*; *SS*: Sum of Squares; *df*: Degrees of Freedom; *MS*: Mean Square; *F*: F-statistic; η^2p: Partial Eta Squared. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

when *OXT rs6133010* was included in the analysis, the interaction of AD × *OXT rs6133010* only showed a significant effect on hostility ($F_{(1,308)} = 5.93$, $p < 0.05$, $\eta^2 p$ = 0.02), while it did not affect physical aggression, verbal aggression, or anger (Table 3). To validate the interaction effects of AD and *OXT rs6133010* on hostility, we conducted a multiple regression analysis. In this analysis, OXT rs6133010 and the interaction of AD × *OXT rs6133010* were entered as predictors of hostility. The results revealed that the AD × *OXT rs6133010* interaction ($\beta = 0.26$, $t = 2.43$, $p < 0.05$) accounted for a significant portion of the variance in hostility. The partial correlation value of 0.137 indicated that approximately 1.87% of the variance in hostility could be explained by the AD × *OXT rs6133010* interaction. Hence, our findings suggest that the interaction between AD and OXT rs6133010 has a significant effect on hostility but not on other dimensions of aggression.

Subsequently, we conducted simple effects analysis and multiple comparisons to examine the robustness of the interaction and investigate the specific forms of the G × E interaction. The results of the simple effects analysis revealed a significant effect of AD on hostility across genotypes, with a larger effect size observed in G allele carriers (AA homozygote carriers: $F_{(1,308)} = 7.09$, $p = 0.01$, $\eta^2 p$ = 0.02; G allele carriers: $F_{(1,308)} = 24.45$, $p < 0.001$, $\eta^2 p$ = 0.07). OXT rs6133010 exhibited a significant simple effect on hostility only in the context of AD ($F_{(1,308)} = 11.89$, $p < 0.001$, $\eta^2 p$ = 0.04) and not in the healthy state ($F_{(1,308)} = 0.11$, $p = 0.74$, $\eta^2 p$ < 0.01). The results of multiple comparisons were consistent with the simple effect analysis, showing that AD patients displayed higher levels of hostility in both genotype subgroups than HCs (AA homozygote carriers: $t = 2.66$, $p < 0.01$; G allele carriers: $t = 4.94$, $p < 0.001$). In the case of *OXT rs6133010*, among AD individuals, there was a significant simple effect, indicating that G allele carriers ($M = 34.24$, $SD = 18.80$) exhibited higher levels of hostility than AA homozygote carriers ($M = 24.84$, $SD = 15.84$) ($t = 3.45$, $p < 0.001$) (see Fig. 2). Conversely, in the HCs group, there were no differences in hostility scores among different gene subgroups (t = -0.34, $p = 0.74$). Overall, our findings demonstrate that the effect of OXT rs6133010 on hostility exists exclusively in the context of AD, rather than during the healthy state. This suggests that the interaction between AD and *OXT rs6133010* aligns with the diathesis-stress model.

Mood disorders

Regarding mood disorders such as anxiety and depression, our findings indicate that AD had a significant main effect on anxiety ($F_{(1,308)} = 12.16$, $p < 0.01$, $\eta^2 p$ = 0.04) but not on depression ($F_{(1,308)} = 0.13$, $p = 0.72$, $\eta^2 p$ < 0.001) (Table 4). Furthermore, we observed a significant interaction between AD and *OXT rs6133010* on anxiety ($F_{(1,308)} = 6.44$, $p < 0.05$, $\eta^2 p$ = 0.02), while no significant interaction was found for depression ($F_{(1,308)} = 0.02$, $p = 0.89$, $\eta^2 p$ < 0.001). The results of the multiple regression analyses were consistent with those of the two-way ANOVA. The interaction term, AD × *OXT rs6133010*, accounted for a significant portion of the variance in anxiety ($\beta = 0.28$, $t = 2.54$, $p < 0.05$). The partial correlation value of 0.143 indicates that approximately 2.04% of the variance in anxiety can be explained by the AD × *OXT rs6133010* interaction.

Additionally, we conducted simple effects analysis and multiple comparisons to explore anxiety scores in relation to G×E interactions. The simple effects analysis revealed a significant simple effect of AD on anxiety in G allele carriers ($F_{(1,308)} = 13.87$, $p < 0.001$, $\eta^2 p$ = 0.04) but not in AA homozygote carriers ($F_{(1,308)} = 0.65$, $p = 0.42$, $\eta^2 p$ < 0.01). Moreover, the simple main effect

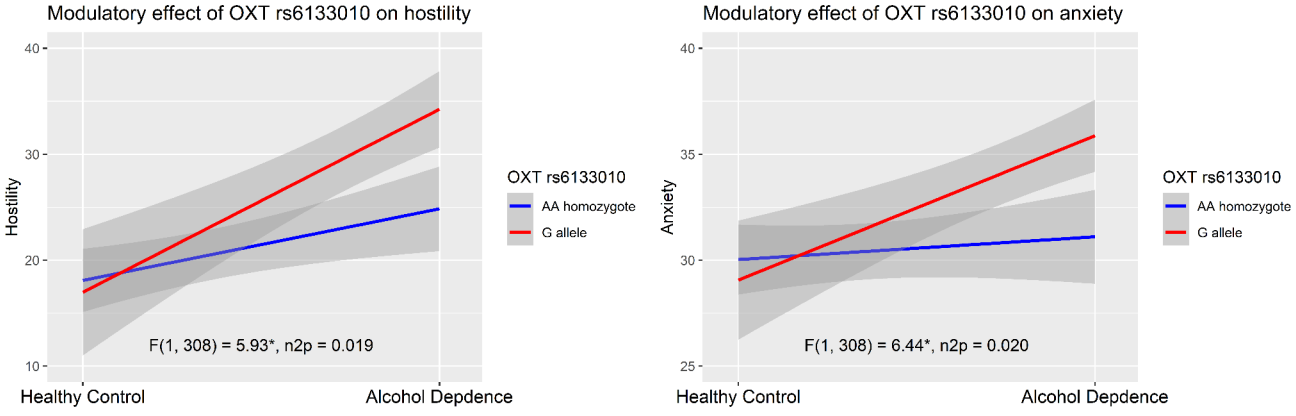

Fig. 2 Interaction effects of *OXT rs6133010* polymorphism and AD on hostility and anxiety in adult males

Note: The interaction effects between alcohol dependence (AD) and *OXT* rs6133010 genotypes (AA homozygote vs. G allele carriers) on hostility (left panel) and anxiety (right panel). Statistical analysis was conducted using two-factor ANOVA to test for interactions between AD status and genotype. The shaded areas represent 95% confidence intervals. F-statistics and partial eta squared ($\eta^2 p$) values are shown for each interaction effect. * $p < 0.05$

Table 4 Two-way ANOVA results for mood disorders (anxiety and depression) by alcohol dependence and *OXT rs6133010* genotype

Parameter	Factor	SS	df	MS	F	*p*	η^2p
Anxiety	AD	11.30	1	11.30	12.16	0.001	0.04
	Rs6133010	2.62	1	2.62	2.82	0.09	0.01
	Interaction	5.98	1	5.98	6.44	0.01	0.02
	Residual	286.04	308	0.93			
Depression	AD	0.13	1	0.13	0.13	0.72	< 0.001
	Rs6133010	1.44	1	1.44	1.44	0.23	0.01
	Interaction	0.02	1	0.02	0.02	0.89	< 0.001
	Residual	308.69	308	1.00			

Note: AD: alcohol dependence; Interaction: AD × *rs6133010*; *SS*: Sum of Squares; *df*: Degrees of Freedom; *MS*: Mean Square; *F*: F-statistic; η^2p: Partial Eta Squared. $^{*}p < 0.05$;$^{**}p < 0.01$;$^{***}p < 0.001$

Table 5 Moderated mediation analysis of the relationship between alcohol dependence, *OXT rs6133010* genotype, hostility, and anxiety

Predictors	Model1 (Hostility)			Model2 (Anxiety)		
	β	*t*	*95% CI*	*β*	*t*	*95% CI*
AD	0.37	2.66^{**}	[0.10, 0.65]	-0.01	-0.09	[-0.24, 0.08]
OXT rs6133010	-0.06	-0.36	[-0.42, 0.30]	-0.08	-0.47	[-0.44, 0.27]
Interaction	0.58	2.44^{*}	[0.11, 1.04]	0.42	1.81	[-0.04, 0.89]
Hostility				0.35	6.24^{***}	[0.24, 0.46]
R^2	0.15			0.18		
F	17.61			17.30		

Note: AD: alcohol dependence; Interaction: AD × *rs6133010; β*: standardized regression coefficient; *95% CI*: 95% confidence interval; $^{*}p < 0.05$;$^{**}p < 0.01$;$^{***}p < 0.001$

of *OXT rs6133010* was significant only in AD patients ($F_{(1,308)} = 11.17$, $p < 0.001$, $\eta^2p = 0.04$) and not in HCs ($F_{(1,308)} = 0.31$, $p = 0.58$, $\eta^2p = 0.001$). Multiple comparison results demonstrated that among AD individuals, OXT rs6133010 had a significant effect on anxiety, with G allele carriers ($M = 35.87$, $SD = 8.31$) displaying higher anxiety scores than AA homozygote carriers ($M = 31.10$, $SD = 9.61$) ($t = 3.34$, $p < 0.001$). In the HCs group, there were no differences in anxiety scores among the different gene subgroups (t = -0.55, $p = 0.58$) (Fig. 2). Consistent with the pattern observed for hostility, the interaction between AD and *OXT rs6133010* on anxiety aligns with the diathesis-stress model, suggesting that the G allele can be considered a risk allele, and its carriers experience more anxiety in stressful situations.

Path analysis

In the aforementioned results, the interaction between OXT and alcohol dependence displayed a similar pattern in relation to hostility and anxiety, both aligning with the diathesis-stress model. Specifically, G allele carriers exhibited greater vulnerability in stressful situations. However, it remains unresolved whether the interaction effects between AD and OXT on hostility and anxiety are independent or potentially related. Therefore, we conducted a path analysis.

Two regression models were constructed and estimated. As presented in Table 5; Fig. 3, OXT rs6133010 exhibited a significant interaction with AD on hostility ($\beta = 0.58$, se = 0.24, $t = 2.44$, $p < 0.05$), and hostility demonstrated a significant association with anxiety ($\beta = 0.35$, se = 0.06, $t = 6.24$, $p < 0.001$). However, after considering the mediating role of hostility, the interaction between OXT rs6133010 and AD did not show a significant effect on anxiety ($\beta = 0.42$, se = 0.23, $t = 1.81$, $p = 0.07$). Thus, the interaction between OXT and AD exclusively occurs in the context of hostility, which serves as a significant positive predictor of anxiety. This finding suggests that the potential mechanism by which OXT modulates anxiety in individuals with alcohol dependence may be through the modulation of hostility.

Discussion

This study aimed to investigate whether the *OXT rs6133010* genetic polymorphism can influence the onset of psychiatric symptoms in Chinese male AD patients. In the following sections, we will first discuss the specific interaction effect between *OXT rs6133010*, AD, and psychiatric symptoms to determine the role of *OXT rs6133010* in aggression and mood disorders among AD patients. We will then explore the contextual importance of oxytocin modulation of psychiatric symptoms, focusing on how *OXT rs6133010* variation moderates vulnerability in the presence of AD. Notably, in healthy individuals, different genotypes of *OXT rs6133010* showed no variations in aggression and mood disorders. Furthermore, we will discuss the mechanism through which OXT influences psychiatric symptoms, highlighting its potential to modulate anxiety by affecting hostility in individuals with alcohol dependence. In conclusion,

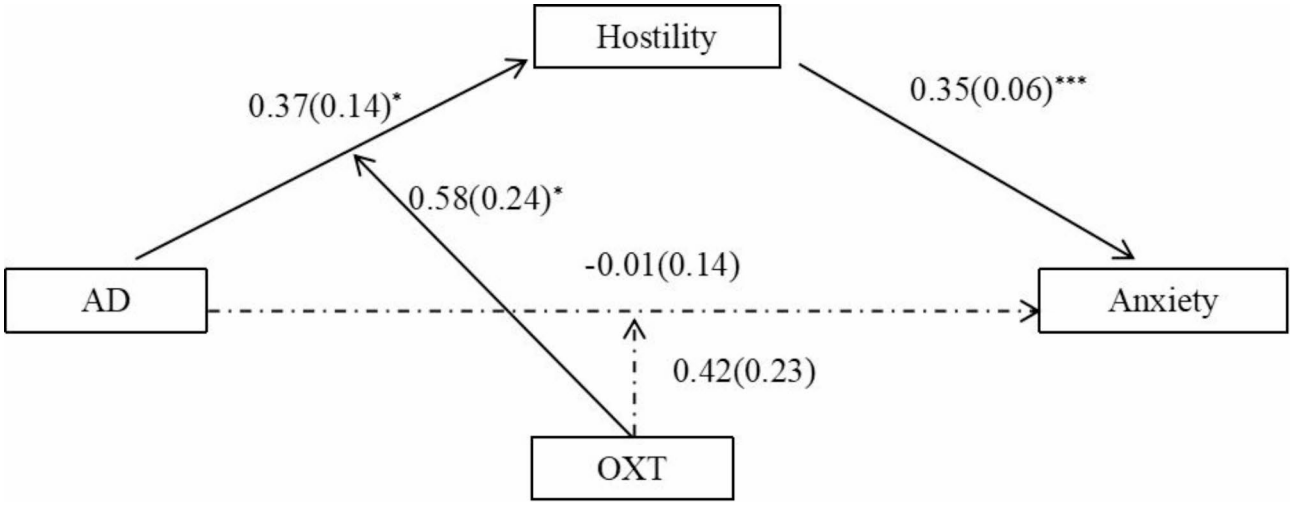

Fig. 3 Results of the path analysis with standardized estimates
Note: AD: alcohol dependence; OXT: *OXT* rs6133010. The diagram presents the results of the path analysis with standardized path coefficients with standard errors in parentheses. Solid lines indicate significant paths, and dashed lines indicate non-significant paths. * $p < 0.05$; *** $p < 0.001$

this study revealed that the *OXT rs6133010* variant influences individual susceptibility to psychiatric symptoms, with the AA genotype appearing to provide protection by reducing anxiety and hostility compared to the G allele. Importantly, this regulatory effect of *OXT rs6133010* was observed only in AD populations, underscoring the significance of environmental and disorder-specific contexts in influencing the function of the oxytocin system.

The first major finding of our study was that OXT has a modulating effect on psychiatric symptoms in male AD patients. Specifically, the *OXT rs6133010* gene polymorphism modulates hostility and anxiety in males with AD. The AA homozygous genotype of *OXT rs6133010* serves as a protective factor against aggression and mood disorders in AD patients, as carriers of this genotype exhibit lower and more stable levels of hostility and anxiety with benefit more from standard withdrawal protocols. Conversely, G allele carriers may require more intensive monitoring and targeted interventions during withdrawal, given their increased vulnerability to hostility and anxiety symptoms. The *OXT rs6133010* variation influences hostility specifically, while its effects on other forms of aggression appear to be limited. This suggests that the effects of OXT on aggression may be domain-specific and not universally applicable. Although previous reports have extensively linked OXT and aggression, the results have not been straightforward [41, 42, 43]. Ne'eman, in particular, has suggested that oxytocin primarily alters the cognitive salience of social stimuli, leading to increased prosocial behavior and decreased aggressive behavior [44]. Another study has shown that oxytocin may modulate cognitive processes by primarily affecting lower brain mechanisms [45]. Furthermore, the *OXT rs6133010* genotype has been associated with the recognition of angry faces, which is part of the cognitive processing involved [20]. Our finding that *OXT rs6133010* moderates hostility but not physical aggression aligns with research indicating that oxytocin acts on lower brain mechanisms involved in cognitive and emotional regulation. From a clinical perspective, genotyping for *OXT rs6133010* could potentially be used as a predictive tool to identify patients who may be at higher risk for experiencing severe hostility and anxiety symptoms during alcohol withdrawal. This information could guide clinicians in developing personalized treatment plans, with G allele carriers potentially benefiting from more intensive psychological support or pharmacological interventions to manage these symptoms. Future research could explore the development of targeted oxytocin-based therapies for AD patients with the G allele, aimed at mitigating hostility and anxiety during withdrawal.

The second interesting finding of this study is that oxytocin modulation requires a priming condition, such as alcohol dependence, highlighting the importance of environmental context for the functioning of the oxytocin system. Oxytocin can act as a stress hormone, with its secretion increasing under physiological or psychological stress, and alcohol withdrawal involves dysregulation of the stress system [46], potentially priming the release of oxytocin. Over the past decade, both animal research and human studies have reported prosocial effects of oxytocin, although the relationships observed have often been weak or inconsistent [47, 48, 49]. More importantly, many studies that have reported no significant main effects have found effects through interactions with task or stimulus variables [50, 51]. This suggests that the more appropriate question is not "Can oxytocin modulate social cognition?" but rather "In what context does

oxytocin modulate social cognition?". Our findings support an interactionist model proposing that the prosocial or regulatory effects of oxytocin depend on individual and environmental factors. The results of this study demonstrate that the regulatory effect of oxytocin occurs only in the context of alcohol dependence. In healthy individuals, there are no differences in aggression and mood disorders based on different genotypes of *OXT rs6133010*. The functioning of the oxytocin system may be highly sensitive to environmental demands, affecting emotional, cognitive, or social processes only under conditions of impaired stress regulation or elevated distress [52, 53]. Therefore, in this study, alcohol dependence served as the triggering factor for the action of oxytocin. In the healthy group, oxytocin did not significantly modulate aggression and mood disturbances, further suggesting that the modulating effect of oxytocin requires a specific context, such as an environment with associated stresses. This result provides important insights for understanding previous inconsistent results on oxytocin. For example, while oxytocin improves performance in social empathy experiments for individuals with a high autism spectrum quotient, it has no effect on empathic accuracy for individuals who are more socially proficient [49]. The likely reason is that the high autism spectrum quotient itself in social empathy experiments serves as a pressure context.

The third finding of this study is related to the anxiolytic mechanism of action of oxytocin. Pathway analysis suggests that the interaction of *OXT rs6133010* on hostility and anxiety may be potentially relevant. Oxytocin may modulate anxiety by influencing hostility in alcohol-dependent individuals. Hostility has previously been linked to anxiety, as higher levels of hostile attribution bias or interpreting others' actions from a hostile perspective are likely to increase anxiety [54, 55, 56]. In turn, individuals with anxiety are more prone to misinterpreting others' behaviors as being hostile [54]. Interestingly, the literature reports that oxytocin reduces anxiety symptoms, particularly in studies focusing on social anxiety or anxiety related to social relationships, but the results regarding trait anxiety are mixed. Specifically, oxytocin did not play a role in the stress response exhibited by Wistar rats bred for high anxiety behavior [57]. Mice with the oxytocin gene deleted exhibited higher corticosterone levels than wild-type mice under psychological stress (such as acutely inserting a rectal probe); however, this phenomenon was not observed under physiological stressors (such as insulin-induced hypoglycemia) [58]. These findings indicate that oxytocin may not directly act as an anxiolytic. Similarly, Engelmann et al.. reported that the role of oxytocin in aggressive encounters may be more related to the stress response to this type of social interaction rather than a direct effect on aggression [59]. Our study suggests that the anxiolytic effects of oxytocin may occur through the reduction of hostile cognition in response to environmental cues and threatening stimuli. This finding is consistent with basic research results from rodents, which indicate that the perception of threatening stimuli increases oxytocin release and that the activation of the oxytocin system regulates behavioral and physiological manifestations of anxiety [60].

Limitations

The present study revealed several interesting findings that contribute to the current understanding of the effect of OXT on psychiatric symptoms in the context of alcohol dependence. However, there are limitations to our study that should be acknowledged. First, our study was cross-sectional in nature, which limits our ability to establish cause-and-effect relationships between alcohol dependence and various psychiatric symptoms. Second, the sample size after PSM was relatively small, which may have reduced the statistical power of our analysis. Third, our sample was restricted to Chinese Han males, which constrains the generalizability of our findings. This demographic homogeneity, while methodologically advantageous for controlling potential confounders, precludes analysis of potential gender differences in genetic susceptibility to withdrawal symptoms and limits extrapolation to other ethnic populations. Due to research funding limitations, only one SNP of OXT was selected for genotyping and subsequent data analysis. Finally, we did not investigate the actual effects of *OXT rs6133010* on oxytocin expression levels using molecular biology methods. Future studies should incorporate larger and more diverse sample sizes, analyze additional genetic variants of interest, and employ molecular biology techniques to elucidate the relationship between *OXT rs6133010* and oxytocin expression levels. In particular, multi-gene combinations and integration with biological sample detection, such as oxytocin levels in plasma or cerebrospinal fluid, could provide a more comprehensive understanding of the genetic and biological mechanisms underlying psychiatric symptoms in alcohol dependence. Additionally, future research should account for potential confounding factors, such as smoking and other lifestyle variables, to provide a more robust and nuanced understanding of the gene-environmental interactions involved.

Conclusion

This study provides novel evidence for the role of genetic variation in OXT in modulating psychiatric symptoms during alcohol withdrawal. Our findings demonstrate that the *OXT rs6133010* polymorphism significantly influences symptom severity specifically in the context of AD, with the AA homozygous genotype conferring protection against both anxiety and hostility symptoms. The

regulatory effect of *OXT rs6133010* was context-dependent, manifesting specifically during alcohol withdrawal rather than in healthy conditions, which highlights the importance of considering environmental factors when studying oxytocin system function in psychiatric conditions. Additionally, the path analysis reveals that OXT's influence on anxiety may be mediated through its effects on hostility, suggesting a hierarchical organization of symptom regulation. This finding provides new insights into the mechanistic pathway through which oxytocin modulates emotional responses during withdrawal. Importantly, the identification of the AA genotype as a protective factor against withdrawal-related psychiatric symptoms has potential implications for personalized treatment approaches, as this genetic variation might serve as a biomarker for predicting symptom severity and tailoring interventions accordingly. These findings advance our understanding of the genetic factors influencing withdrawal symptom variability and suggest potential pathways for developing targeted therapeutic strategies in alcohol dependence treatment.

Abbreviations

AD	Alcohol Dependence
OXT	Oxytocin
HCs	Healthy Controls
MANOVA	Multivariate Analysis of Variance
ANOVA	Analysis of Variance
PSM	Propensity Score Matching
SNP	Single Nucleotide Polymorphism
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
BPAQ	Buss-Perry Aggression Questionnaire
SAS	Self-Rating Anxiety Scale
SDS	Self-Rating Depression Scale
AA	Homozygous AA Genotype
AG/GG	Heterozygous AG or Homozygous GG Genotypes
MAF	Minor Allele Frequency
η^2p	Partial Eta-Squared
GWAS	Genome-Wide Association Studies

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Author contributions
Li Chen, Fan Wang, Yanlong Liu, Wei Wang contributed conceptualization and project administration; Yuyu Wu, Yimin Kang performed the data curation; Xinguang Luo, Kexin Wang, Yu-Hsin Chen were involved in writing - review & editing, Guanghui Shen contributed significantly to investigation and writing - original draft.

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Data availability
The datasets presented in this article are not readily available because data use sharing agreements would be necessary. Requests to access the datasets should be directed to benjaminlyl@wmu.edu.cn.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures were performed in accordance 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. All procedures involving human subjects/patients were approved by IRB in Inner Mongolia Medical University (No. YKD2015003). Written informed consent was obtained from all participants prior to their participation in the study.

Competing interests
The authors declare no competing interests.

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References

1. Schuckit MA. Alcohol-use disorders. Lancet Lond Engl. 2009;373:492–501.
2. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 Alcohol Use Disorder: results from the national epidemiologic survey on Alcohol and related conditions III. JAMA Psychiatry. 2015;72:757–66.
3. Kadam M, Sinha A, Nimkar S, Matcheswalla Y, De Sousa A. A comparative study of Factors Associated with Relapse in Alcohol Dependence and Opioid Dependence. Indian J Psychol Med. 2017;39:627–33.
4. Castro VJ. Management of drug and alcohol withdrawal. N Engl J Med. 2003;349:405–7. author reply 405–407.
5. Day E, Daly C. Clinical management of the alcohol withdrawal syndrome. Addict Abingdon Engl. 2022;117:804–14.
6. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3:760–73.
7. Stephens MAC, Wand G. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol Res Curr Rev. 2012;34:468–83.
8. Volkow ND, Michaelides M, Baler R. The neuroscience of drug reward and addiction. Physiol Rev. 2019;99:2115–40.
9. Goldberg LR, Gould TJ. Multigenerational and transgenerational effects of paternal exposure to drugs of abuse on behavioral and neural function. Eur J Neurosci. 2019;50:2453–66.
10. Lesch K-P. Alcohol dependence and gene x environment interaction in emotion regulation: is serotonin the link? Eur J Pharmacol. 2005;526:113–24.
11. Bogdan R, Nikolova YS, Pizzagalli DA. Neurogenetics of depression: a focus on reward processing and stress sensitivity. Neurobiol Dis. 2013;52:12–23.
12. Spagnolo PA, Ramchandani VA, Schwandt ML, Kwako LE, George DT, Mayo LM, et al. FAAH gene variation moderates stress response and Symptom Severity in patients with posttraumatic stress disorder and Comorbid Alcohol Dependence. Alcohol Clin Exp Res. 2016;40:2426–34.
13. Lee H-J, Macbeth AH, Pagani JH, Young WS. Oxytocin: the great facilitator of life. Prog Neurobiol. 2009;88:127–51.
14. Buisman-Pijlman FTA, Sumracki NM, Gordon JJ, Hull PR, Carter CS, Tops M. Individual differences underlying susceptibility to addiction: role for the endogenous oxytocin system. Pharmacol Biochem Behav. 2014;119:22–38.
15. McGregor IS, Bowen MT. Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm Behav. 2012;61:331–9.
16. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev. 2001;81:629–83.
17. Sarnyai Z, Kovács GL. Oxytocin in learning and addiction: from early discoveries to the present. Pharmacol Biochem Behav. 2014;119:3–9.

18. de Jong TR, Neumann ID. Oxytocin and Aggression. Curr Top Behav Neurosci. 2018;35:175–92.
19. Yang L, Wang F, Wang M, Han M, Hu L, Zheng M, et al. Association between oxytocin and receptor genetic polymorphisms and aggression in a northern Chinese Han population with alcohol dependence. Neurosci Lett. 2017;636:140–4.
20. Kucharska K, Kot E, Biernacka K, Zimowski J, Rogoza R, Rybakowski F, et al. Interaction between polymorphisms of the oxytocinergic system genes and emotion perception in inpatients with anorexia nervosa. Eur Eat Disord Rev J Eat Disord Assoc. 2019;27:481–94.
21. Crabbe JC, Phillips TJ, Buck KJ, Cunningham CL, Belknap JK. Identifying genes for alcohol and drug sensitivity: recent progress and future directions. Trends Neurosci. 1999;22:173–9.
22. Crabbe JC, Metten P, Cameron AJ, Wahlsten D. An analysis of the genetics of alcohol intoxication in inbred mice. Neurosci Biobehav Rev. 2005;28:785–802.
23. Zhou R, Wang M, Li W, Wang S, Zhou Z, Li J, et al. Gene-gene interactions among SPRYs for nonsyndromic cleft Lip/Palate. J Dent Res. 2019;98:180–5.
24. Wall TL, Luczak SE, Hiller-Sturmhöfel S. Biology, genetics, and environment: underlying factors influencing alcohol metabolism. Alcohol Res Curr Rev. 2016;38:59.
25. Vuoksimaa E, Rose RJ, Pulkkinen L, Palviainen T, Rimfeld K, Lundström S, et al. Higher aggression is related to poorer academic performance in compulsory education. J Child Psychol Psychiatry. 2021;62:327–38.
26. Shanahan L, Steinhoff A, Bechtiger L, Murray AL, Nivette A, Hepp U, et al. Emotional distress in young adults during the COVID-19 pandemic: evidence of risk and resilience from a longitudinal cohort study. Psychol Med. 2022;52:824–33.
27. Manly JJ, Smith C, Crystal HA, Richardson J, Golub ET, Greenblatt R, et al. Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV + and HIV- women: the women's interagency HIV Study (WIHS) Neurocognitive Substudy. J Clin Exp Neuropsychol. 2011;33:853–63.
28. Gómez-Pérez E, Ostrosky-Solís F. Attention and memory evaluation across the life span: heterogeneous effects of age and education. J Clin Exp Neuropsychol. 2006;28:477–94.
29. Kitsios GD, Zintzaras E. Genome-wide association studies: hypothesis-free or engaged? Transl Res J Lab Clin Med. 2009;154:161–4.
30. Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score matching and its alternatives. Eur J Cardio-Thorac Surg off J Eur Assoc Cardio-Thorac Surg. 2018;53:1112–7.
31. Kaster TS, Vigod SN, Gomes T, Sutradhar R, Wijeysundera DN, Blumberger DM. Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study. Lancet Psychiatry. 2021;8:686–95.
32. Bi G, Liang J, Shan G, Zhan C. Propensity score matching for Bias reduction in genomic profiling. J Clin Oncol off J Am Soc Clin Oncol. 2022;40:1259–60.
33. Giancola PR, Levinson CA, Corman MD, Godlaski AJ, Morris DH, Phillips JP, et al. Men and women, alcohol and aggression. Exp Clin Psychopharmacol. 2009;17:154–64.
34. Maxwell JP. Development and preliminary validation of a Chinese version of the Buss-Perry Aggression Questionnaire in a population of Hong Kong Chinese. J Pers Assess. 2007;88:284–94.
35. Zung WW. A rating instrument for anxiety disorders. Psychosomatics. 1971;12:371–9.
36. Wang Z. Chinese version of Zung's self-rating anxiety scale. J Shanghai Psychiatry. 1984;2:73–4.
37. Dunstan DA, Scott N. Norms for Zung's self-rating anxiety scale. BMC Psychiatry. 2020;20:90.
38. Zung WW, A self-rating depression. SCALE Arch Gen Psychiatry. 1965;12:63–70.
39. Lee HC, Chiu HF, Wing YK, Leung CM, Kwong PK, Chung DW. The Zung self-rating Depression Scale: screening for depression among the Hong Kong Chinese elderly. J Geriatr Psychiatry Neurol. 1994;7:216–20.
40. Soósová MS, Macejová Ž, Zamboriová M, Dimunová L. Anxiety and depression in Slovak patients with rheumatoid arthritis. J Ment Health Abingdon Engl. 2017;26:21–7.
41. Hirosawa T, Kikuchi M, Higashida H, Okumura E, Ueno S, Shitamichi K, et al. Oxytocin attenuates feelings of hostility depending on emotional context and individuals' characteristics. Sci Rep. 2012;2:384.
42. Pfundmair M, Reinelt A, DeWall CN, Feldmann L. Oxytocin strengthens the link between provocation and aggression among low anxiety people. Psychoneuroendocrinology. 2018;93:124–32.
43. Samuni L, Preis A, Deschner T, Wittig RM, Crockford C. Cortisol and oxytocin show independent activity during chimpanzee intergroup conflict. Psychoneuroendocrinology. 2019;104:165–73.
44. Ne'eman R, Perach-Barzilay N, Fischer-Shofty M, Atias A, Shamay-Tsoory SG. Intranasal administration of oxytocin increases human aggressive behavior. Horm Behav. 2016;80:125–31.
45. Ebner NC, Horta M, Lin T, Feifel D, Fischer H, Cohen RA. Oxytocin modulates meta-mood as a function of age and sex. Front Aging Neurosci. 2015;7:175.
46. Gilbertson R, Frye RF, Nixon SJ. Nicotine as a factor in stress responsiveness among detoxified alcoholics. Alcohol Alcohol Oxf Oxfs. 2011;46:39–51.
47. Alvares GA, Hickie IB, Guastella AJ. Acute effects of intranasal oxytocin on subjective and behavioral responses to social rejection. Exp Clin Psychopharmacol. 2010;18:316–21.
48. Bartz JA, Zaki J, Ochsner KN, Bolger N, Kolevzon A, Ludwig N, et al. Effects of oxytocin on recollections of maternal care and closeness. Proc Natl Acad Sci U S A. 2010;107:21371–5.
49. Bartz JA, Nitschke JP, Krol SA, Tellier P-P. Oxytocin selectively improves empathic accuracy: a replication in men and Novel insights in Women. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4:1042–8.
50. Guastella AJ, Mitchell PB, Mathews F. Oxytocin enhances the encoding of positive social memories in humans. Biol Psychiatry. 2008;64:256–8.
51. Marsh AA, Yu HH, Pine DS, Blair RJR. Oxytocin improves specific recognition of positive facial expressions. Psychopharmacology. 2010;209:225–32.
52. MacDonald K, Feifel D. Oxytocin's role in anxiety: a critical appraisal. Brain Res. 2014;1580:22–56.
53. Zunhammer M, Geis S, Busch V, Eichhammer P, Greenlee MW. Pain modulation by intranasal oxytocin and emotional picture viewing - a randomized double-blind fMRI study. Sci Rep. 2016;6:31606.
54. Buck B, Browne J, Gagen EC, Penn DL. Hostile attribution bias in schizophrenia-spectrum disorders: narrative review of the literature and persisting questions. J Ment Health Abingdon Engl. 2023;32:132–49.
55. Pisano S, Catone G, Pascotto A, Iuliano R, Tiano C, Milone A, et al. Paranoid thoughts in adolescents with social anxiety disorder. Child Psychiatry Hum Dev. 2016;47:792–8.
56. Stopa L, Clark DM. Social phobia and interpretation of social events. Behav Res Ther. 2000;38:273–83.
57. Landgraf R, Wigger A, Holsboer F, Neumann ID. Hyper-reactive hypothalamo-pituitary-adrenocortical axis in rats bred for high anxiety-related behaviour. J Neuroendocrinol. 1999;11:405–7.
58. Amico JA, Cai H, Vollmer RR. Corticosterone release in oxytocin gene deletion mice following exposure to psychogenic versus non-psychogenic stress. Neurosci Lett. 2008;442:262–6.
59. Engelmann M, Ebner K, Landgraf R, Holsboer F. Wotjak1 CT. Emotional stress triggers intrahypothalamic but not peripheral release of oxytocin in male rats. J Neuroendocrinol. 1999;11:867–72.
60. Sabihi S, Durosko NE, Dong SM, Leuner B. Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. Psychoneuroendocrinology. 2014;45:31–42.

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