Gene–environment interaction: Oxytocin receptor (OXTR) polymorphisms and parenting style as potential predictors for depressive symptoms

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A B S T R A C T

Depression is a common mental health problem that is thought to develop through a combination of genetic, psychological, and environmental factors, including parental behaviours and parental mental health. The present study investigated the potential interaction between oxytocin receptor (OXTR) single nucleotide polymorphisms (SNPs) (rs53576, rs237880, rs237887, rs237889, rs1042778, rs2268490, rs2268491, rs4686302, rs6770632, rs13316193) and parenting style in adolescence in relation to depressive symptoms among young adults. The sample consisted of 1,098 Caucasian participants (63.6% females) and their parents. The present study included data from the Survey of Adolescent Life Cohort study collected in 2012 at wave I (m_{age} 14.4 years; DNA collection), 2015 at wave II (m_{age} 17.36 years; Estimation of parenting style, depressive symptoms, and parental depression) and 2018 at wave III (m_{age} 20.19 years; Depressive symptoms). Evidence for an interaction effect between OXTR SNP rs6770632 and negative parenting style on depressive symptoms among young adults was found with support for the diathesis–stress theory. The rs6770632 was associated with depressive symptoms at higher levels of negative parenting, with A:A allele carriers reporting higher levels of depressive symptoms than C:C and C:A allele carriers. The present study provides preliminary knowledge about the potential moderation effects of perceived negative parenting on the effect of OXTR SNPs on depressive symptoms among young adults, independent of sex, previous reports of depressive symptoms, and parental depression.

1. Introduction

Depression is a leading mental health illness (Beesdo-Baum et al., 2015; Essau, 2005; Kessler et al., 2007) and has its typical onset during adolescence (Kessler et al., 2012; Patton et al., 2008). Adolescence is a sensitive period associated with heightened sensitivity to social evaluation, development into independency, development of autonomous behaviours, hormonal changes due to puberty, and poor emotional control, all of which have been linked to depression (Patton et al., 2008; Rice et al., 2003; Steiner et al., 2005).

Depression seems to develop through a combination of genetics, psychological aspects, and environmental factors, including parenting style (Hankin, 2015; McLeod et al., 2007; Pinquart, 2017; Yap and Jorm, 2015). Negative parenting has been linked to children’s psychiatric illnesses (Frazer and Fite, 2016; Heaven et al., 2004; Infurna et al., 2015; Liu and Merritt, 2018; Parker and Roy, 2001; Smokowski et al., 2015; Tang et al., 2018; Tollenaar et al., 2017) while positive parenting, on the other hand, has been associated with lower levels of depression among adolescents (Liu and Merritt, 2018; Keijser et al., 2020b), suggesting a buffering effect for negative environmental stressors and protection against future depression (Hazel et al., 2014; Milne and Lancaster, 2001; Odgers et al., 2012; Pinquart, 2017; Sanders et al., 2014; Oppenheimer et al., 2018).

An additional risk factor for the development of depression is parental depression; children and adolescents who grow up with a parent who suffers from mental illness are more likely to develop different interpersonal problems, such as depression, themselves (Beardslee et al., 1998; Keijser et al., 2020b). Notably, individuals may vary in the degree to which they are affected by environmental stressors depending on different factors, such as temperament, physiology, and

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1 The Depression Self-Rating Scale – DSRS; The parents as Social Context Questionnaire - PASCQ.

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genotype (Belsky and van Ijzendoorn, 2017; Ellis et al., 2011; Frazer and Fite, 2016). The study of candidate gene by environment (cG × E) interactions may expand knowledge on individual differences in environmental sensitivity.

The environmental stressors included in cG × E analyses should ideally be selected from appropriate developmental timing, in line with the aim of the planned evaluation (Dick et al., 2015). Adolescence, which is a sensitive developmental period in life (Patton et al., 2008; Rice et al., 2003; Steiner et al., 2003), is a desirable time window for choosing an environmental stressor for the cG × E interaction. It is, however, important to note that the occurrence of Early Life Stress (ELS) such as abuse may be more important than the form, severity, or duration of the abuse (Briere and Jordan, 2009), and that one type of childhood abuse is almost always accompanied by other types of abuse (Vachon et al., 2015). Therefore, when investigating the effect of one type of ELS, it must be considered that other types of ELS, as well as poly-victimization, are also likely to be occurring (Fisher et al., 2015). There are also cumulative family risks of ELS that should be taken into account. The combined effects of socio-economic difficulties, such as low parental income, unemployment, and housing instability, as well as parental characteristics, such as mental and physical health, use of alcohol, and domestic violence may elevate the risk (Patwardhan et al., 2017), but are not measured in most of the conceptualized cG × E models. This concern has previously been addressed as the predictor-intersection problem (Nilsson et al., 2018). Another way of conceptualizing both positive and negative environments in relation to adolescent depression is parenting style, such as warmth and rejection in parent–child social relationships. Parenting style has both psychological (Clayborne et al., 2020) and immunological (Robles, 2020) bindings to depression. Parenting style during adolescence, which has a known linkage to mental illness (Frazer and Fite, 2016; Heaven et al., 2004; Infurna et al., 2015; Liu and Merritt, 2018; Parker and Roy, 2001; Smokowski et al., 2015; Tang et al., 2018; Tollenaar et al., 2017) may, therefore, be a good choice of environmental stressor for the cG × E interaction. Furthermore, parenting style has not been investigated to the same extent as traditional ELS, such as childhood trauma.

The other part of measuring the cG × E interaction is the choice of gene. The neuropeptide hormone oxytocin has primarily been associated with emotional bonding between infants and parents and child–parent synchrony, and has generally been suggested to be involved in human social behaviour, the formation of social bonds and emotional reactivity (Carter, 2014; Kirsch, 2015; Tollenaar et al., 2017). Growing evidence suggests that oxytocin has a role in psychiatric illness with a deficit in social functions and mood disorders (Kirsch, 2015), however, the link between oxytocin and depression seems uncertain (McQuaid et al., 2014). The effects of oxytocin appear to vary depending on environmental and/or individual factors (Bartz et al., 2011). Oxytocin may not be uniquely beneficial but reliant on the interpretation of the situation or on interindividual factors that increase its effect through a heightened sensitivity to environmental cues (Olff et al., 2013).

Researchers have investigated genetic variability in the oxytocin system in relation to depression with a primary focus on single nucleotide polymorphisms (SNPs) located in the OXTR gene (Bakermans-Kranenburg and van Ijzendoorn, 2014; McQuaid et al., 2014). Strauss et al. (2010) composed one of the first genetic analysis studies to examine the potential association between variants in neuroendocrine genes and depression onset during childhood, but no significant association between gene variants and childhood onset of mood disorders were found. Myers et al. (2014) also found no significant unconditional relationship between rs237898 and depression. In a study conducted by Costa et al. (2009), a significant main effect of the OXTR SNP rs53576 was found on unipolar depression, where G:G allele carriers were at less risk of developing depression. A significant main effect of the OXTR SNP rs53576 was also found on depressive symptomatology in a non-clinical sample, where A:A allele carriers were at greater risk of developing depression (Saphire-Bernstein et al., 2011). The OXTR SNP rs53576 has further been evaluated in a mediation analysis where findings proposed that A:A allele carriers reported higher levels of depressive symptomatology and effects that were mediated by psychological resources (Saphire-Bernstein et al., 2011; McQuaid et al., 2013). Moreover, carriers of the G:G allele of rs53576 were at greater risk of displaying depressive symptoms if they also reported experiences of a negative environment during early childhood (McQuaid et al., 2013; Saphire-Bernstein et al., 2011).

A considerable amount of literature has been published on OXTR SNPs and mental health. Studies of associations between OXTR SNPs and depression symptomatology have included analyses of unconditional main effects or conditional interaction effects from a risk perspective, without considering both positive and/or negative environment. The findings of these studies are inconclusive and further studies may be beneficial for the research field.

A common approach in cG × E studies is the diathesis–stress model, which proposes that vulnerable individuals are disproportionately likely to be affected adversely by harmful stressors (Belsky and Pluess, 2009), an approach implemented by Caspi et al. (Caspi et al., 2003; Caspi et al., 2002) in their hallmark studies of cG × E interaction effects. An alternative perspective is the differential susceptibility theory, which proposes that certain gene variants may be considered as susceptibility alleles rather than vulnerability alleles (Belsky et al., 2007a). According to this theory, carriers of susceptibility variants are more responsive to both positive and negative environments and, therefore, disproportionately likely to be affected favourably and adversely in a ‘for better and for worse’ manner (Belsky et al., 2016; Belsky et al., 2007b; Belsky and Pluess, 2009).

If cG × E effects consistent with differential susceptibility were present, carriers of susceptibility alleles would be more sensitive to parenting styles, leading to them having higher or lower levels of depressive symptoms than carriers of non-susceptibility alleles.

1.1. Aims

The primary aim of the present study was to evaluate the potential interaction between different OXTR SNPs and parenting style during adolescence in relation to the development of depressive symptoms in young adulthood. A secondary aim was to explore the type of cG × E interactions from the perspectives of the diathesis–stress and differential susceptibility frameworks.

2. Methods

2.1. Study sample

The Survey of Adolescent Life in Västmanland Cohort Study (SALVe-Cohort) collects data from individuals born in either 1997 or 1999 in Västmanland, Sweden. The SALVe-Cohort population is a representative sample of the larger community in Sweden regarding proportions of employed parents (92%), separated parents (30%), single-parent households (19%), and foreign-born adolescents (9%) (SCB, 2012).

The present study includes data collected in wave I (2012), participants were 13 and 15 years old (m_age 14.4 years; DNA collection), in wave II (2015) participants were 16 and 18 years old (m_age 17.36 years; Estimation of parenting style, depressive symptoms, and parental depression) and in wave III (2018) participants were either 19 or 21 years old (m_age 20.19 years; Depressive symptoms). There were 1868 participants in wave I (response rate 40%), 1541 in wave II (response rate from wave I 82%), and 1176 in wave III (response rate from wave II 76%).

The present study sample consisted of 1,098 Caucasian participants (63.3% females, m_age 20.19 years) after exclusion of missing data from the study variables. Based on self-reports on the Depression Self-Rating Scale (DSRS) (Svanborg and Ekselius, 2003), 18% of the males and 34.9% of the females met the Diagnostic and Statistical Manual of Psychiatry Research 303 (2021) 114057

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Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 2000) A-criteria for major depressive disorder at wave III. The study sample was also consistent of 1098 parents, 10.2% reported a lifetime diagnosis of depression. The study was approved by the Ethical Review Board of Uppsala (Dnr 2012/187).

2.2. Measurements

2.2.1. Depressive symptoms

Depressive symptomatology was measured through the DSRS (Sjöberg et al., 2006; Svanborg and Ekselius, 2003) during wave II and wave III. The DSRS consists of 14 items with yes/no statements based on the A-criteria for major depressive disorder from the DMS-IV (American Psychiatric Association, 2000) (Sjöberg et al., 2006; Svanborg and Ekselius, 2003). The DSRS includes questions on the following symptom categories occurring during the past two weeks: 1. Dysphoric mood/irritability (2 items), 2. Loss of interest or pleasure in most activities (1 item), 3. Sleep disturbances (2 items), 4. Weight loss or gain/appetite disturbances (2 items), 5. Psychomotor agitation or retardation (2 items), 6. Fatigue or loss of energy (1 item), 7. Feelings of worthlessness or guilt (2 items), 8. Concentration disturbances (1 item), 9. Thoughts of suicide (1 item).

A continuous depressive symptom summation index was created from all symptom categories, where no = 0 and yes = 1. The possible range of scores was 0–9 (number of depressive symptoms). The DSRS scale demonstrated good internal consistency (Cronbach’s α = 0.865).

2.2.2. Parenting styles

Perceived parenting style was assessed through the Parents as Social Context Questionnaire (PASCQ) (Skinner et al., 2005) translated into Swedish (Keijser et al., 2020a), during wave II. The PASCQ is a 24-item self-rating scale providing scores on six dimensions: Warmth, Rejection, Structure, Chaos, Autonomy support, and Coercion. Each dimension comprises four questions with a response scale for each item ranging from 0 (not at all true) to 3 (very true). For a further description of the PASCQ, please see Keijser et al. (2020a).

A positive summation index (PASCQpos) was created for the dimensions of Warmth, Structure, and Autonomy support, and a negative summation index (PASCNeg) was created for the dimensions of Rejection, Chaos, and Coercion. For a further description of the summation index construction, please see Keijser et al. (2020b). Both summation indices ranged from 0 to 36 points and demonstrated good internal consistency (PASCQpos Cronbach’s α = 0.853, PASCQneg Cronbach’s α = 0.846) in the current sample.

2.2.3. Covariates

Information of lifetime parental depression was assessed through a questionnaire on which caregivers indicated diagnosed illnesses or mental health problems within the family by marking a check box in a list of specified disorders, including an item regarding previous or present paternal or maternal depression. The answers regarding paternal and maternal lifetime depression were then clustered and dichotomized into presence (1) or absence (0) of lifetime diagnosis of depression in either parent (1). The models were also adjusted for sex (male = 0, female = 1), and previous depression scores on DSRS (further described above), during wave II.

2.3. Genotyping

Saliva samples for genotyping were collected using the Oragene® DNA self-collection kit (Ottawa, Ontario, Canada) and extracted in accordance with the manufacturer’s guidelines. Genotyping was performed using a fluorescence-based competitive allele-specific PCR (KBSiScience®). Allele discrimination was completed using SNPVviewer®. The genotype calling was performed blind to psychosocial data.

Thirteen oxytocin polymorphism receptors (OXTR SNPs: rs53576, rs237880, rs237887, rs237889, rs1042778, rs2268490, rs2268491, rs4564970, rs4686302, rs6770632, rs1488467, and rs13316193) were evaluated. Two OXTR SNPs, rs4564970 and rs1488467, were excluded from further evaluation, as they had only four and two participants, respectively, being minor allele homozygous (Table 1). The 11 genotypes included in the analyses were in Hardy–Weinberg equilibrium (Table 1). Genotypes were coded assuming an additive function and based on minor allele count: 0 = homozygous for the major allele, 1 = heterozygous, and 2 = homozygous for the minor allele.

2.4. Missing data

The total numbers of missing values on DSRS, PASCQpos and PASCNeg items were 0.117%, 0.275%, and 0.299%, respectively. Little’s (Little, 1988) Missing Completely at Random (MCAR) test was performed and showed that the missing data values should be treated as missing completely at random ($\chi^2 = 770.860, df = 737, p = 0.188$).

2.5. Statistical analyses

Descriptive data were obtained using the Mann–Whitney U test. The main effects of the study variables (OXTR SNPs, PASCQpos, PASCNeg) on depressive symptoms were obtained through multiple linear regression. The suggested relation between OXTR SNPs and depressive symptoms moderated by PASCQpos or PASCNeg, adjusting for parental depression, previous depressive symptoms, and sex, was evaluated through different moderation models (Moderation Model 1 in PROCESS) (Hayes, 2018). The models consisted of one OXTR SNP (rs53576, rs237880, rs237887, rs237889, rs237898, rs2268490, rs2268491, rs4686302, rs6770632, or rs13316193) with the independent variable, PASCQpos or PASCNeg, as the moderator and depressive symptoms as the dependent variable, adjusted for the covariates.

All analyses were performed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The PROCESS macro for SPSS version 3.5 was used to test all interaction models and visualize interaction effects (Hayes, 2018).

Partial correlation was used to explore the relationship between the study variables while adjusting for lifetime parental depression, previous depressive symptom scores and sex, to rule out multicollinearity. No significant correlations were seen and, therefore, multicollinearity was not considered to be present in the study variables (data not shown). The assumption of multivariate normality was not violated. Normal P-P Plot of regression standardized residuals was used to evaluate the linearity and homogeneity (figure not shown). Heteroscedasticity was evaluated through a scatterplot with standardized residuals (figure not shown). Outcomes were all satisfactory, indicating a good model fit.

An a priori power analysis was conducted using G*Power (Faul et al., 2009) to test the effect of the dependent variables using linear regression models, with a small effect size ($f^2 = 0.02$), and an α of 0.05. Results indicated that a sample of 688 participants was required to achieve a power of 0.80.

The Johnson–Neyman regions of significance test (RoS) was used to evaluate support for the differential-susceptibility theory or the diathesis–stress model in the evaluation of $\text{cG} \times \text{E}$ interaction effects (Lazar and Zerbe, 2011; Roisman et al., 2012). The RoS test was used to evaluate whether there were significant associations between genotype and depressive symptoms at low and/or high scores of the PASCQpos. As recommended by Roisman et al. (Roisman et al., 2012), the RoS index was restricted to a range of interest ± 2 SD from the mean of the PASCQpos. Because the assumption of equal variances was violated, the heterocedasticity-consistent (HC) standard error estimator HC3 was used (Darlington and Hayes, 2017; White, 1980).

For the consideration of significance through all analyses, a two-sided $p$-value of 0.05 was considered (Fleiss, 1986), as recommended.
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Methods for handling multiple testing are Bonferroni correction (Rice et al., 2008) and the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Both methods are too conservative for cG × E studies (Craiu and Sun, 2008), where multiple testing is necessary and the chance of susceptibility allele effect sizes reaching significance is low or absent (Rice et al., 2008). In a setting where exploratory microarray

Table 1. Characteristics of the study sample.

| Measure          | Mean (SD) | Mann–Whitney U test |
|------------------|-----------|---------------------|
|                  | Male      | Female              |
| PASCQpos         | 7.48 (5.41) | 7.54 (5.67)   |
| PASCQneg         | 28.17 (5.19) | 28.73 (5.18)   |
| Depressive symptoms | 2.18 (2.55) | 3.65 (2.84)   |
| N                | 400       | 698                 |

Table 2. Correlation estimates of the independent variables, moderation of OXTR SNP rs6770632 and negative parenting on depressive symptoms among young adults, and region of significance values of PASCQneg.

| Moderation models | Correlation estimates | Regression estimated | Region of significance |
|-------------------|-----------------------|----------------------|------------------------|
| Model composition | r6770632 PASCQneg     | Sex                  | Previous depressive symptoms |
|                   |                       | Interaction          |                        |
| r6770632          | -                     | -.003                | 0.002                  |
| PASCQneg          | -.006                 | 0.028                | 0.328**                |
| Sex               | -                     | -.020                | 0.311**                |
| Parental depression| -                    | -.085**               | 0.226                  |
| Previous depressive symptoms | - | -.005                 | 0.352                  |
| r6770632 × PASCQneg |                |                       |                        |
| Model summary     |                       | Test of highest order unconditional interaction | Upper 13.992 |
| R                 | 0.419                 | ΔR2                  | 0.004                  |
| R2                | 0.176                 | F(HC3)               | 35.746                 |
| F(HC3)            | 35.746                | df (1,2)             | 1.955                  |
| p                 | 0.034                 |                       |                        |
| Correlation estimates |                       |                       | Region of significance |
| r6770632          | Not applicable        | Test of highest order unconditional interaction | 0.241 |-0.798 | 0.425 |
| PASCQneg          |                       |                       |                        |
| Model summary     |                       |                       | Region of significance |
| R                 | 0.185                 | ΔR2                  | 0.002                  |
| R2                | 0.034                 | F(HC3)               | 1.743                  |
| F(HC3)            | 10.270                | df (1,2)             | 1.972                  |
| p                 | <.001                 |                       |                        |

*p < .05, **p < .01, ***p < .001
1 Model adjusted for sex, parental depression, and previous depressive symptom scores at wave II
2 non-adjusted model; b = unstandardized regression coefficient; ΔR2 = R2 change due to interaction
3 Johnson–Neyman region of significance on PASCQneg; PASCQneg = Parents as Social Context Questionnaire, negative dimension; % above = per cent of the sample above ReS values; HC3 = heteroscedasticity-consistent (HC) standard error
analyses are conducted, a less conservative correction may be more suitable for identifying promising genes (Craiu and Sun, 2008). Therefore, as the aim of the present study was to evaluate potential interaction effects on depressive symptoms, no correction for multiple analyses was made, and the positive findings might not survive conventional testing for multiple comparisons.

3. Results

Genotype frequencies and characteristics of the study sample are described in Table 1. Non-significant two-way interactions are described in supplementary Table 1 and significant two-way interactions are described in Table 2 and visualized in Figs. 1 and 2.

3.1. Unconditional main effects

The variables PASCQpos, PASCQneg, and OXTR SNPs rs53576, rs237880, rs237887, rs237898, rs1042778, rs2268490, rs2268491, rs4686302, rs6770632, and rs13316193 were tested as unconditional main effects on depressive symptoms in multiple linear regression models. There was a significant main effect for the OXTR SNP rs1042778, $b = -0.473$, $t(13) = 3.079$, $p = 0.002$, where T:T carriers reported the highest levels of depressive symptoms, followed by G:G carriers reporting the least amount of depressive symptoms. There were no significant main effects for the other OXTR SNPs (data not shown).

The environmental variables of parenting styles were significant as main effects, $b = -0.060$, $t(13) = -2.769$, $p = 0.006$, where high levels of PASCQpos were associated with low levels of depressive symptoms and high levels of PASCQneg were associated with high levels of depressive symptoms, $b = 0.050$, $t(13) = 2.468$, $p = 0.014$. The genetic main effects on depressive symptoms are displayed in a boxplot (Supplementary Figure 1).

3.2. Two-way interaction effects

Moderation analyses were conducted by estimating how self-reported depressive symptoms among young adults (wave III) could vary dependent on OXTR SNP (rs53576, rs237880, rs237887, rs237889, rs237898, rs1042778, rs2268490, rs2268491, rs4686302, rs6770632, rs13316193) and perceived positive or negative parenting style while adjusting for parental depression, previous reports of depressive symptoms (wave II), and sex.

Significant two-way interaction effects were seen between OXTR SNP rs6770632 and negative parenting style on depressive symptoms among young adults (Table 2). The total model variance accounted for approximately 18%, where the model significantly predicted depressive symptoms, $F(6, 955) = 35.746$, $p < 0.001$.

The two-way interaction of rs6770632 × PASCQneg, $b = -0.051$, $t (955) = -2.128$, $p = 0.034$, accounted for $R^2 = 0.004$ of the variance in depressive symptoms, $F(1, 955) = 4.529$, $p = 0.034$.

Probing the interaction showed that the conditional effect of rs6770632 on depressive symptoms among young adults transitioned from non-significant to significant at a negative parenting style level of 19.072 points (i.e., the RoS value). The RoS value corresponded to negative parenting levels at approximately +2SD and above, $t(955) = -1.962$, $p = 0.05$, indicating that rs6770632 was associated with depressive symptoms only at higher levels of negative parenting style (Fig. 1). The two-way interaction of rs6770632 × PASCQpos was then visualized in a graph with rs6770632 as the grouping variable (A:A, C:A, and C:C). The graph was evaluated at the higher end of PASCQpos as the RoS suggested, indicating that A:A carriers of the rs6770632 who reported higher levels of negative parenting were more likely to report higher levels of depressive symptoms than C:A and C:C carriers (Table 2, Fig. 2).

No significant findings were observed for the other OXTR SNPs with negative parenting style or any of the OXTR SNPs with positive parenting style (Supplementary Table 1).

To evaluate the possible raw effects of cG × E on depressive symptoms in wave III, all moderation models containing depressive symptoms (wave III), one OXTR SNP, and negative parenting style were tested without the adjustment for parental depression, previous reports of depressive symptoms (wave II), or sex. No significant cG × E effects were found (Table 2; additional model).

4. Discussion

The present study investigated potential conditional effects of

![Fig. 1. Johnson–Neyman region of significance of scores on negative parenting style with values of ± two standard deviations, 95% confidence intervals (upper and lower), and effect measurement on depressive symptoms among young adults.](attachment:image)
negative and positive parenting style in adolescence on the development of depressive symptoms in young adulthood depending on oxytocin receptor gene polymorphisms (OXTR SNPs). The results indicated weak longitudinal effects of the OXTR SNP rs6770632 in the model when adjusted for parental depression, sex, and previous depressive symptom scores. No significant effects of the other OXTR SNPs were found.

The OXTR SNP rs6770632 was significant in a two-way interaction with negative parenting style (rs6770632 × PASCQ\textsuperscript{neg}), supporting the diathesis-stress theory. However, the full statistical model accounted for 18% of the variance in depressive symptoms, which indicates that there might be other explanatory factors for differences in depressive symptoms. The interaction term rs6770632 × PASCQ\textsuperscript{neg} accounted for 0.4% of the variance in depressive symptoms which, although significant, could be interpreted as a null finding. Some potential explanations for the small variance could be that depression is linked to a cognitive processing bias to negative stimuli (McLeod et al., 2007). Oxytocin seems to reduce attentional bias towards negative stimuli among individuals with heightened depression levels (Ellenhorn et al., 2012). Moreover, even if the interaction is theoretically plausible, it may end in weak results with a small effect, and the power to detect interactions will be even more limited in a small population (Dick et al., 2015).

The findings of the present study indicated a weak pattern of OXTR SNP rs6770632 A:A carriers being more sensitive to negative parenting style than C:A and C:C carriers, yet no differences in the aspect of a positive parenting style. Previous research in genotype OXTR SNP rs53576 has suggested that A:A carriers seemed less responsive to a positive environment that could enhance future well-being, and that the same individuals also seemed less responsive towards a negative environment, a finding that might confer a risk for future stress-related disorders such as depression (McQuaid et al., 2014). Therefore, the effect of negative parenting on depression may be reduced in combination with some OXTR SNPs. In addition, the inconsistent results regarding relations between oxytocin and depression in previous research enhance the importance of further research and the necessity of clarifying and understanding such relationships (Kirsch, 2015).

Primary analyses showed a lack of significant interaction effects between the OXTR SNPs and positive parenting in relation to depressive symptoms. These findings may be due to different aspects. Positive parenting, as measured by the PASQ (Skinner et al., 2005), is not structured as an extension of negative parenting with a range from very negative to extensively positive, but has its own dimensions of low positive aspects and high positive aspects. A low score in positive parenting is, therefore, not necessarily equal to negative parenting and thereby a positive measure might not be robust enough to influence depressive symptoms as an interaction term with a genetic aspect. Previous research has stated that positive parenting is associated with decreased levels of depression among adolescents (Liu and Merritt, 2018; Keijser et al., 2020b) and that it could also serve as a buffering effect for negative environmental stressors and as a protector against future depression (Hazel et al., 2014; Milne and Lancaster, 2001; Odgers et al., 2012; Pinquart, 2017; Sanders et al., 2014). The lack of significance of cG × E with positive parenting suggests that a negative parenting style was more robust in the cG × E interaction in our sample as an effect on depressive symptoms among young adults.

An important aspect of the field of cG × E is the choice of environmental stressor. It is critical that the measurement is reliable, sets an empirical precedent, and is theoretically plausible (Dick et al., 2015). The research field of parenting styles has been studied for more than five decades (Baumrind and Black, 1967; Baumrind, 1971). The PASQ was conceptualized by Skinner et al. (2005) and is based on a theoretical framework of parenting. The PASQ has moreover been evaluated in different cultures, settings, and aspects (Keijser et al., 2020a; Skinner et al., 2005; Egeli et al., 2015; Chew and Wang, 2013; Ekim and Ocakci, 2016), and has also been linked to depressive symptoms (Keijser et al., 2020b). The time aspect of the environmental stressor included in the cG × E is important as well, and in some ways critical, because social and biological impacts tend to vary as a function of different developmental stages (Dick et al., 2015). In the present study, parenting style was measured during adolescence, which is known to be a sensitive period (Patton et al., 2008; Rice et al., 2003; Steiner et al., 2003). In summary, the PASQ was considered a valid environmental measurement in a cG × E context.

An additional finding of the present study was that the OXTR SNP rs1042778 had a significant main effect on depressive symptoms among young adults yet was not significant as an interaction effect. However, effects of genes should preferably be interpreted in interaction with an environmental factor. Kendler and Eaves (1986) stated that the aetiology of mental disorders is based on an understanding of relevant genetic factors, relevant environmental factors, and knowledge of the genetic and environmental interaction. Kendler and Eaves (1986) concluded that research on the genetic aetiology, and the environmental causation, of mental disorders would benefit from the interpretation of interaction effects.

Furthermore, oxytocin per se might not be uniquely beneficial but reliant on the interpretation of the situation, or on interindividual factors, and strengthens its effect through a heightened sensitivity to environmental cues (Ollif et al., 2013). It has been proposed that certain genotypes endorse increased plasticity and susceptibility to the effects of different environmental aspects and the carriers might, disproportionately, be affected adversely by a negative environment (Belsky and Pluess, 2009). Additionally, in the present study, 18% of the males and 34.9% of the females met the DSM-IV (American Psychiatric Association, 2000) A-criteria for major depressive disorder on the DRSR
The present study did not find any cG × E effects of OXTR SNP rs53576 and parenting style and, therefore, did not support either the diathesis-stress or differential susceptibility model, contrary to the previous findings of McQuaid et al. (2014), which suggested A:A carriers of the OXTR SNP rs53576 showed lower sensitivity to negative environments, and that these could lead to a decreased risk for developing stress-related disorders. Saphire-Bernstein et al. (2011) found an effect among A:A carriers of the OXTR SNP rs53576 in a negative environment, whereas Costa et al. (2009) found a positive unconditional effect between the G:G carriers of the OXTR SNP rs53576 and unipolar depression. A relationship between OXTR SNP rs2254298, negative life events, and depression was established in a study by Thompson et al. (2010), where female adolescent carriers of the A:G allele who had experienced negative life events due to maternal depression presented increased scores of depression. In line with the findings of Myers et al. (2014), no significantly observed relationship between OXTR SNP rs2377898 and depression was found in the present study. Contrary to the findings of Kawamura et al. (2010), no significant effects including either of the OXTR SNPs rs13316193 or rs226849 were seen in the present study. Kawamura et al. (2010) found an unconditional association between depressive temperament and a haplotype of OXTR SNPs including rs13316193 and rs226849. In a study conducted by Strauss et al. (2010), no significant associations between different SNPs in the OXTR, including rs237798, and childhood onset of mood disorders, such as depression, were found. In line with the study by Strauss et al. (2010), no significant association was found in the present study between rs237798 and depressive symptoms among young adults.

The OXTR SNPs rs6770632, rs1488467, and rs4564970 have individually been linked to aggressive behaviour (Ebstine et al., 2012; Hovy et al., 2016; Malik et al., 2012). Aggression or irritability is among the symptom criteria for Major Depressive Disorder (MDD) in the DSM-IV (American Psychiatric Association, 2000). The link between the OXTR SNP rs6770632 and depressive symptoms might be partly explained by the association between the genotypes and aggression because the DSRS measures symptoms of aggression and irritability as well. As outlined above, the present study did not find any robust interaction between the OXTR SNPs and parenting styles during adolescence in relation to the development of depressive symptoms in young adulthood. These findings thereby provide important information to the field of cG × E influence on mental illness.

4.1. Strengths and limitations

The present study has some strengths. The approximately equal distribution of the sexes and the study sample’s representativeness of the general population of Västmanland and of the county in relation to the general Swedish society can be considered strengths in terms of generalizability (SCB, 2012). Several recommendations for improving cG × E studies were followed: Empirical support for the selection of genes, a theory-driven selection of environment, presentation of power calculations for the detection of reasonable effect sizes, and tests of the robustness of the interaction (Dick et al., 2015; Salvatore and Dick, 2015). The adjustment for previous depressive symptom reports and parental depression in the two-way analyses brings robustness to the findings due to the high levels of heritability (Parker and Roy, 2001; Thapar et al., 2012; Weller et al., 2018).

The study also has several limitations. Depressive symptoms and parenting style were measured through self-report questionnaires, which includes a risk of information bias from false-positive or false-negative participant reports. The present study did not control for psychiatric comorbidity in the participants, although this is common in the presence of depressive symptoms (Parker and Roy, 2001; Thapar et al., 2012; Weller et al., 2018). The models did not account for other confounding factors, such as parental divorce, family size, sexual abuse, or other dysfunctionality within the family (Parker and Roy, 2001). The present study did not account for other environmental factors such as peer stressors, even though previous research has shown the impact of such factors in the onset of depression (Oppenheimer et al., 2018). Moreover, no information on psychopharmacological treatment or therapeutic treatment was available, which is problematic because it might allow the misclassification of participants with ongoing depression as non-depressive. Europeans are often considered a homogeneous group (i.e., Caucasian) (Price et al., 2008), as in the present study, even though their genetic structure is strongly correlated with geographical location (Nelis et al., 2009). To prevent Type-I/II error caused by population stratification, and to detect differences in genetic variants that contribute to disease risk in association studies (Price et al., 2008), certain considerations need to be made. The present study did not account for differences within the Caucasian span that could affect the findings with false positive or false negative results. Therefore, a limitation of population stratification is present, and the findings should be interpreted carefully in this regard.

Information regarding the allele frequencies among the parents, which could have further contributed to our analyses, was not available. A further limitation is that multiple analyses were conducted on the same dependent variable, which inflates the risk of Type I error (Armstrong, 2014). There are methods for handling multiple testing, such as the Bonferroni correction (Rice et al., 2008). However, in cG × E research, where multiple testing is necessary, the Bonferroni correction is not practical because it does not account for correlations between the different models due to linkage disequilibrium; it is too conservative in that sense (Rice et al., 2008). Moreover, the chance of the susceptibility allele effect sizes reaching significance is low or absent (Rice et al., 2008) and, therefore, the number of false negatives may be large (Kim, 2015; McDonald, 2014). Another method to handle multiple testing is the FDR (Benjamini and Hochberg, 1995). FDR is an expected proportion of false positive findings (Benjamini and Hochberg, 1995), but even though it is less conservative than the Benferroni correction, it may still be too conservative in the cG × E context (Craiu and Sun, 2008). The Bonferroni correction (Kim, 2015; McDonald, 2014) and the FDR (Benjamini and Hochberg, 1995) might not be useful in a study that aims to screen for many predictors to be used in future research (Craiu and Sun, 2008). No method of correction was used in the present study and, therefore, the positive findings might not survive conventional testing for multiple comparisons. The absence of correction is a limitation; however, as the aim of the present study was to evaluate potential interaction effects on depressive symptoms, the significant findings should be considered an indication for future research.

One way to decrease the Type I and II error levels in the data is to use a fairly large sample size, which reduces standard errors when all other conditions remain the same; a large sample size can produce acceptably low levels of both types of errors (Kim, 2015). However, in genetic analyses, a sample size of >1000 should be considered fairly small and the significant results from the present study should thereby be interpreted with caution.

5. Conclusion

The present study investigated the potential interaction between different OXTR SNPs and parenting style in relation to depressive symptoms among young adults. The findings indicate that OXTR was a less robust gene in the cG × E interaction models, where one out of eleven SNPs displayed a modest effect. Despite this, the evaluation of OXTR SNPs may contribute to the understanding of oxytocin’s role in depressive symptomatology among young adults because the field is still
novel with results that vary. Researchers involved in mental health and development could benefit from an awareness of these findings.

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Authors’ contributions

All authors were involved in the conception of the present study and the study design. CA and RK were involved in the collection of data. RK and SO performed the statistical analyses and all authors interpreted the results. RK drafted the manuscript and SO, KWN and CÅ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Data availability

The raw data required to reproduce these findings are available from the authors upon request.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.114057.

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