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Oxytocin receptor genotype moderates the association between maternal prenatal stress and infant early self-regulation

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ABSTRACT

Introduction: Maternal prenatal stress may have long-term adverse consequences for child development. Accumulating evidence shows that the oxytocin-receptor genotype may play a role in differential susceptibility to early-life adversity, but no studies have examined whether this moderation extends to the prenatal stress exposures.
Methods: In the FinnBrain Birth Cohort Study, a sample of 1173 mother-child dyads were examined. We studied the possible moderating effect of the cumulative effect of infant oxytocin-receptor risk genotypes (rs53576GG and rs2254298A) in the association between maternal prenatal stress, and infant negative reactivity and emerging self-regulation at 6 months of age.
Results: The number of OTr risk genotypes moderated the association between maternal prenatal anxiety and infant self-regulation, implying a cumulative effect of genotype, although effects sizes were small. In infants with two risk genotypes, a negative association between prenatal anxiety and self-regulation was observed, whereas in infants with one or no risk genotypes, the association between maternal prenatal anxiety and temperament was non-significant.
Conclusion: Oxytocin-receptor genotype may moderate the association of maternal stress during pregnancy and child social-emotional development. Possible mechanisms for this moderation effect are discussed. Further studies with a more comprehensive polygenic approach are needed to confirm these results.

1. Introduction

Accumulating evidence both in animals and humans shows that maternal psychosocial stress during pregnancy may have persistent adverse effects for offspring development (Gray et al., 2017; Van den Bergh et al., 2020; Madigan et al., 2018; Meaney, 2018). Maternal prenatal stress (PS) has been associated with subsequent cognitive delays, emotional problems, as well as aberrant brain structure in the infant (Bergman et al., 2007; Blair et al., 2011; Buss et al., 2011, 2012; Lehtola et al., 2020). However, the mechanisms behind these associations are still largely unclear (Beijers, Buitelaar and de Weerth, 2014). It has been proposed that increased exposure to stress-related peptides and hormones in utero likely plays a role in programming the emotional development of the offspring (Sandman et al., 2011; Entringer et al., 2015; Van den Bergh et al., 2020).

Furthermore, it is widely acknowledged that individuals vary in the

Abbreviations: PS, Prenatal stress; OT, Oxytocin; OTr, Oxytocin receptor; SNP, Single nucleotide polymorphism.

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degree to which they are affected by environmental influences, but little is known about the mechanisms that convey such individual resilience and vulnerability. The same seems to be true for the prenatal psychosocial stress influences, given the evidence that not all individuals are affected by such exposures (Abbott et al., 2018). The environmental sensitivity frameworks (Greven et al., 2019), including that of differential susceptibility (Belsky and Pluess, 2009b), sensory processing sensitivity (Aron and Aron, 1997) and biological sensitivity to context (Boyce, 2016) hypotheses suggest that this variation in environmental sensitivity is due to genetic makeup, and propose the existence of plasticity genes that confer higher susceptibility to both adverse and favorable influences in the environment (Belsky and van IJzendoorn, 2017). In other words, the same individuals that are most adversely affected by environmental adversity may also benefit most from the favorable environments (Belsky and Pluess, 2009b; Ellis et al., 2011; Pluess, 2015), but these models also include the possibilities of the individual only being affected by the adversity (i.e. diathesis-stress model; Monroe and Simons, 1991) or only by the favorability aspects (i.e. vantage sensitivity). However, since the basic understanding of genes or polygenic networks related to plasticity to different environmental contexts, including that of prenatal stress, is still incomplete, also the applicability of these models in different contexts is still inconsistent.

Oxytocin (OT) is a mammalian hormone and neuromodulator which has been found to be a key regulator of social attachment and parental behavior (Insel, 1997; Meyer-Lindenberg et al., 2011; Fineberg and Ross, 2017). Aberrant functioning of the brain's OT-system has been implicated in many psychiatric conditions involving social impairments, most notably autism spectrum disorders, schizophrenia and addictive disorders (Bartholomeusz et al., 2015; Bowen and Neumann, 2017; Young and Barrett, 2015). In studying the mechanisms of differential susceptibility to prenatal stress, the OT system is an interesting candidate. Individual differences in OT genotype may alter stress-sensitivity (Chen et al., 2017), as OT is released during exposure to stressors, and may have a neuroprotective role in stress-related glucocorticoid effects (Matsushita et al., 2019; Winter and Jurek, 2019).

Genetic research on OT implies that two common single nucleotide polymorphisms (SNP) (rs53576 and rs2254298) in the OT-receptor gene may be of particular importance for laying the foundation for interindividual differences in stress-sensitivity, social-cognitive development and psychopathology (Meyer-Lindenberg and Tost, 2012; Feldman et al., 2016; Toepfer et al., 2017). It has been proposed that rs53576 G, and rs2254298 A may be conceptualized as plasticity alleles, rendering the individual more sensitive to environmental influences (Toepfer et al., 2017); thus, reflecting environmental sensitivity introduced previously. In the case of rs53576, GG-homozygosity has been associated with many positive traits, such as higher trust and prosocial temperament (Tost et al., 2010; Krueger et al., 2012), higher parental sensitivity (Bakermans-Kranenburg and van IJzendoorn, 2008), and a higher predisposition to seek and benefit from social support (Kim et al., 2010; Chen et al., 2011). On the other hand, there is evidence that carriers of this genotype are also more vulnerable to the effects of early adversity. For example, Dannlowski et al. (2016) found that rs53576 GG-homozygotes showed stronger gray matter reduction with increasing experience of childhood adversity, whereas A-allele carriers did not. Similar results have been reported regarding the A-allele of rs2254298 (Brüne, 2012; Toepfer et al., 2017). Compared to GG-homozygotes, girls carrying the A/G genotype of rs2254298 showed increased susceptibility to depressive and anxiety symptoms if their mothers had a history of recurrent MDD (Thompson et al., 2011). Furthermore, Marusak et al. (2015) showed that A-allele carriers had higher amygdala activity when viewing emotional facial pictures compared to GG-homozygotes, and only among them, an association between stressful life-events and amygdala activity was observed. Overall, these findings speak for both genotypes possibly being involved in processes related to environmental sensitivity.

Previous studies suggest that several forms of maternal PS, including maternal perceived stress, depressive and anxiety symptoms, are associated with the child's temperament, more specifically, with higher negative emotional reactivity and poorer self-regulation (Korja et al., 2017; Van den Bergh et al., 2020), which in turn may predict higher risk for mental health problems in later life (De Pauw and Mervielde, 2010; Blair et al., 2011; Nielsen et al., 2019). Furthermore, in line with the environmental sensitivity frameworks, it is suggested that genotype may moderate the association between maternal PS and child temperament (Babineau et al., 2015; Pluess et al., 2011), although the evidence concerning specific single-nucleotide polymorphisms is inconsistent (Braithwaite et al., 2013). However, to our knowledge, there are no studies concerning the possible moderating effects of OTr genotype in the association between PS and infant temperament, although SNPs in the OTr gene have also been associated with temperament traits in adults (Tost et al., 2010). Furthermore, the possible cumulative effect of the OTr risk genotypes in predicting sensitivity to maternal PS has not been studied. Thus, the aim of this study was to expand on our earlier findings on maternal pregnancy-specific anxiety and depressive symptoms during pregnancy, and infant temperament (Nolvi et al., 2016). More specifically, we tested whether the cumulative effect of hypothesized risk genotypes in the OTr gene (rs53576 GG, rs2254298 A) contributes to the interindividual susceptibility to maternal PS, measured as maternal depressive and anxiety symptoms during pregnancy, in terms of infant temperament traits of negative emotional reactivity and emerging self-regulation at 6 months age. Based on the lack of previous research on the models of environmental sensitivity as well as the problem of prenatal stress lacking the aspects of positive environment (e.g. positive mental health) we did not set any hypothesis on the models (i.e. differential susceptibility vs. diathesis-stress); however, we conducted a supplementary analysis of these models.

2. Methods

2.1. Study and sample characteristics

This study is based on the prospective FinnBrain Birth Cohort Study (www.finnbrain.fi) (Karlsson et al., 2018). Subjects were recruited between December 2011 and April 2015 from maternal welfare clinics in the South-Western Hospital District and the Åland Islands in Finland. The study population (Cohort N = 3808 families) comprises of consecutive women attending the free of charge ultrasound [coverage close to 100% in the population (www.thl.fi)] at the gestational week 12, their children-to-be-born and fathers of the children/partners of the mothers. Here, we included those families from whom genotyped data from the infants was available, and where the mother had filled in all the questionnaires relevant for this study (n = 1173). After recruitment, the participants in this study filled in a set of self-report questionnaires three times during pregnancy, specifically at gestational weeks 14, 24, and 34, and at 6 months postpartum. Attrition analyses revealed that compared to the whole cohort, the subsample in this study had higher age (30.5 vs. 31.2 years, $p < 0.001$), was more highly educated ($p < 0.001$), and scored marginally lower in prenatal depression (mean EPDS score 4.89 vs. 5.35, $p < 0.001$) and general anxiety (3.18 vs 3.39, $p = 0.040$) in the first trimester of pregnancy. There were no significant differences in parity or pregnancy-specific anxiety ($p > 0.05$ for all).

2.2. Questionnaires

Basic information on the study participants included maternal age, parity, antidepressant use, and education level divided into three classes: 1. High school or lower, or vocational degree 2. Applied university/polytechnics degree 3. University degree. Information on parity, maternal age, maternal Body Mass Index (BMI) measured prepregnancy, smoking during pregnancy, infant sex and gestational age were drawn from national birth registers. Maternal stress was measured as depressive symptoms (in each trimester of pregnancy and at 6 months

postpartum), pregnancy-specific anxiety (in the second and third trimesters of pregnancy), as well as general anxiety symptoms (in each trimester of pregnancy). In the analyses, we standardized the maternal stress scores during pregnancy.

Depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden & Sagovsky 1987), a widely used questionnaire for screening postnatal depression, also validated in the prenatal period (Bergink et al., 2011). It is a 10- item self-report scale that asks respondents to rate their mood and other symptoms in the previous 7 days. Prenatal general anxiety was measured using the Symptom Checklist (SCL-90) (Derogatis et al., 1973; Holi et al., 1998), a self-report questionnaire to assess intensity of symptoms on many subscales. In this study, only the anxiety subscale that asks the respondent to report anxiety symptoms experienced in the previous month, was used. Pregnancy-specific anxiety was measured using the Pregnancy-related Anxiety Questionnaire (PRAQ), a validated 10-item questionnaire (Huizink et al., 2016). In all measures, higher scores indicated higher symptoms. Internal consistencies for all symptom scales was adequate (Cronbach's α 0.842–0.849 for SCL-90, 0.819–0.838 for EPDS, 0.817–0.820 for PRAQ).

Infant temperament, namely negative reactivity and emerging self-regulation were assessed using the widely used and validated Infant Behavior Questionnaire Revised Short Form (Gartstein and Rothbart, 2003; IBQ; Putnam et al., 2014). It consists of 94 items, where the parent is asked to assess the respective infant behavior based on the past week or two weeks on a scale from 1 to 7. The IBQ-R consists of three main dimensions, Surgency/Extraversion, Negative Affectivity and Orienting/Regulation, of which the two latter most commonly linked with PS were used in the present study and were named "Negative Reactivity" and "Emerging Self-Regulation". Both dimensions demonstrated adequate internal consistency in the present study (Cronbach's α 0.855 for negative reactivity, and 0.829 for emerging self-regulation). Higher scores on each dimension indicate higher respective temperament.

2.3. Genotyping

Umbilical cord blood sample was drawn from each newborn at birth. DNA samples were extracted according to standard procedures at the National Institute for Health and Welfare. DNA samples were genotyped with Illumina Infinium PsychArray BeadChip comprising 603132 SNPs (single nucleotide polymorphism) at Estonian Genome Centre and quality control (QC) was performed with PLINK 1.9 (www.cog-genomics.org/plink/1.9/) (Chang et al., 2015). Markers were removed for missingness (>5%) and Hardy-Weinberg equilibrium (p-value $< 1 \times 10^{-6}$). Individuals were checked for missing genotypes (>5%), relatedness (identical by descent calculation, PI_HAT>0.2) and population stratification (multidimensional scaling). After QC genotyped data was available for 2095 individuals. Genotyped data was imputed with IMPUTEv2 (Howie et al., 2009) using the 1000 Genomes project phase 3 haplotypes and a haplotype set of 1941 whole genome sequenced Finnish individuals as reference panels. Consistent with previous studies in other populations (reviewed in Chen et al., 2017), SNPs rs53576 and rs2254298 show no linkage disequilibrium ($r^2 = 0.002$) among the FinnBrain sample.

2.4. Statistical methods

Statistical tests were conducted using IBM SPSS version 24.0. Normality of distribution within variables was assessed visually and by using the cutoff values of ≤ 2 for skewness and ≤ 7 for kurtosis (Kim, 2013). Infant self-regulation followed normal distribution in its original form, while infant negative reactivity was log-transformed, after which it followed normal distribution. General linear models (GLM) were conducted to examine the cumulative OTr gene x PS interactions in predicting infant temperament when controlled for maternal education level, BMI, smoking, postnatal depressive symptoms, infant sex, and gestational age as covariates (see Supplement for more details). The models for each genotype separately are included in the Supplement. P-values were corrected for multiple testing using the FDR-method (Benjamini-Hochberg correction).

To test differential sensitivity to PS, we followed the guidelines proposed by Roisman et al. (2012) and made a set of post-hoc tests for the significant interactions identified using the cumulative OTr genotype. First, interactions were probed by testing whether the association between PS and each temperament trait in question was observed among the different genetic subtypes (0, 1, or 2 risk genotypes). Furthermore, a regions of significance analysis was conducted to test whether the individuals with more susceptibility genotypes showed sensitivity to both low and high levels of maternal PS in question (see Supplement). Both analyses were conducted using PROCESS Macro (Hayes, 2017) using indicator coding for the risk genotypes and controlled for the same covariates as the main models. The scatterplots were drawn using the R program and ggplot2 package (Wickham, 2016).

3. Results

3.1. Basic information and sample characteristics

The final sample consisted of 1173 mother-child dyads, and their sociodemographic information is presented in Table 1. Education was not associated with infant negative reactivity or self-regulation ($p > 0.05$ for both comparisons). Genotype frequencies are displayed in the supplementary material. Rs2254298 was dichotomized because AA-homozygosity was rare (0.6%, N = 7).

3.2. Bivariate associations

Bivariate associations showed main effects for prenatal anxiety and depression in predicting infant temperament. In the whole sample, prenatal anxiety (SCL-90), pregnancy-specific anxiety (PRAQ) and depressive symptoms were all associated with higher infant negative reactivity and poorer emerging self-regulation (Table 2). OTr genotypes in turn showed no main effects for either domain of infant temperament ($p > 0.05$ for all comparisons).

3.3. General linear models for cumulative genetic risk and maternal PS in predicting infant temperament

In bivariate analyses, in children carrying two risk genotypes, PS measures were most strongly associated with both higher negative reactivity and poorer self-regulation. In turn, in children with 0 risk genotypes, association between PS and negative reactivity was more

Table 1
Demographic information on the study sample.

Infant sex	627 girls (53.5%)546 boys (46.5%)	
Maternal education	low 31.8%mid 30.5%high 37.7%	
Parity	Primiparous 53.8%Multiparous 46.2%	
Maternal smoking	Non-smokers 90.5%1st trimester 6.5%Whole pregnancy 3.0%	
	Mean	SD
Maternal age (years)	31.2	4.3
Length of gestation (days)	279.6	9.9
Maternal prenatal EPDS	4.6	3.3
Maternal prenatal SCL	3.2	3.5
Maternal prenatal PRAQ	22.7	6.1
Maternal postnatal EPDS	4.4	4.1

EPDS = depressive symptoms (Edinburgh postnatal depression scale), SCL = anxiety symptoms (Symptom Checklist), PRAQ = Pregnancy-specific anxiety

Table 2
Zero-order correlations (Spearman's rho) between prenatal anxiety and depression, and infant temperament by number of risk genotypes.

		SCL-90		PRAQ		EPDS	
		NEG	REG	NEG	REG	NEG	REG
Whole sample		0.160**	-0.100**	0.165**	-0.042	0.199**	-0.096**
Number of risk genotypes	0 (N = 584)	0.167**	-0.047	0.151**	0.028	0.177**	-0.018
	1 (N = 514)	0.115**	-0.128**	0.137**	-0.089*	0.191**	-0.168**
	2 (N = 75)	0.428**	-0.326**	0.406**	-0.296**	0.386**	-0.202

**p < 0.01*p < 0.05

modest, and no association between PS and poorer self-regulation was observed (Table 2). The associations between prenatal anxiety symptoms and infant emerging self regulation are illustrated in Fig. 1.

In GLMs controlling for the range of covariates, the number of risk genotypes interacted with both maternal general anxiety (F=4.98, adj. p = 0.030, partial η^2 = 0.009), as well as pregnancy-specific anxiety (F=4.67, adj. p = 0.030, partial η^2 = 0.008) in predicting infant self-regulation. Infant negative reactivity showed no statistically significant interaction with maternal general anxiety (F=1.46, adj. p = 0.234) or pregnancy-specific anxiety (F=2.99, adj. p = 0.102). Maternal prenatal depression showed no interaction effects with the number of risk genotypes in predicting infant negative reactivity or self-regulation (p > 0.1 for both comparisons).

3.4. Post-Hoc analysis: probing the interactions

Simple slope analysis confirmed that maternal general anxiety was associated with poorer emerging infant self-regulation among the infants with 2 risk genotypes (rs53576 GG and rs2254298 A) (B = −0.07 [95% CI with 5000 bootstrapped samples −0.11, −0.03], p < 0.001) but not among the infants with 1 (B = −0.01, p = 0.26) or 0 risk genotypes (B = 0.001, p = 0.95). Similarly, pregnancy-specific anxiety was associated with poorer infant self-regulation only among infants with 2 risk genotypes (B = −0.08, [95% CI −0.15, −0.01], p = 0.027) but not among the infants with 1 (B = −0.02, p = 0.27) or 0 risk genotypes (B = 0.03, p = 0.15).

3.5. Supplementary analysis: regions of significance

The infants with 2 risk alleles showed poorer parent-reported self-regulation when exposed to higher levels of maternal general anxiety (Z = 3.38, 10% of cases above this threshold) and pregnancy-specific anxiety (Z = 2.98, 7% of cases above this threshold). However, there was no "vantage sensitivity" effect, thus, the infants did not show better self-regulation when exposed to lower levels of maternal anxiety (Z = −2.51 for general anxiety, 1.7% of cases falling into this group; no threshold was observed for pregnancy-specific anxiety). Altogether, the findings point out to the diathesis-stress model, thus, the infants with risk genotype being more vulnerable to the adversity (higher PS) in terms of their self-regulation.

4. Discussion

In the present study, OTr-genotype moderated the association between maternal prenatal anxiety and poorer self-regulation at 6 months of age. The association between maternal prenatal anxiety and infant temperament is a relatively well-established link that has been reported in several previous studies (Nolvi et al., 2016; Korja et al., 2017; Van den Bergh et al., 2020; Madigan et al., 2018). The cumulative genetic risk score of OTr single-nucleotide polymorphisms Rs53576 GG and rs2254298 A, was associated with higher infant susceptibility to the effects of maternal prenatal anxieties. However, although the preliminary analyses pointed out to similar interaction between maternal anxiety and OTr genotype in predicting infant negative reactivity, this association was not confirmed after multiple comparisons were taken into account, perhaps since a main effect was observed across genotypes. Our study is the first to demonstrate that OTr genotypes may play a role in determining susceptibility to prenatal influences. However, our results highlight the importance of a polygenic approach, as the examined risk genotypes individually showed small or non-significant interaction effects, and effect size even for the combined genotype was modest.

Our findings are well in line with the recent work on oxytocin

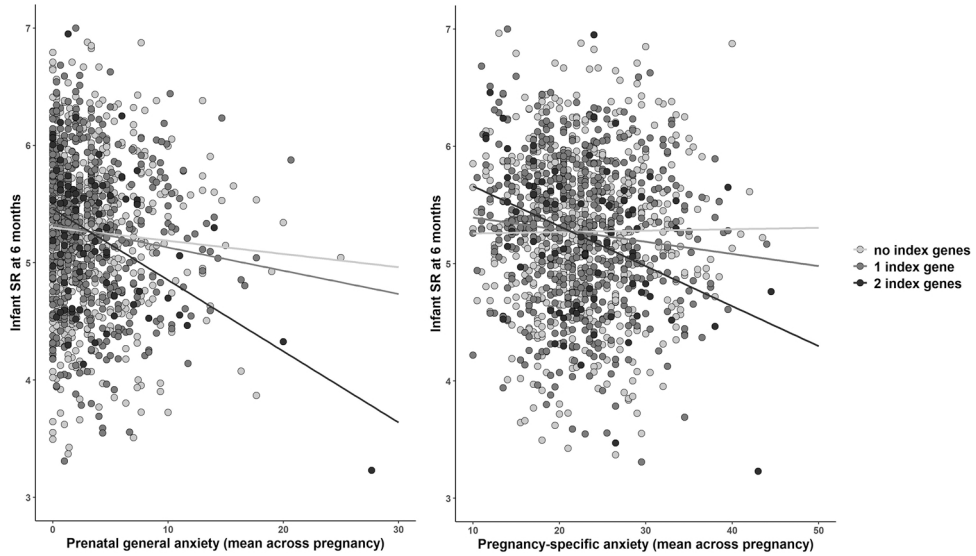

Fig. 1. The association between maternal general anxiety (left) and pregnancy-specific anxiety (right) during pregnancy and infant emerging self-regulation at 6 months.

receptor genetics suggesting that the G-allele of rs53576 and the A-allele of rs2254298 could function as plasticity alleles, increasing susceptibility to both favorable as well as harmful environmental influences (reviewed in Toepfer et al., 2017). G-allele carriers of rs53576 display several positive traits such as higher trust, empathy and prosociality (Rodrigues et al., 2009; Tost et al., 2010; Krueger et al., 2012). However, in the context of early-life adversity, the same GG-homozygosity seems to increase the risk for depressive symptoms, emotional dysregulation and altered brain structure (Bradley et al., 2011; McQuaid et al., 2013; Dannlowski et al., 2016). Importantly, our results suggest that the increased sensitivity to environmental influences conveyed by OTr plasticity alleles may already apply to *in utero* exposures.

The potential mechanism for this gene-environment interaction, however, warrants further investigation. The effects of maternal prenatal psychosocial stress for offspring development are thought to be largely mediated by excessive cortisol effects, due to chronic hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis (Beijers et al., 2014; Van den Bergh et al., 2020; O'Donnell and Meaney, 2017). Exposure to exogenous glucocorticoids is associated with harmful offspring outcomes both in animals in humans (Kapoor et al., 2008; Khalife et al., 2013). However, endogenous maternal cortisol levels during pregnancy have not been consistently linked to either maternal subjective stress or child outcomes (Zijlmans et al., 2015; Mustonen et al., 2019), suggesting that cortisol is unlikely the sole underlying mechanism in the effects of PS. More recently, attention has turned towards placental regulation of maternal cortisol, particularly the role of 11β-hydroxysteroid dehydrogenase 2 (11β-HSD-2), an enzyme that is highly expressed in fetal tissues and the placenta. 11β-HSD-2 converts maternal cortisol into its inactive form cortisone, thus protecting the fetus from excess glucocorticoid effects (Wyrwoll et al., 2011; Conradt et al., 2013).

Similarly, the OT system may play a role in buffering the harmful effects of prolonged glucocorticoid exposure. Chen, Heinrichs and Johnson (2017) have reviewed preliminary evidence showing that the SNPs examined in the present study (rs53576 and rs2254298) may contribute to individual differences in stress-sensitivity and regulation. The interaction between OT and physiological stress responses is complex, but several studies have shown that OT attenuates cortisol responses to stress, and may have neuroprotective effects in the context of increased glucocorticoid exposure (Heinrichs and Domes, 2008; Matsushita et al., 2019; Winter and Jurek, 2019). Physiological OT concentrations are increased in response to stressful stimuli, and in humans, exogenous OT administration decreases both subjective ratings and objective measures of stress (reviewed in Olff et al., 2013). Although the functional relevance of the SNPs studied here, as well as the role of OT in fetal development are incompletely understood, several studies suggest that G-allele carriers of rs53576 show higher stress reactivity, although discrepant findings have also been reported (Rodrigues et al., 2009). In a population-based sample of older adults, GG-homozygotes of rs53576 showed higher sympathetic reactivity to psychological stress, compared to A-allele carriers (Norman et al., 2012). G-allele carriers of rs53576 also show increased amygdala reactivity to emotional cues – a finding first reported by Tost et al. (2010) and later replicated by Dannlowski et al. (2016).

Finally, epigenetic alterations induced by PS and modulated by OTr genotype could also play a role in explaining these findings. Epigenetic changes, especially altered DNA methylation, have been widely observed in both animals and humans following PS exposure (reviewed in Cao-Lei et al., 2017). Altered DNA methylation patterns in the OTr gene have been observed in several psychiatric disorders (Kraaijenvanger et al., 2019), and some studies suggest PS could induce changes in the OTr epigenome (Cecil et al., 2014; Unternaehrer et al., 2016), although findings are inconclusive (Reviewed in Sosnowski et al., 2018). More important to the findings of the current study, few studies have examined the role of OTr genotype in these epigenetic patterns. Rijlaarsdam et al. (2017) recently reported that overall DNA methylation in the OTr gene was associated with child autistic traits only in GG-genotype carriers of rs53576. However, in their study DNA methylation in the OTr gene was not related to PS. In another study examining clinically depressed women and healthy controls, DNA methylation in the OTr gene was associated with depression, and this association was moderated by OTr genotype (rs53576) (Reiner et al., 2015). In sum, preliminary evidence shows a possible role of both PS and OTr genotype in epigenetic changes in the OTr gene, which in turn has been associated with psychopathologies also predicted by poorer self-regulation observed as an outcome in this study. However, given the scarcity of studies and partly contradictory findings, more research is needed in this area.

Interestingly, we observed that specifically maternal forms of anxiety interacted with OTr genotype to predict infant emerging self-regulation. The observed moderations were more robust for emerging self-regulation, whereas negative reactivity was more clearly associated with PS exposure regardless of the offspring genotype, which may explain the lack of significant interaction effects. This is in line with the large literature describing the link between PS and negative reactivity (Van den Bergh et al., 2020; Korja et al., 2017), suggesting that for self-regulation, the effects vary by susceptibility factors such as fetal genotype, as observed in the present study. However, notably, we observed a trend-like moderation by OTr genotype specifically concerning the association between pregnancy-specific anxiety and negative reactivity but not when examined with other types of PS – the finding we reported previously in a subsample of the current study (Nolvi et al., 2016). This finding may open further avenues on the understanding of the specific role of pregnancy-related anxiety in determining child behavioral development (O'Donnell and Meaney, 2017), and hint that there may be more complex pathways that link maternal response to pregnancy and offspring development, and most importantly, that oxytocin may play a role in these pathways. However, it must be noted that the magnitude of the effect observed in the present study was modest, and calls for further studies with more developed polygenotypes.

Strengths of our study include a longitudinal setting in a population-based cohort, and a relatively large sample size. Further, in the present study, maternal PS was assessed twice (pregnancy-specific anxiety) or thrice (other measures) during pregnancy, which provides a robust measure of maternal overall stress levels throughout the pregnancy, not only at single time point as in several similar studies. Some limitations of our study should be acknowledged. Firstly, we did not have data on the mothers' OTr genotype. It could be that the moderating effect described here is conveyed by maternal, not infant genotype. Similarly, maternal anxiety and infant temperament are both influenced by genotype. Therefore, our findings should be considered correlational, not proving causation. Secondly, maternal mental health affects postnatal mother-infant interaction that is as important environmental influence for emotional development as prenatal stressors. In this sample, although we corrected for postpartum depressive symptoms, we could not assess the association between interaction quality and temperament, and future studies should preferably take into account both prenatal and postnatal environment using more complex modelling. Thirdly, we only used mothers' reports on infant negative reactivity and self-regulation, which may be biased by maternal emotional state, including depression and anxiety (Goldsmith and Rothbart, 1991; Leerkes and Crockenberg, 2003). Future studies should also examine observations or physiological reactivity of infants which are more independent of the association between genotype and maternal ratings, although rarely available in sample sizes large enough for genotype research. Fourthly, attrition analyses revealed that compared to the whole cohort, the sample used in this substudy had higher age, was more educated, and scored slightly lower in prenatal depression and general anxiety, but not pregnancy-specific anxiety. This may have caused our sample to have less variation in the PS than in the main population and thus affected the findings, especially regarding the effects of higher end of PS on infant

temperament. Finally, as mentioned previously, we only examined two SNPs in the OTr gene that have been previously implicated in stress-sensitivity. Also, although the examined risk genotypes (rs53576 GG and rs2253298 A) were common, the combination of the two was relatively rare. Therefore the high-risk group was small (N = 75) compared to the study sample. Based on this study, however, this combination of OTr genotypes may be particularly relevant for individual differences in sensitivity. We underscore that as the effect sizes were modest, additional factors likely contribute to individual differences in sensitivity to PS.

5. Conclusions

In the current study, two common SNPs in the OTr gene additively moderated the association of maternal PS and infant temperament, more specifically, early development of regulatory ability. Rs53576 G and rs2254298 A that have been previously identified as risk genotypes increasing susceptibility to psychosocial stress, additively moderated the association of maternal PS and infant temperament. Our findings indicate that OTr genotype is involved in the interindividual variation in susceptibility to maternal distress, and that this increased susceptibility may already be observed during the prenatal period. However, the functional relevance of OTr genotype in humans, as well as the (polygenic) effects of OT in fetal development are still poorly understood and warrant further investigation.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105669.

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