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Journal

Journal of the American Academy of Child & Adolescent Psychiatry, 58(12)

ISSN

0890-8567

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Publication Date

2019-12-01

DOI

10.1016/j.jaac.2019.03.006

Peer reviewed

HHS Public Access

Author manuscript

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2019 December ; 58(12): 1207–1216. doi:10.1016/j.jaac.2019.03.006.

A Role of Oxytocin Receptor Gene Brain Tissue Expression Quantitative Trait Locus rs237895 in the Intergenerational Transmission of the Effects of Maternal Childhood Maltreatment

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Data from this study were presented at the Society of Biological Psychiatry's 73rd Annual Meeting, New York, NY, May 10-12, 2018.

Disclosure: Drs. O'Donnell, Entringer, Heim, Lin, MacIsaac, Kobor, Meaney, Provençal, Binder, Wadhwa, and Buss and Mr. Toepfer report no biomedical financial interests or potential conflicts of interest.

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Abstract

Objective: Women exposed to childhood maltreatment (CM) are more likely to exhibit insensitive parenting, which may have consequences for their offspring's development. Variation in the Oxytocin-receptor gene (*OXTR*) moderates risk of CM-associated long-term sequelae associated with mother-child attachment, although functionality of previously investigated SNPs remained elusive. Here, we investigated the role of *OXTR* rs237895, a brain tissue expression quantitative trait locus (eQTL), as a moderator of the relationship between CM and maternal behavior (MB) and the association between MB and offspring attachment security.

Method: Of 110 women with information on rs237895 genotype (T-allele=64, CC=46), n=107 have information on CM (CTQ) and n=99 on standardized observer-based ratings of MB at 6 months postpartum (responsivity and detachment), which were used in principal components analysis to obtain a latent factor representing MB. Offspring (n=86) attachment was evaluated at 12 months age. Analyses predicting MB were adjusted for socioeconomic status (SES), age, postpartum depression (PPD), and genotype-based ethnicity. Analyses predicting child attachment were adjusted for infant sex, SES, and PPD.

Results: rs237895 significantly moderates the relationship between CM and MB ($F_{1;66}$=7.99, p<.01), indicating that CM was associated with maternal insensitivity only in high *OXTR*-expressing T-allele carriers but not in low *OXTR*-expressing CC homozygotes. Moreover, maternal insensitivity predicted offspring insecure attachment (B= −.551; p<.05).

Conclusion: Women with a high *OXTR* expressing genotype are more susceptible to CM-related impairments in MB that, in turn, predicts attachment security in their children, supporting the role of the OT-system in the intergenerational transmission of risk associated with maternal CM.

Keywords

gene-environment interaction; childhood maltreatment; intergenerational transmission; cxytocin receptor gene; parenting

Introduction

The potentially deleterious long-term consequences of exposure to childhood maltreatment (CM) on mental and physical health are well established.[1] Furthermore, the detrimental effects of CM exposure do not seem to be restricted to the exposed individual alone, but might also impact the next generation.[2] There is empirical evidence that offspring of CM-exposed mothers are at increased risk for depressive symptoms and insecure attachment.[3,4] In the context of maternal CM exposure, this intergenerational transmission of CM-associated sequelae is hypothesized to occur during the pre- and postnatal periods of development via multiple, partly overlapping pathways,[5,6] including altered gestational maternal-placental-fetal stress physiology in CM-exposed women,[7] increased risk for maternal depression,[8] and non-optimal maternal behavior (MB).[9] To date, most research has focused on behavioral aspects of the postnatal mother-to-child transmission of maternal CM exposure. It is, however, evident that not all women (and their offspring) are equally vulnerable to the long-term consequences of CM exposure. Addressing this issue of inter-individual differences in susceptibility, we have proposed a conceptual framework[6] that highlights the crucial role of the oxytocin (OT) neuropeptide system in the intergenerational transmission of maternal CM exposure for the following reasons: First, substantial evidence highlights the importance of OT in MB,[10] which is considered a primary postnatal transmission pathway of maternal CM exposure to her offspring.[11] Second, women with exposure to CM exhibit decreased concentrations of OT in plasma and cerebrospinal fluid.[12,13] Lower OT concentrations, in turn, have been shown to be associated with non-optimal MB,[14] which is a significant predictor for offspring attachment problems.[15] Third, growing evidence suggests an important role of genetic variation in oxytocin pathway genes (i.e., oxytocin receptor gene [*OXTR*] and the oxytocin gene [*OXT*]) for MB[16] in moderating the association between CM exposure and subsequent risk for psychopathology,[17] and sub-optimal MB amongst others.[18] At the neural level, genetic variation in *OXTR* predicts differential activation within the social salience network (SSN) during perception of social stimuli.[19,20] Within the SSN that is comprised of highly interconnected meso-cortico-limbic structures (e.g., ventral striatum [VS], anterior cingulate cortex [ACC], amygdala), oxytocin, via its receptor, synchronizes neural activity between SSN-nodes,[19] providing a potential mechanism to confer greater sensitivity to the social environment. Most studies of gene-environment interactions investigating OT-pathway genes have focused on specific single nucleotide polymorphisms (SNPs) in *OXTR*, i.e., rs53576 and rs2254298, without clarifying their functionality.[6] The first study to address functionality of *Oxtr* SNPs demonstrated that in monogamous prairie voles, genetic variation in *Oxtr* strongly predicted *Oxtr* gene expression in the nucleus accumbens, accompanied by significant behavioral effects.[21] Compared to animals carrying the “low *Oxtr*-expression” genotype, homozygous “high *Oxtr*-expression” genotype carriers displayed significantly more attachment towards their partner providing first mechanistic insight into the behavioral consequences of a striatal *Oxtr*

expression quantitative trait locus (eQTL).[21] Although not considering the moderating role of environmental variation, this study added a critical piece of evidence to better understand how *Oxtr* genetic variation may contribute to behavioral differences. Collectively, these data suggest that genetic variation in *OXTR* might contribute to individual differences in sensitivity to the (early) social environment, mediated by increased reactivity of neural circuits that underlie response to the social environment as well as MB. Based on this evidence, we hypothesize that a genetic predisposition for increased social sensitivity (due to increased *OXTR* expression) may be associated with higher risk for suboptimal MB after CM exposure, with ensuing consequences for offspring development. We took advantage of publicly-available resources providing information on genetic variation and genotype-specific gene expression in discrete post mortem brain tissues – so-called brain tissue eQTLs.[22,23] Here, we test the hypothesis that women carrying a "high *OXTR*-expressing" genotype are more sensitive to their (early) environment, and we expect them to exhibit greater CM-associated long-term adaptations in their MB compared to "low *OXTR*-expressing" genotype carriers. Moreover, we expect variation in MB to predict attachment security in the next generation, as has been shown previously,[15] thus providing evidence for a pathway transmitting the effects of maternal CM exposure to the next generation. To test these hypotheses, we conducted a prospective longitudinal study in a total of N=121 mother-child dyads. Mothers were genotyped and provided information on their own CM exposure. During a home visit at six months postpartum, MB was assessed by video recording behavior of mother-child dyads in standardized situations, which was later coded by trained observers. At one year of age, infant attachment security was characterized during the Strange Situation Paradigm (SSP).

Method

Participants:

The study was conducted at the University of California, Irvine, Development, Health and Disease Research Program in a sample of N=121 pregnant women with singleton pregnancies and their children. The cohort is described in greater detail elsewhere.[24] The UCI Institutional Review Board approved all study procedures, and all participants provided written informed consent.

Genotyping, SNP imputation and *OXTR* eQTL selection:

DNA extraction was performed on fasting blood samples collected during the first trimester of pregnancy (N=121). Whole-genome SNP genotyping was performed using Illumina HumanOmniExpress BeadChip according to the manufacturer's standard protocols. Quality control (QC) of genotype data was performed using PLINK v1.9.48, where variants with call rates < 98%, minor allele frequency (MAF) < 5%, or Hardy-Weinberg Equilibrium (HWE) test $P < 1\times10-6$ were removed. A total of 599.935 genotypes passed QC and all mothers had genotyping rates > 98% with no gender mismatches. Twelve mothers were identified as relatives (i.e., >25% shared genotype), where one individual of each related pair was removed (n=6), leaving n=115 mothers for the analysis. To complete the dataset and obtain genotype information of variants not covered on the array, we used imputation to predict the unobserved genotypes by linkage disequilibrium (LD) with the genotyped SNPs of the array

based on an external reference panel of haplotypes. Genotype data were imputed to the 1000 Genomes Phase 3 reference panel using SHAPEIT2[25] and IMPUTE2.[26] After imputation, variants with a MAF < 5% or an INFO metric < 0.8 were removed. The information metric (INFO metric) takes ranges between 0 and 1, where values near 1 indicate that a SNP has been imputed with high certainty. The INFO metric is used to remove poorly imputed SNPs. Although there is no consensus in filtering the imputed datasets based on uncertainty of imputation, we used a conservative threshold of 0.8. To select a functional *OXTR* variant in this subset of n=115 women, we used the GTEx database (gtexportal.org).[22] Using the tissue eQTL visualizer, we identified a haplotype of twelve *OXTR* brain tissue eQTLs (LD cutoff: $r^2 \geq .2$) spanning approximately 8kb (Chr20: 8804371-8812411bp). From this haplotype, we sought to identify an *OXTR* brain tissue eQTL that satisfies two criteria. First, the eQTL should significantly predict gene expression in brain areas known to be involved in MB and social information processing (i.e., ventral striatum, amygdala, anterior cingulate cortex and frontal cortex). To achieve this, GTEx provides a multi-tissue eQTL visualizer indicating the strength, direction and p-value of an eQTL as well as a metric (m-value for posterior probabilities ranging between 0 and 1) that indicates whether a given SNP has meta-analytical evidence for having an eQTL effect (m-value ≥ .9) in a discrete brain region.[27] Second, the eQTL should best represent this *OXTR* eQTL haplotype in our study sample consisting primarily of two ethnicity groups (self-identified non-Hispanic white and self-identified Hispanic). To that end, we conducted a SNP-tagging analyses (https://snpinfo.niehs.nih.gov/snpinfo/snptag.html) for the two ancestry groups separately (based on 1000 genomes CEU and MXL populations) by applying a LD threshold of $r^2 \geq .2$. The resulting SNP that meets these two criteria is rs237895 (T > C). In all brain regions of interest, this SNP has a significant eQTL effect, i.e., predicts gene expression in caudate nucleus (normalized effect size/NES = −0.517, −log10 p-value = 1.2e-10, m-value = 1), putamen (NES = −0.419, p = 1.1e-5, m-value = 1), amygdala (NES = −0.428, p = 6.6e-4, m-value = 1), nucleus accumbens (NES = −0.317, p = 7.6e-4, m-value = 1), ACC (NES = −0.387, p = 2.1e-5, m-value = 1), and frontal cortex (NES = −0.324, p = 7.0e-5, m-value = 1; see Table S1; available online). The negative direction of the effect indicates that the reference allele (T) is associated with higher gene expression compared to the alternative allele (C). As an example, Figure S1 (available online) depicts *OXTR* gene expression in the caudate nucleus, which is allele-load dependent, i.e. the homozygous T-allele carriers exhibit the highest, T/C heterozygotes intermediate, and the homozygous C-allele carriers the lowest gene expression. Furthermore, also using the xQTL database (http://mostafavilab.stat.ubc.ca/xQTLServe), in an independent sample of post mortem brain tissue (N=494) rs237895 significantly predicts *OXTR* expression in the dorsolateral prefrontal cortex (r=−.523; p < 8.0e-10).[23] Since rs237895 is not covered on the HumanOmniExpress BeadChip, genotypes of rs237895 from the N=115 genetically unrelated women were extracted from the imputed data for all participants in this study. Rs237895 genotype could be imputed for N=110 women (T/T = 18, T/C = 46, C/C = 46) with sufficient quality (i.e., INFO metric >0.8), who were subsequently included in the statistical analyses. For the analyses, we assigned women to two genotype-groups depending on the presence of the high *OXTR* expressing T-allele (T/T and T/C combined, n=64) or absence of the same, i.e., low expressing CC-homozygotes (n=46).

Maternal CM Exposure:

Women provided self-reports about CM exposure using the Childhood Trauma Questionnaire (CTQ),[28] one of the most widely-used, reliable, and valid instruments to retrospectively assess early experiences of abuse and neglect. The CTQ assesses five different types of CM: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.[28] For each individual CTQ-subscale, we used established cut-off values (emotional abuse ≥ 13; physical abuse ≥ 10; sexual abuse ≥ 8; emotional neglect ≥ 15; and physical neglect ≥ 10) to create a binary variable indicating moderate or severe exposure for any of the five CTQ-subscales. Additionally, an overall binary variable was computed based on the CTQ to indicate moderate/severe childhood maltreatment (CM+) on at least one of the five CTQ-scales vs. no exposure to childhood maltreatment (CM−). We chose to not use the CTQ sum score as a predictor in the statistical analyses because it was not normally distributed as indicated by a Kolmogorov-Smirnov test ($D_{(107)}$= .20; p<.001).

Maternal Postnatal Behavior:

At six months postpartum, a home visit was conducted. Research staff was trained to reliably assess maternal emotional and verbal responsivity towards the infant using the Home Observation Measurement of the Environment Infant-Toddler version (HOME-IT).[29] Raters were considered reliable once they had two consecutive observations where 95% of responses matched the responses of a rater with extensive experience in coding the HOME-IT. The responsivity scale of the HOME includes 11 items capturing different aspects of maternal responsivity including maternal vocal reactivity to the infant or display of positive affect towards the infant. The internal consistency was moderate (*Cronbach's alpha* =.61) and comparable to previous studies reporting psychometric properties of this scale.[29,30] At the same visit and in addition to the HOME assessment, mothers were instructed to engage in a 15-minute standardized play situation as described in Jaeger.[31] The play situation was video-recorded and subsequently coded by two trained and reliable independent observers (intra-class correlation coefficient [ICC] >.9) using the coding manual of the NICHD Early Child Care Research Network.[31] We here focused on non-optimal MB and coded maternal detachment (1 = "not at all characteristic" – 5 = "highly characteristic"). Highly detached mothers appear emotionally uninvolved and disengaged during dyadic play, do not react to the child's signals in a contingent manner and can thus be considered unresponsive. In a next step, we conducted a principal component analysis (PCA) using the two maternal behavioral phenotypes responsivity and detachment. Results of the PCA indicated a one-factor solution (eigenvalue of factor 1 = 1.19; eigenvalue of factor 2 =.81). Detachment (.78) loaded positively, while maternal responsivity (−.78) loaded negatively on this extracted latent factor. Our one-factor solution explained 60% of the total variance. Higher scores on this latent variable indicate less optimal MB (i.e., higher detachment and lower responsivity) and we thus termed it "maternal insensitivity".

Infant Attachment at 12 Months Age:

Infant attachment security was assessed at twelve months during the Strange Situation Procedure (SSP).[32] The SSP, a standardized laboratory observation consists of eight episodes, each three minutes long. These episodes include short periods of interaction

between the mother and child, interaction between the child and an unfamiliar female stranger, and separation of the child from the mother followed by a reunion episode during which infant attachment is coded. Infants were categorized into three different types of attachment: securely attached (B), insecure-avoidant (A), and insecure-ambivalent (C). The relative frequencies of attachment categories was as follows: 62.2% were classified as securely attached (B), 30.6% as insecure-avoidant (A), and 7.1% as insecure-ambivalent (C). We used the dichotomous secure-insecure grouping (i.e., B vs. A and C) for data analysis because of the relatively small group size of type C attachment. Classification of attachment was completed by one rater with extensive experience in the assessment of attachment.

Covariates:

Analyses testing the predictive value of maternal CM and rs237895 genotype interactions for MB were adjusted for the potential confounding effects of variables that have been shown to be associated with CM exposure, the observed phenotype (MB), or both (see Table S2, available online). For this set of analyses, the covariates included maternal age, socio-economic status (SES), maternal depressive symptoms and racial/ethnic differences in genetic background. Information on annual household income and education (highest degree obtained) were aggregated to a composite measure indicative of socio-economic status (SES) as previously described in our study sample.[24] Women provided self-reports on postpartum depressive symptoms (PPD symptoms) using the Edinburgh Postnatal Depression Scale (EPDS),[33] a widely-used valid screening tool for PPD symptoms on three occasions during the first postnatal year (i.e., at one, six and twelve months). In order to account for the different time points in assessing the maternal phenotype (at six months) and infant attachment (at twelve months), we averaged EPDS-scores (all highly correlated across postnatal visits: r= .606 - .767; all correlation p-values <.001) depending on the predicted outcome. More specifically, we used an average of EPDS scores including the one and six month's assessments for analyses predicting maternal behavior at six months and an average including all three EPDS scores (one, six, twelve months) in the model predicting infant attachment at twelve months. Racial/ethnic differences in genetic background were accounted for by population stratification using principal component analysis on genotype data obtained using the Illumina OmniExpress array (Illumina, Inc., San Diego, CA). Genotype data for 593.229 SNPs survived quality control and SNP filtering (minor allele frequency ≥ 5%). The first three principal components were added to account for differences in genetic background (see Figure S2, available online). We also took parity status into account, which has been shown to predict differences in MB. All analyses testing the association between MB and offspring attachment were adjusted for SES, infant sex, and PPD symptoms.

Statistical Analyses:

All statistical analyses were performed using IBM SPSS version 22©. Prior to testing the gene-environment interaction in the prediction of MB, we evaluated the main effect of CM exposure on maternal behavior using a linear regression model, while controlling for all potential confounding variables (i.e., maternal age, SES, PC1-3, PPD symptoms). Maternal G-E analyses, were conducted using the SPSS PROCESS macro.[34] In the simple moderation analyses (Model 1), the binary maternal CM exposure variable (CM+/CM−) was entered as

the main predictor, the latent MB factor as the outcome, maternal dichotomous *OXTR* rs237895 genotype (T-allele vs. CC-homozygotes) as the moderator and maternal age, SES, genotype-based ethnicity, and maternal PPD symptoms as the covariates. For the prediction of attachment security (secure vs. insecure), a logistic regression analysis was performed using MB as the predictor and infant sex, SES, and PPD symptoms as covariates.

Results

Sample characteristics:

Information on socio-demographic characteristics, CM-experience, MB, PPD symptoms, and infant attachment are shown in Table 1 for the total sample (N=110) and stratified by rs237895 genotype as well as CM-exposure status. Importantly, neither CM-exposure ($p > .93$), nor maternal insensitivity ($p > .82$), nor infant attachment ($p > .5$) were significantly different between the genotype groups. Compared to women in the CM – group, CM+ subjects have a lower SES ($p < .01$) and report more PPD symptoms throughout the first year postpartum (all p-values <.05). CM groups did not differ in MB or infant attachment (see Table 1). Inter-correlations of all study variables are displayed in Table S2, **available online**.

Maternal CM exposure and rs237895 genotype effects on MB:

The linear regression model that tested the association between CM exposure and MB revealed no significant main effect of CM exposure ($b = -.31$, $p=0.2$). The main moderation model accounted for 38.36% of the variance in MB ($F(9,66) = 4.56$, $p < 0.001$; see Table 2). The maternal CM x rs237895 interaction was significantly associated with MB ($F(1,66) = 7.99$, $p < 0.01$). Confirming our hypothesis, post-hoc analyses revealed that only women carrying the high *OXTR* expressing T-allele showed significant differences in maternal insensitivity depending on CM exposure ($t = -.26$; $p = 0.015$; Cohen's $d = .92$), with CM-exposed women showing greater maternal insensitivity than non-CM exposed women. (Figure 1). In low-expressing CC-homozygous women, CM was not associated with MB ($t=.83$; $p =0.4$; Cohen's $d = -.26$).

MB and Infant Attachment at 12 Months:

MB significantly predicted offspring attachment security at 12 months ($B= -.551$; $p<.05$; Cohen's $d = -.51$; Figure 2) after controlling for SES, infant sex, and PPD symptoms. Infant attachment was higher in children of women with less maternal insensitivity. In other words, securely attached infants are overrepresented in the group of women who, based on median split, exhibited higher sensitivity (77.8% securely attached infants versus 22.2% insecurely attached). In women with greater insensitivity (> median), the prevalence of insecurely attached children increased 2-fold (45.0 % insecure attachment) compared to the group exhibiting low insensitivity.

Discussion

To the best of our knowledge, the findings described here provide first evidence of the moderating role of a functional *OXTR* variant in the process of intergenerational transmission of the effects of maternal CM exposure. Only women carrying the high *OXTR*

expressing T-allele exhibited significant differences in MB in conjunction with CM experience, with CM-exposed women experiencing greater insensitivity than non-CM-exposed women do. MB in C-allele homozygous women appears to be less impacted by CM exposure, indicating reduced behavioral adaptations after CM exposure in these individuals. Unlike previous studies that have either demonstrated a main effect of CM exposure[9] or *OXTR* genotype[16] in predicting MB, our findings highlight the importance of gene-environment interactions to predict MB. It appears that these observations are in accordance with the Differential Susceptibility Theory (DST).[35] However, the mere absence of early adversity (i.e., CM−) (conditions under which T-allele carrying mothers show the least amount of insensitivity) does not, *per se*, implicate the presence of a supportive and enriched early environment, which is an important premise of the DST framework that cannot be addressed in the current study. The CTQ, our environmental exposure, is not designed to capture positive aspects of the early environment. Nevertheless, our results support *OXTR* rs237895 functioning as a genetic moderator, and they are in line with prior research. It has been previously shown that genetic variation in *OXTR* predicts limbic reactivity to social cues[20] and MB[16] and moderates the association between CM exposure and depression as well as disorganized adult attachment.[17,36] By adopting a biologically informed SNP-selection strategy,[22,23] the present study corroborates, extends, and strengthens this line of research. In accordance with recent theoretical frameworks that postulate a role for oxytocin in modulating the salience of social cues,[37] we propose that genetic variation in *OXTR* eQTLs (e.g., rs237895) may operate through increased genotype-dependent *OXTR* expression in socially sensitive neural networks as an important neurobiological mechanism conferring heightened social-environmental susceptibility.

But why would mothers differ in the degree to which they adapt their reproductive (i.e., MB) strategies after CM exposure? Environmental variation, especially early social experiences (e.g., the mother's CM exposure) may operate via MB to shape offspring development, thereby ultimately promoting reproductive fitness in the next generation.[38] Strong support for this "maternal mediation hypothesis" comes from rodent studies showing how natural variations in MB (licking and grooming [LG]) may induce persistent behavioral and neurobiological changes in offspring.[38] As examples, offspring of low LG dams exhibit heightened stress-reactivity[39] and increased fearfulness,[40] phenotypes that promote survival in a dangerous environment. Furthermore, female offspring of low LG dams show alterations in MB consistent with their own rearing experience.[41] Directly translating this line of research to humans, we would predict that women exposed to CM should adapt their MB (i.e., lower responsivity, higher detachment) accordingly to transmit information about their own past aversive environment to their offspring. However, our data suggest otherwise, since the association between maternal CM exposure and MB appears to be dependent on maternal *OXTR* genotype. A possible explanation for this observation is the concept of bet-hedging.[42] Since the future is inherently unpredictable and early experiences (e.g., CM exposure) may not always accurately predict the future environment (e.g., dangerous/adverse environment for offspring), natural selection has maintained genes for both environmentally susceptible (e.g., high *OXTR* expression) as well as less susceptible (e.g., low *OXTR* expression) developmental strategies, to ultimately increase fitness payoffs regardless of environmental continuity.[35]

These possibly adaptive reproductive strategies may, however, come at a cost from the lens of a developmental psychopathology perspective rather than an evolutionary one. We show that less responsive and more detached MB is associated with insecure attachment in her child at 12 months age, which is in accordance with prior research.[15,32] Insecure attachment itself predicts anxiety,[43] internalizing and externalizing behavior[44] among other phenotypes, closing the cycle of intergenerational transmission of early life experiences.

Previous research in humans and animals has shown that MB is hormonally primed, and that this process starts as early as during pregnancy itself,[45] partly mediated via estrogen-induced up-regulation of oxytocin receptors.[46] An open question now is whether *OXTR* eQTLs exert their effects on brain gene expression through variable accessibility of transcription factors to chromatin. Given the fundamental role of sex-steroids in regulating *OXTR* gene expression and the fact that sex-steroids dramatically increase during pregnancy, this period represents a time window of critical importance to better understand the contribution of *OXTR* genetic variation in the association between CM and MB. Moreover, it is possible that additional prenatal factors, such as alterations in CM-associated maternal-placental-fetal stress physiology operate as mechanisms in the intergenerational transmission of risk associated with maternal CM exposure.[5] It remains to be elucidated whether these transmission pathways differ systematically between women carrying high or low susceptibility variants of rs237895. Moreover, in addition to maternal interactive behavior, future studies in the context of intergenerational transmission during the postnatal period should consider other postnatal variables such as breastfeeding status and breast milk composition, which may be different based on maternal CM experience. This is a relevant avenue of research aimed at understanding the mechanisms underlying intergenerational transmission of maternal CM given the common underlying neurobiology for breastfeeding and MB that crucially involve efficient OT-signaling.[47]”

MB is a complex phenotype emerging from extensive inter-connected neural circuitry underlying a wide array of executive, cognitive, motivational and self-regulatory functions,[48] and can be modulated by early childhood experiences,[6,11,41] OT-signaling,[49] and interactions of OT with other neurotransmitters such as dopamine among many others.[48] It would be informative for future studies to employ neuroimaging assessments to characterize neural functional and/or structural differences after CM exposure in genetically susceptible women. This will then provide further insights into the neural underpinnings of the associations between CM exposure and variation in MB. The SNP under investigation here, rs237895, predicts *OXTR* expression across multiple brain regions that are critical for MB, cognition and motivation (e.g., amygdala, ventral striatum [VS], ACC, PFC), raising the possibility that alterations in some or even most of the above-mentioned OT-associated functions might be critically altered in T-allele carriers after CM. Intriguingly, a previous study by Loth and colleagues has shown that another intronic *OXTR* SNP (rs237893, A>G), which tags the same *OXTR* eQTL haplotype as rs237895, predicts activity in the VS in response to social cues in an allele-load dependent manner.[20] VS reactivity was highest in high *OXTR*-expressing AA carriers and lowest in low expressing GG carriers.[20] Bearing in mind the well-documented role of OT-signaling in the VS for MB (e.g., affecting salience and reward of infant stimuli as well as infant-directed behavior),[50] the findings by Loth et al, by supporting the notion of higher social sensitivity in individuals carrying a high *OXTR*-

expression genotype, provide important insights into intermediate phenotypes at the intersection of gene-behavior associations that may theoretically vary depending on the early environment.

There are several limitations of the current study including the relatively small sample size and the lack of an independent replication sample. From a methodological point of view, a moderated mediation analyses would have been more suitable to test the entire intergenerational pathway from maternal CM-exposure to infant attachment in the next generation. However, the resulting sample size in the full model with no missing data for both mothers and children would have been relatively small (n=69). Consequently, the full model predicting attachment security, while including all covariates would have been vulnerable to overfitting in such a small sample, which is why we decided to test the paths in 2 separate models. In addition, we had to group the T-allele carrying women together for practical reasons because the homozygous T-allele group only included n=18 individuals. Given the allele-load dependent eQTL effect of rs237895, it would be interesting, in future larger samples to test the CM-MB association for all three groups of genotype separately. Also, rs237895 is not covered on the array used for genotyping. Thus, we performed an LD-based imputation and applied a conservative threshold (INFO metric >0.8) to acquire maternal genotype data with sufficient, albeit not perfect certainty. Moreover, only healthy pregnant women and their children participated in the study, limiting the number of women with severe CM exposure. Nevertheless, the prevalence estimate of CM exposure in the study sample is comparable with recent epidemiological data on CM exposure in the general population.[51] A retrospective self-report measure (CTQ) was used to assess maternal CM. While there were no differences in reported severity of CM between genotype groups and analyses adjusted for current mood, other potential variables that may influence self-reported childhood experiences (e.g., forgetting, recollection bias, or non-disclosure) cannot be ruled out entirely. Following recent recommendations,[52] we utilized objective observation-based ratings of MB to quantify our outcome, and raters were blind to maternal genotype and CM exposure, thereby strengthening confidence in the current findings. Also, we did not investigate offspring rs237895 genotype as a potential moderator in the association between MB and attachment security at 12 months. To do so, we would have needed to statistically control for maternal genotype (with whom children share 50% of genetic variation), thereby greatly reducing our ability to detect moderation effects that are exclusively attributable to offspring genotype in this small sample. Lastly, it is noteworthy that no infant was classified as being disorganized during the Strange Situation Procedure. This finding indicates that our study sample may not be entirely representative with respect to this characteristic, given prevalence estimates of disorganized attachment of approximately 15% in low-risk populations.[53]

With these caveats in mind, we conclude that OT-associated bio-behavioral mechanisms may be implicated in the postnatal transmission of the effects of maternal CM exposure to her offspring. From a translational point of view, two issues warrant particular attention. First, the SNP-selection strategy used here critically advances interpretability of gene-environment interactions involving *OXTR* gene variants in conferring differential susceptibility to the environment. Investigating the role of genetic variants with known effects on gene expression in the brain could help identify susceptible individuals at increased risk for

possible maladaptive developmental trajectories after CM exposure. Second, once identified, women at risk and their children could benefit from early interventions that have proven effective in promoting maternal sensitivity and secure attachment. As we have argued earlier, [6] it is likely that individuals with a genetic predisposition for increased social sensitivity may not only show greater impairments after adverse early experience, but also may be the ones who disproportionately profit from psychosocial interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was funded by a European Research Area Network (ERA Net) Neuron grant (MecTranGen 01EW1407A to C.B.), National Institutes of Health grants (R01 HD-060628 to P.D.W., R01 MH-091351 and R01 MH-105538 to C.B. and P.D.W., Environmental influences on Child Health Outcomes grant 5UG3OD023349 to C.B. and P.D.W.), and a European Research Council-Starting grant (ERC-639766 to C.B.).

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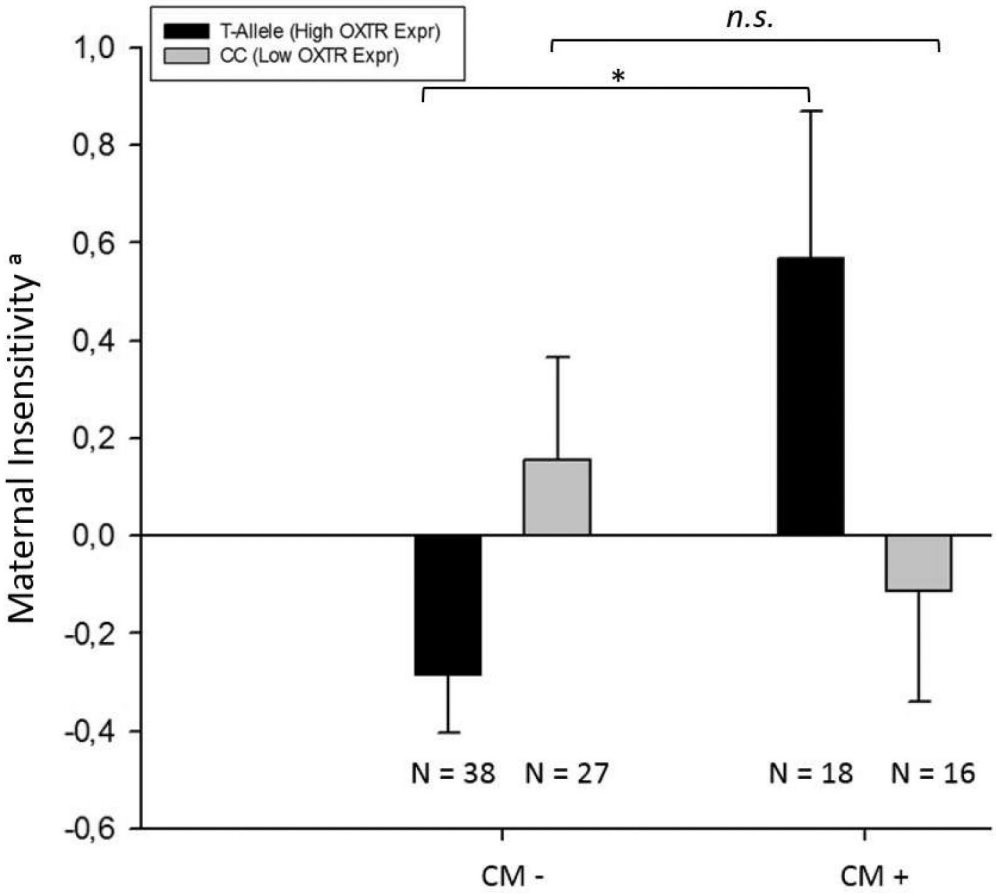

Figure 1:

Maternal Insensitivity Stratified by Maternal Childhood Maltreatment (CM) Exposure and *OXTR* rs237895 Genotype

Note: CM–indicates no Childhood Trauma Questionnaire (CTQ). Q-category above moderate cut-off. CM+ indicates one or more CTQ-categories above moderate cut-off. *OXTR* = Oxytocin Receptor Gene.

[a]Latent factor representing maternal insensitivity includes measures of maternal responsivity (HOME) and maternal detachment during play (see Method section for details). Higher scores indicate greater insensitivity.

* $p < .05$.

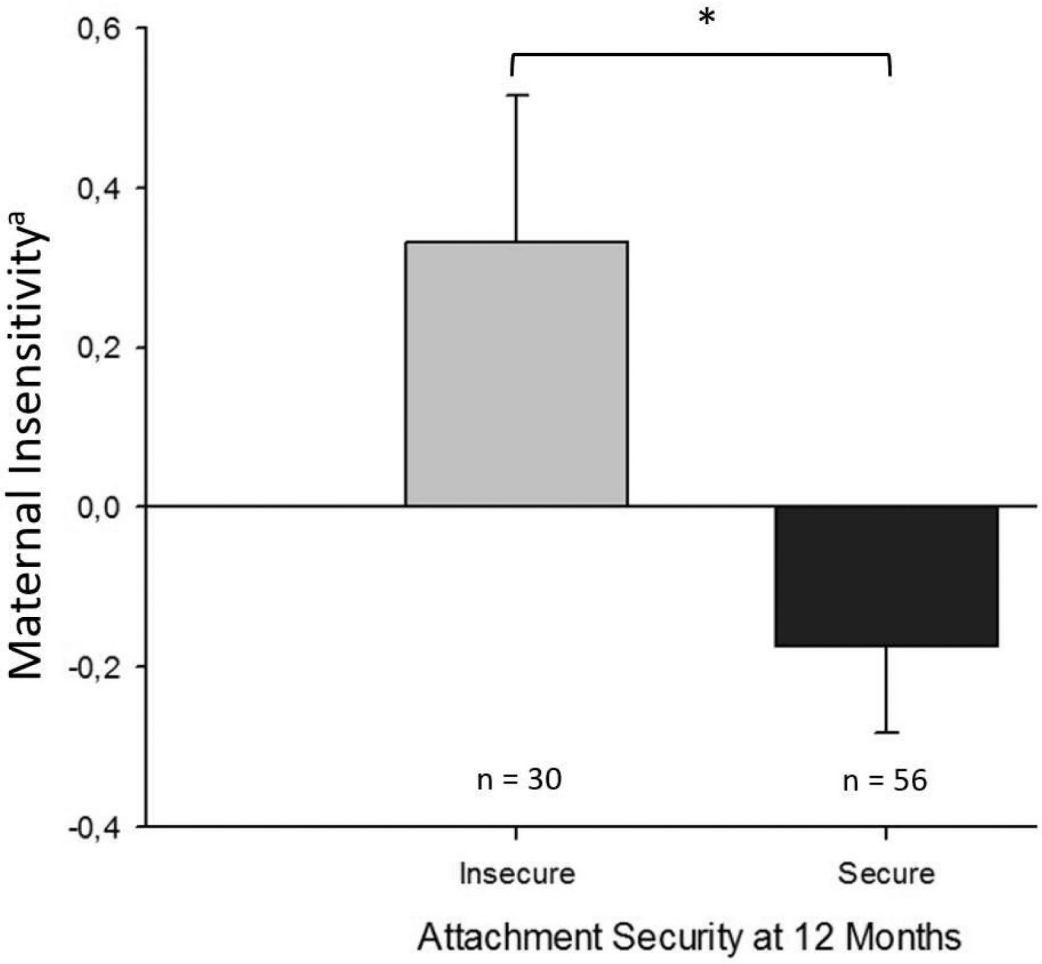

Figure 2:
Maternal Insensitivity Stratified by Offspring Attachment Security
Note: [a]Latent factor representing maternal insensitivity includes measures of maternal responsivity (HOME) and maternal detachment during play (see Method section for details). Higher scores indicate greater maternal insensitivity.
* $p<.05$

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2020 December 01.

Table 1

Characteristics of the Total Sample and Stratified by Maternal *OXTR* rs237895 Genotype and CM Exposure

Characteristics		***OXTR* rs237895 genotype**		***p-value***	**CM-exposure**[a]		***p-value***
	Total sample (N = 110)	**T-Allele carriers (n = 64)**	**CC-carriers (n = 46)**	**CM + (n = 38)**	**CM − (n = 69)**		
Maternal age (years; ± SD) at study entry	27.80 (5.07)	27.41 (5.14)	28.44 (4.71)	n.s.	26.81 (5.79)	28.37 (4.39)	n.s.
Maternal SES[b]	3.25 (0.97)	3.21(0.96)	3.27 (0.98)	n.s.	2.87 (0.91)	3.44 (0.94)	<.01
Maternal race/ethnicity (self-report; n, %)[c,f]							
Non-Hispanic White	44 (43.1%)	21 (35%)	23 (54.8%)	n.s.	9 (25.7%)	33 (51.6%)	n.s.
Hispanic White	38 (37.3%)	25 (41.7%)	13 (31%)	n.s.	18 (51.4%)	20 (31.3%)	n.s.
Asian	7 (6.9%)	5 (8.3%)	2 (4.8%)	n.s.	4 (11.5%)	3 (4.7%)	n.s.
Other	13 (12.8%)	9 (15%)	4 (9.6%)	n.s.	4 (11.4%)	8 (12.4%)	n.s.
Maternal behavior[d]							
Responsivity (HOME; range 0 −11)	8.28 (1.81)	8.17 (2.12)	8.42 (1.38)	n.s.	7.87 (2.43)	8.47 (1.46)	n.s.
Detachment (Play Situation, range 1 −5)	1.49 (0.83)	1.41 (0.76)	1.61 (0.92)	n.s.	1.61 (0.90)	1.45 (0.81)	n.s.
PPD symptoms (EPDS score ± SD; 1 month)	6.00 (4.66)	5.63 (4.25)	6.56 (5.24)	n.s.	7.54 (4.91)	5.16 (4.41)	<.05
PPD symptoms (6 months)	4.96 (4.66)	4.63 (4.02)	5.43 (5.50)	n.s.	6.30 (5.88)	4.16 (3.70)	<.05
PPD symptoms (12 months)	5.51 (4.37)	5.62 (4.17)	5.34 (4.72)	n.s.	7.92 (4.35)	4.29 (3.87)	<.01
CTQ Total Score (range 25-125)[a]	37.39 (14.97)	38.13 (16.46)	36.89 (12.80)	n.s.	51.37 (17.55)	30.04 (4.46)	<.001
CM+ (n, %)	38 (35.5%)	21 (33.3%)	17 (38.6%)				
CM− (n, %)	69 (64.5%)	42 (66.7%)	27 (61.4%)				
Infant attachment at 12 months[e,f]							
Securely attached (n, %)	56 (65.1%)	29 (61.7%)	27 (69.2%)	n.s.	18 (66.7%)	37 (64.9%)	n.s.
Insecurely attached (n, %)	30 (34.9%)	18 (38.3%)	12 (30.8%)	n.s.	9 (33.3%)	20 (35.1%)	n.s.

Note: CM = Childhood Maltreatment; CTQ = Childhood Trauma Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; *OXTR* = Oxytocin Receptor Gene; PPD = Postpartum depression; SES = Socioeconomic Status.

[a]Missing values in CM-exposure: n=3.

[b]SES is a composite measure of maternal education and annual household income, coded from 1 [low SES] to 5 [high SES].

[c]missing values in race/ethnicity self-report: n = 8 (n = 4 in each genotype group).

[d] missing values for maternal behavior: n = 11

[e] missing values for attachment security: n = 24.

[f] For categorical variables (Race/Ethnicity and Infant attachment), *Chi-square* tests were calculated.

Table 2:

Regression Table for Maternal CM x rs237895 Predicting Maternal Insensitivity[a]

Predictor	Coefficient	SE	t-statistic	p-value	95% CI
Constant	2.00	.62	3.21	<.01	.76 – 3.25
Maternal Age	−.08	.02	−3.18	<.01	−.13–−.03
SES[b]	−.05	.13	−.39	.70	−.32 – .21
PC1[c]	−3.72	1.35	−2.75	<.01	−6.41 – −1.02
PC2	1.41	1.14	1.24	.22	−.87 – 3.7
PC3	−.54	1.47	−.34	.71	−3.47 – 2.40
PPD symptoms[d]	.47	.23	2.02	<.05	.01 – .93
OXTR rs237895[e]	.23	.21	1.05	.30	−.21 – .66
Maternal CM[f]	−.26	.25	−1.05	.30	−.76 – .23
CM x rs237895	−1.18	.42	−2.83	<.01	−2.02 – −.35

Note: CM = Childhood Maltreatment; *OXTR* = Oxytocin Receptor Gene; PC = Principal Component; SES = Socioeconomic Status.

[a] maternal insensitivity: Latent factor derived from principal components analyses (see methods section for details).

[b] maternal SES comprised of annual household income and highest degree of education obtained (see methods for details);

[c] PC = Principal component representing maternal genotype-based ethnicity (see methods)

[d] Postpartum depressive symptoms: mean 6 months postpartum symptoms assessed at 1 month and 6 months (Edinburgh Postnatal Depression Scale [EPDS]);

[e] maternal *OXTR* rs237895 genotype dichotomized (T-allele vs CC-homozygous);

[f] maternal CM-exposure (dichotomous groups: CM− vs CM+; see methods for details).