Research Article

MATERNAL DEPRESSION AND CHILD OXYTOCIN RESPONSE; MODERATION BY MATERNAL OXYTOCIN AND RELATIONAL BEHAVIOR

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Background: *Maternal postpartum depression (PPD) carries long-term detrimental effects on children's well-being, yet the mechanisms of transmission remain unclear. One possible pathway of vulnerability involves the oxytocinergic (OT) system, which is transferred from mother to child via sensitive caregiving and is disrupted in PPD.* **Method:** *A large birth cohort (N = 1983) of women were repeatedly assessed for depression from birth to 6 years. Utilizing an extreme case design, two matched cohorts were formed; mothers chronically depressed from birth to 6 years and nondepressed controls (N = 97, depressed = 41, nondepressed; N = 56). At 6 years, mothers and children underwent psychiatric diagnosis, urinary OT was assayed from mother and child before and after social contact, and mother–child interactions were coded.* **Results:** *Baseline OT and OT response of mother and child were interrelated and children of depressed mothers showed low baseline OT and attenuated OT response. Child OT response was negatively predicted by maternal depression, child Axis-I psychopathology, maternal expressed negative affect, and child social withdrawal. Interaction effect of maternal baseline OT and depression emerged. Slope analysis indicated that when maternal OT was medium or low, child OT response was negatively impacted by maternal depression. However, when maternal OT was high, child OT was unaffected, suggesting that maternal OT functionality buffers the effects of depression on the child.* **Conclusion:** *Results suggest involvement of the OT system in the cross-generational transfer of vulnerability, as well as resilience, from depressed mothers to their children. Because the OT system is open to interventions that enhance maternal touch and contact, findings have important implications for targeted early dyadic inventions. Depression and Anxiety 0:1–12, 2015.*

Key words: *oxytocin; maternal depression; mother–child interaction; cross-generation transmission; child psychopathology; longitudinal studies*

INTRODUCTION

Maternal postpartum depression (PPD), affecting approximately 15% of women in industrial societies,[1] exerts long-term negative impact on children, including greater propensity to psychopathology, diminished emotional and behavioral regulation, lower social competencies and academic achievement, and disrupted stress response.[2–5] While the cross-generation transfer of psychiatric vulnerability from depressed mother

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to their children has been repeatedly demonstrated,[5–9] mechanisms of transmission remain unclear. One possible pathway involves the oxytocinergic (OT) system, which underpins the capacity to form affiliative bonds, read social signals, and function competently within the social world, abilities compromised in children of depressed mothers.[3,10] In this study, we use a well-selected birth cohort of mothers who were repeatedly assessed for depression from birth and up to the child's sixth year of life to test associations between OT functionality of mother and child and observed mother–child interactions, which are known to be disrupted in cases of PPD.[11–14]

The child's OT system develops in the context of the mother–infant bond and is shaped by parental OT and early caregiving experiences.[15,16] Studies across mammalian species have shown that maternal behavior during the sensitive postpartum period, including licking and grooming in rodents,[17] grooming and touch in primates,[18] and well-adapted synchronous parenting in humans,[19,20] shapes the infant's brain OT and peripheral OT response. The OT system is among the most evolutionary ancient and conserved systems, with receptors widely distributed throughout body and brain, including heart, pancreas, gut, and sexual organs. OT has a pulsatile nature of activity, which renders it particularly susceptible to environmental changes,[21,22] and it is a system highly open to epigenetic effects by the maternal–infant context during the first months of life.[17] In humans, measures of OT functionality in parents, such as allelic variations on the *OXTR*,[23,24] peripheral levels in plasma, saliva, and urine,[25,26] and intranasal OT administration,[20,27] predicted reciprocal parenting behavior. Furthermore, parent–child interactions containing more parental touch increased the parent's OT following parent–infant social contact.[28] Consistent with research in animals, human studies demonstrated associations between indices of OT functionality in parent and child, expressed in correlations between parent's and infant's baseline OT, coordinated increase in salivary OT following administration, and matched increase in OT response to well-adapted interactions.[19,20] Although human studies cannot demonstrate casual effects of parental OT on the child's OT response, as shown in animal models,[29] these studies appear to chart a sequence for the experience-dependence maturation of the OT system via mechanisms of cross-generation transmission in humans as well.[17,30] Accumulating evidence suggests that high maternal OT underpins a more positive maternal style,[15,26] leading to the consolidation of higher baseline OT in the child and greater OT response to mother–child interactions, [19,31] although few studies reveal inconsistent results.[32] Through mechanisms of positive feedback, supported by the autoregulated dendritic release of OT and its hormone-like function in the brain,[33,34] this sequence establishes a greater propensity in the child to respond with OT increase to future social contacts, particularly with close friends and intimate partners. Yet, the entire sequence leading from maternal OT to the child's OT response as mediated by variations in maternal and child's social behavior has not been tested in a single study, nor has it been tested in the context of PPD.

Associations between major depressive disorder (MDD) and the OT system have been shown in several studies. Most studies found that individuals with MDD have lower levels of OT,[35–42]; however, one study found higher levels,[43] and two showed greater OT variability in MDD.[44,45] Furthermore, intranasal administration of OT showed opposite effects on depressed and nondepressed individuals.[46] Taken together, these studies suggest that although more research is needed for conclusive statements, studies have consistently shown impairments of OT functioning in MDD. Moreover, in the context of PPD, all studies found negative associations between OT levels and the degree of maternal depression.[38,39,47–51] For instance, higher levels of maternal depressive symptoms throughout pregnancy predicted lower maternal plasma OT in the postpartum;[51] depressed mothers showed lower increase in OT following breastfeeding;[38,49] and maternal depressive symptoms moderated the relations between more functional variant on the *OXTR* and women's reaction to their infant's cry.[52] Depressed mothers and their children showed lower peripheral OT, which predicted reduced child social engagement and lower empathy.[48] Finally, mothers' OT moderated the relation between psychosocial stress and maternal depression and interactive behavior.[50] Thus, it appears that in the context of PPD the negative associations between OT and depressive symptoms have been more consistently found than in relation to MDD in general.

In addition to OT, maternal depression has been repeatedly linked with deficient caregiving. Depressed mothers express significantly more negative affect, anger, and intrusive behavior and their infants display greater social withdrawal.[53,54] Angry, controlling mothering also characterizes interactions between depressed mothers and their children beyond infancy,[55] and high child withdrawal is an early risk marker for later depression.[56] These findings suggest that familial risk for depression may be associated not only with emotion dysregulation and stress reactivity,[57] but may stem from the child's difficulty in forming close relationships and master social competencies, abilities learned within the parent–child relationship. Yet, while substantially more children of depressed mothers develop psychopathology, some children growing up in the context of chronic maternal depression appear to be well functioning. Possibly, variability in maternal OT and mother–child interaction patterns may be among the factors associated with resilience in children of depressed mothers. Understanding the factors that differentiate vulnerable from resilient children may be important for early identification and for the construction of more targeted early interventions.

As such, the goal of the current study was to examine the development of children's OT response in the

context of maternal depression across the child's first years of life. The wide variability in baseline OT levels in humans[58] suggests that whereas some depressed mothers are likely to exhibit reduced baseline OT, others may not. We thus examined how maternal depression interacts with the mother's baseline OT to shape the child's OT response. Additionally, we examined the contribution of the child's psychiatric status, mother's parenting behavior, and the child's social withdrawal in shaping the OT response.

Following the research program of Meaney and colleagues[30] in animal models, which demonstrates how natural variations in maternal behavior in the population fall into two distinct OT phenotypes at the extreme ends of the distribution. We recruited a large cohort of women ($N = 1983$) from the general population on the second postpartum day. Women were repeatedly assessed for depression from birth to 6 years and two matched cohorts were formed at six years: mothers who were depressed throughout the child's first 6 years, and those not reporting elevated depressive symptoms at any time-point from birth to six. At 6 years, mother and child underwent psychiatric diagnosis, urinary OT was measured from mother and child before and after social interactions and mother–child interaction behaviors were coded.

Four hypotheses were formed. First, we expected depressed mothers and their children to exhibit lower baseline OT and reduced OT response to social interactions. Second, maternal behavior was expected to predict the child's OT response; children experiencing sensitive parenting and low maternal anger would show higher OT response following mother–child contact. Third, interactive effects of maternal baseline OT and maternal depression were expected so that in the context of low maternal OT, depression would negatively impact the child's OT response but in cases of high maternal OT, children's OT would not be affected by maternal depression. Finally, we expected to find differential effects of maternal depression on the child's OT response in children with high and low baseline OT.

METHOD

PARTICIPANTS

The initial cohort included 1983 women who were recruited on the second postpartum day in three maternity wards. To avoid the confounding effect of comorbid conditions that independently affect maternal behavior and the OT system, we recruited only mothers who were healthy, completed high school, were at least 21 years old, above poverty cutoff, were married or cohabitating with the child's father, and whose infants were born at term and were healthy, and singleton.

Women with Beck Depression Inventory scores in the highest and lowest quartiles completed measures of anxiety and depression at 6 months (900 were approached and 680 responded, 76%) and again at 9 months (350 were approached and 254 responded, 73%). Women with high levels of anxiety symptoms (State Trait Anxiety Inventory score above 43) were excluded since mothers with anxiety and depression were found to display different patterns of maternal behavior and the focus of this study was on the biobehavioral correlates of maternal depression.[54] Of the responding mothers at 9 months, 192 (76%) were clinically diagnosed and observed. Of these women's families, 156 (81%) were visited when the child was 6 years old. Detailed graphic presentation of the sample and recruitment appears in Fig. 1. The children's mean age during the visit was 6.33 years (SD = 1.25), the mother's age was 38.66 years (SD = 4.40), and the father's age was 41.04 years (SD = 4.74). Eighty percent of the parents had college degrees, 91% were married, and 89% of the mothers were employed. Among the children, 51% were boys and 36% were the firstborn. Of the mothers diagnosed with depression, two (4%) were treated with medication, and four depressed mothers (9%) and 10 comparison mothers (10%) received psychotherapy, with no effect on OT or any maternal or child outcomes.

The study was approved by the IRB. Procedures were explained to the adult participants before the beginning of the study and all signed informed consent. Parents received a gift certificate for participation.

PROCEDURE AND MEASURES

Families were visited at home in the afternoon (after 15:00) hours to control for diurnal variability in OT levels. [59,60] To further control for variability in OT, mothers from both groups were matched in their BMI levels and were instructed not to drink caffeine or alcohol and not to smoke in the hour prior to giving the urine samples. Mothers and children were instructed not to drink in the hour prior to urine collection.

MATERNAL PSYCHIATRIC DIAGNOSIS

The mother's psychiatric status was assessed using the Structured Clinical Interview for DSM-IV Axis-I disorders SCID-I.[61] Of the 156 families visited at 6 years, 41 mothers (29.6%) were defined as chronically depressed. These mothers showed high depressive symptoms (BDI > 11) at birth, 6, and 9 months, received a clinical diagnosis of MDD at both 9 months and 6 years, and reported being depressed throughout the child's first 6 years. In order to avoid the confounding effect of comorbid psychopathologies that independently affect maternal behavior and the OT system, seven mothers were excluded due to other psychiatric diagnoses (anxiety, eating disorder). One hundred and three mothers (66%) reported no depression and received no other psychiatric diagnosis from birth to 6 years and were considered as the healthy controls. From this group we selected 56 mothers and children to serve as controls and selection focused on families who showed the closest match to the depressed group in terms of child gender and age in months, leading to a total N of 97 mothers and 97 children in the current study.

CHILD PSYCHIATRIC DIAGNOSIS

Children's psychiatric status was assessed with the Development and Well-Being Assessment—DAWBA.[62] The DAWBA is a structured interview designed to generate DSM-IV psychiatric diagnoses in children 4–16 with good reliability and validity, including a large validation study in Israel.[63]

MOTHER–CHILD INTERACTION

Ten minutes of mother–child interactions with a set of preselected toys were filmed [64]. Interactions were coded with the Coding Interactive Behavior (CIB) manual, a well-validated global system of 45 codes aggregated to several relational constructs (for review[65]). Coding was conducted by trained coders and reliability on 20% interactions exceeded 90% on all codes. The maternal sensitivity, maternal negative mood/anger, and child social withdrawal constructs of the CIB, which have been shown to be sensitive to maternal depression,[54,66] were used.

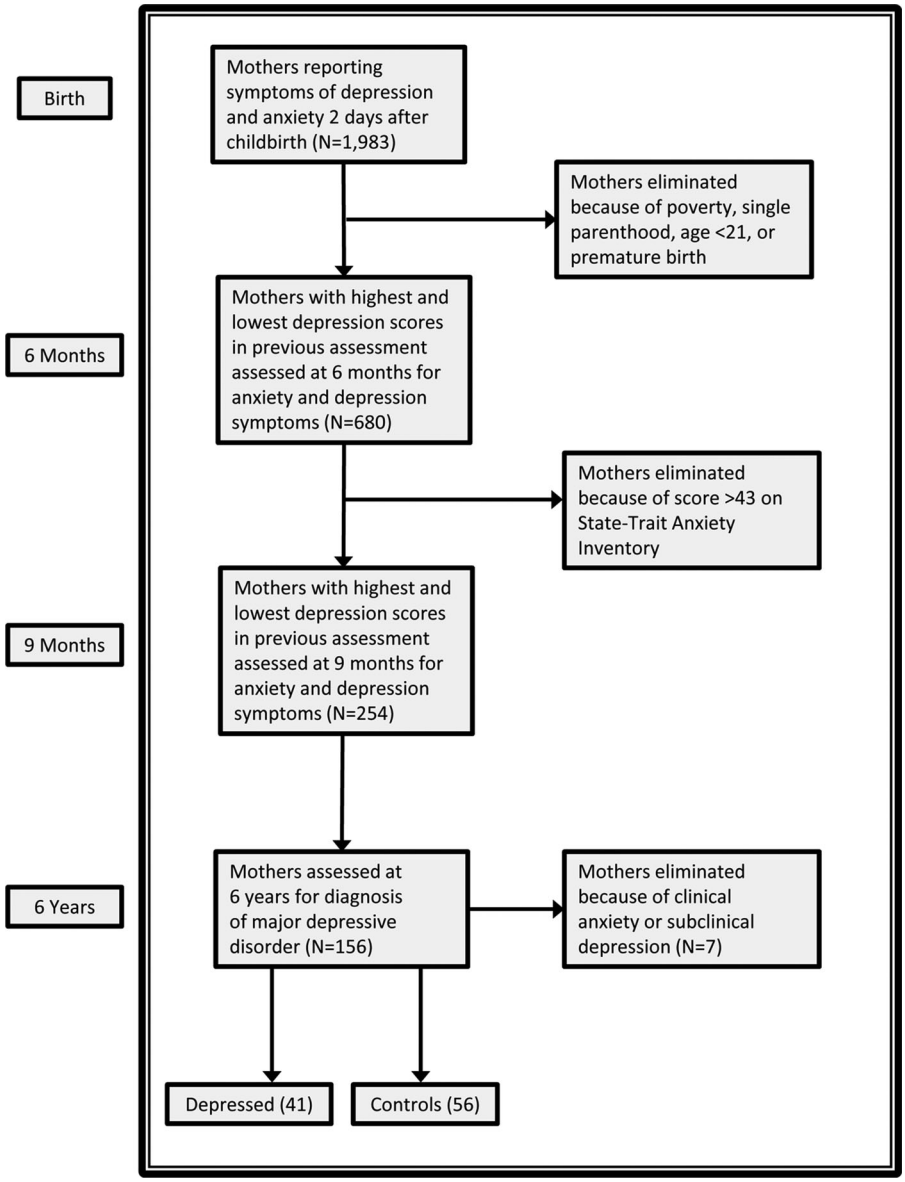


Figure 1. Mother and child recruitment process.

URINARY OT

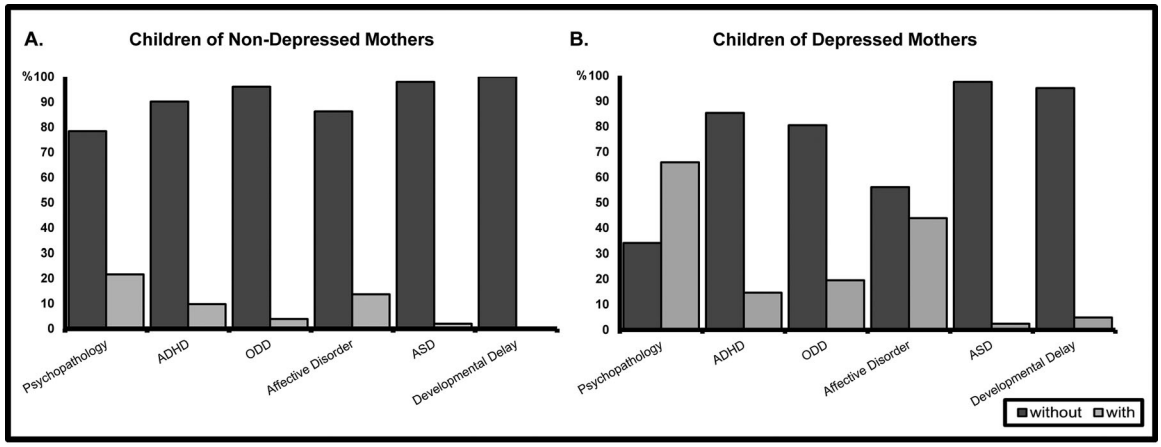
Urine samples were collected from mother and child twice, at baseline and following a 25-minute session of parent–child contact (including dual interactions with mother and father separately, and a triadic interaction). Method for OT extraction was taken from the kit insert, with the following modifications to adjust the low concentration of urinary OT. Two milliliters of urine was loaded on HBL extraction cartridge 3 cc/60mg (Waters Oasis, MA). The cartridges were washed twice with 0.1% Trifluoroacetic Acid (TFA) and 10% acetonitrile solution. Samples were eluted by 0.1% TFA and 80% acetonitrile solution, dried by SpeedVac, and kept in −20°C until assayed. For each urine collection the process was repeated twice. The dry samples were reconstructed in the assay buffer immediately before analysis by OT EIA commercial Kit.

OT was determined using a commercial OT ELISA kit (Assay Design, MI) consistent with previous research.[25] Measurements were performed in duplicate and the concentrations of samples were calculated by using MatLab-7 according to relevant standard curves. The intraassay and interassay coefficient are <12.4 and 14.5%, respectively.

STATISTICAL ANALYSIS

Prior to the analysis missing values were imputed by regression analysis. Extreme values in child OT response were excluded (five subjects with values more than four SD from the mean) resulting in an *N* of 92 (51 healthy mothers and their children and 41 depressed mothers and their children).

To test our first hypothesis we calculated two repeated measures ANOVA, one with child OT as a dependent variable and one with mother OT. Mother depression and child psychopathology were used as the between-subject factors and time of OT measurement (baseline and response OT) as the within-subject factor. In order to test our *second*, *third*, *and fourth hypotheses*, we conducted a regression



Child mean age at diagnosis = 6.33, SD = 1.25

Figure 2. Distribution of child psychopathology across the study groups.

analysis to predict child OT response. Prior to this analysis, we calculated Pearson's correlations between all variables. Following, the independent variables were *z* normalized, and we calculated the interaction variables by multiplying the *z* normalized variables with one another. Finally, the regression equation was computed to assess child's OT response from maternal and child hormones and social behavior. In the first block, mother's depression and child's clinical status were entered. The second block included mother and child baseline OT. These two blocks were entered in order to assess the contribution of relational variables above and beyond psychopathology and baseline OT. The third block (hypothesis 2) included mother–child interaction variables (mother sensitivity, mother negative mood, child withdrawal). The fourth block included interaction terms of maternal depression and mother baseline OT (hypothesis 3), and of maternal depression and child baseline OT (hypothesis 4). Interaction in regression effects was analyzed post hoc via simple slope analysis.[67]

RESULTS

MOTHER DEPRESSION AND CHILD PSYCHOPATHOLOGY

Distribution of child Axis-I disorders in relation to maternal depression is presented in Fig. 2. As can be seen, children exposed to maternal depression exhibited higher rates of child psychopathology especially affective disorders. Means and SDs for the hormone and interaction variables according to maternal depression and child Axis-I disorder are presented in Table 1.

Hypothesis 1: Consistent with our first hypothesis, the repeated measures ANOVA with child OT as the dependent variable showed a significant main effect for maternal depression ($F(1, 91) = 7.06$, $P < 0.01$). There was no effect for time of OT measurement or interaction between time and psychopathology, that is, children of depressed mothers showed lower baseline OT and attenuated OT response to social interactions (Fig. 3). The repeated measures ANOVA for mother OT as an independent variable similarly showed a significant main effect only for maternal depression ($F(1, 91) = 4.88$, $P < 0.05$) with depressed mothers showing lower OT levels than controls (see Table 1 for group means) and no additional significant effects.

CORRELATIONS BETWEEN STUDY VARIABLES

Pearson correlations between mother and child OT concentrations and interaction behaviors are presented in Table 2. As seen, baseline OT and OT response of both mother and child were highly correlated, as expected. Additionally, mother's and child's baseline levels as well as their OT response were interrelated (Fig. 3). Mother sensitivity was negatively correlated with child withdrawal. Child OT response was negatively related to child social withdrawal and maternal baseline OT was negatively related to mother negative mood/anger.

PREDICTING CHILD OT RESPONSE

Results of the regression analysis predicting child OT response are presented in Table 3.

Hypothesis 2: With regards to our second hypothesis, that maternal behavior during mother–child interaction will predict child OT response, results reveal that mother negative mood/anger uniquely predicted child OT response, but maternal sensitivity did not. Additional independent predictors of child OT response were; mother depression, child psychopathology, child baseline OT, and child withdrawal.

Hypothesis 3: Regarding our third hypothesis, that mother baseline OT would moderate the relationship between maternal depression and child OT response, a significant interaction effect was found between maternal depression and mother baseline OT. Simple slopes analysis[67] indicated that among low (−1 SD from the mean; $b = -7.77$, SE = 2.28, $P < .001$) and mean ($b = -3.78$, SE = 1.29, $P < .01$), levels of mother baseline OT there was a negative correlation between maternal depression and child OT response, but in high (+1 SD from the mean) levels of mother baseline OT this correlation was not significant ($b = 0.21$, SE = 2.26, NS).

TABLE 1. Group means of depressed and nondepressed mothers, and children with or without psychopathology, in the mother–child interaction and OT variables

	Mother depression				Child psychopathology			
	Yes ($N = 41$)		No ($N = 51$)		Yes ($N = 44$)		No ($N = 48$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Child baseline OT	6.74	4.31	9.91	9.08	7.47	7.09	9.4	7.79
Child response OT	6.88	4.64	11.62	8.31	7.43	6.09	11.42	7.83
Mother baseline OT	5.81	5.17	8.04	7.93	5.93	4.92	8.03	8.18
Mother response OT	6.68	3.48	8.82	8.14	6.74	4.57	8.94	7.92
Mother sensitivity	3.36	0.88	3.78	0.68	3.57	0.78	3.62	0.82
Mother negative mood	1.55	0.77	1.41	0.57	1.53	0.69	1.46	0.69
Child withdrawal	1.62	0.81	1.64	1.05	1.69	1.03	1.57	0.88

Hypothesis 4: The fourth hypothesis predicted that child baseline OT would moderate the relationship between maternal depression and child OT response. Consistent with the hypothesis, results indicated a significant interaction effect between maternal depression and child baseline OT. Simple slopes analysis indicate that in mean ($b = -3.74$, SE = 1.41, $P < .01$) and high (+1 SD from the mean; b = −9.35, SE = 2.93, $P < .01$) levels of child baseline OT there was a significant negative correlation between maternal depression and child OT response, but in low (−1 SD from mean) levels of child baseline OT the association was not significant ($b = 1.86$, SE = 2.46, NS). Graphic presentation of the simple slope analysis is presented in Fig. 4.

DISCUSSION

Results of the current study suggest that the OT system is implicated in the cross-generation transmission of vulnerability from depressed mothers to their children. In this process, our findings describe two mechanisms of risk related to lower functionality of maternal OT and the mother's nonoptimal caregiving and a resilience

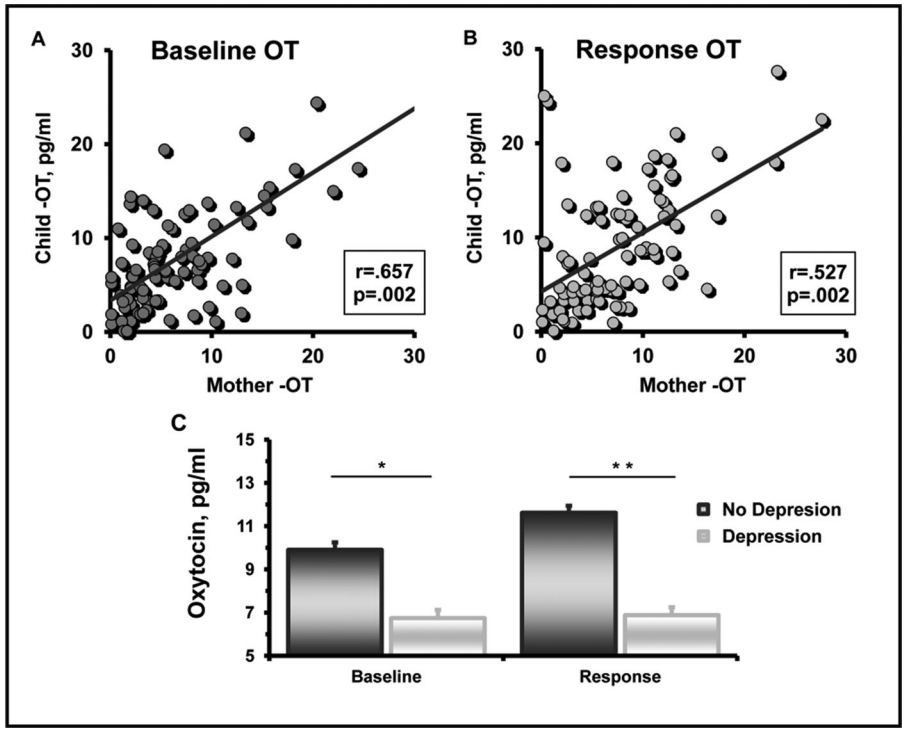


Figure 3. Mother and child OT. (A) Correlation between mother and child OT at baseline. (B) Correlation between mother and child OT response. (C) Variation between children of depressed and nondepressed mothers in their OT levels. OT levels of children of depressed mothers are significantly lower both at baseline and in response to mother–child interaction.

TABLE 2. Correlation matrix

	2	3	4	5	6	7
1. Child OT baseline	0.426**	0.609***	0.249*	−0.042	−0.028	−0.111
2. Child OT response		0.333**	0.527***	−0.319**	0.153	−0.242*
3. Mother OT baseline			0.317**	−0.269*	0.093	−0.188
4. Mother OT response				−0.276**	0.115	−0.222*
5. Child withdrawal					−0.250*	−0.016
6. Mother sensitivity						0.057
7. Mother negative mood						

*$P < .05$; **$P < .01$; ***$P < .001$.

mechanism of high maternal baseline OT. Depressed mothers exhibited low OT and an attenuated OT response to moments of social contact with their children and a similar low baseline OT and decreased OT response was found in their children, suggesting a cross-generational effect. Child OT response was shaped by maternal and child social behavior, including low maternal negative affect and anger and reduced child social withdrawal, as well as by child psychopathology. Furthermore, our findings indicated interactive effects of maternal OT and maternal depression on children's OT response. This is the first study to show such interactive effects on children's OT functionality within a prospective longitudinal design that followed children from birth to 6 years and included concrete observations of the rearing environment and hormonal measures of both mother and child before and after social contact. Our study is also the first to carefully tease apart maternal depression from other typical comorbid conditions that carry independent effects on child development and may have different effects on the OT system, such as poverty, single parenthood, teenage pregnancy, and premature birth, and this was achieved by recruiting only mothers without those high-risk conditions. Furthermore, to address the potentially different effects of anxiety and depression on OT and relational behavior, in this study we excluded cases of anxiety disorders or comorbidity of anxiety and depression. Although comorbidity of anxiety and depression may be as high as 30%[68] since different mechanisms may underpin the effects of depression and anxiety on the OT system,[69] we wished to test first the generational effect of maternal depression and future research is required to extend findings to cases of comorbidity. Yet, it is important to note that although the findings suggest a cross-generational process, this study is correlational and no causal effects can be inferred. In general, it is difficult to demonstrate clear cross-generational effects in human research and

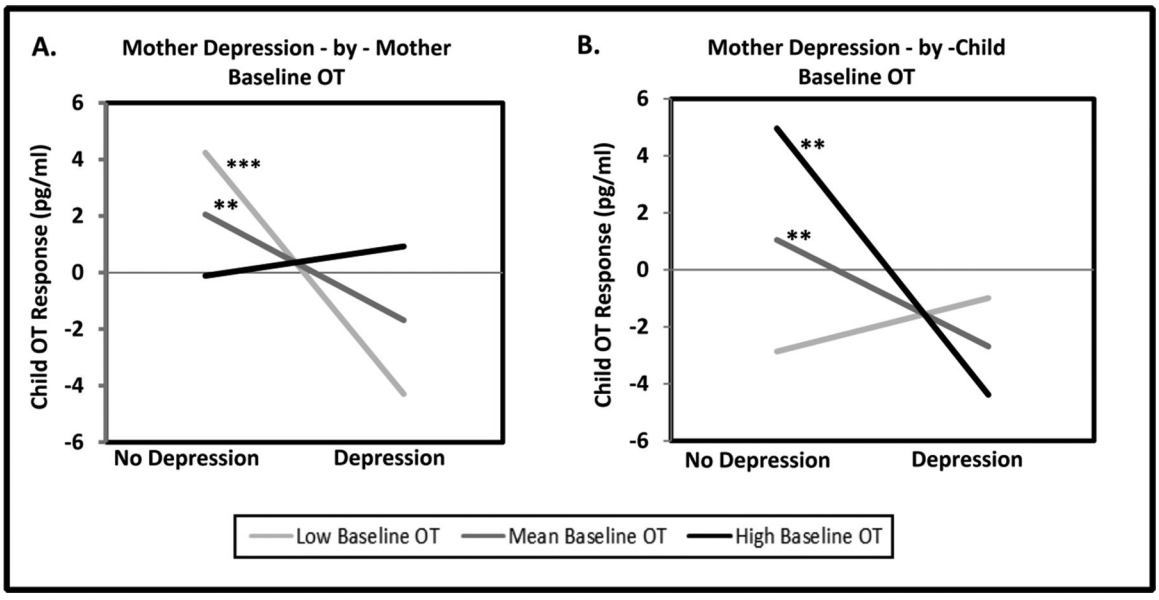


Figure 4. Simple slope analysis of interaction effects predicting child OT response. (A) Significant negative correlation between mother depression and child OT response when mothers have low (−1SD) or mean levels of baseline OT, but not when mothers have high (+1SD) levels of OT. (B) Significant negative correlation between mother depression and child OT response when children have high (+1SD) or mean levels of OT at baseline, but not when child baseline OT is low (−1SD).$P < .01$; ***$P < .001$.**

consistency between human data and animal studies point to the likelihood of comparable mechanisms but cannot verify causality.

Consistent with the *biobehavioral synchrony* model,[16] maternal and child's OT changed in a parallel manner and this coordinated hormonal increase was associated with mother and child's interactive behavior. Interestingly, at 6 years the relational elements susceptible to maternal depression and impacting on the OT response were not those observed in infancy, such as maternal sensitivity, affectionate touch, or social reciprocity,[26,54] but reduction in the negative components of the relationship; maternal negative affect/anger and child social withdrawal. Possibly, at this age, once the synchronous components in the maternal style are encoded in the infant's brain and endocrine systems, children are more sensitive to variability in negative maternal signals.[55] Research points to two different styles of depressed mothers; those who are merely withdrawn and those that are both withdrawn and angry.[53] Our findings suggest that open maternal negativity and anger is the component more closely related to attenuation of the child's OT response, above and beyond maternal depression and child psychopathology, and that mothers who are both depressed and angry may render their child's OT system particularly vulnerable.

Another possible explanation for the links between OT and the negative elements of the interaction may relate to the fact that OT measured in urine is especially sensitive to the stressful components of the parent–child relationships. This is consistent with research showing that orphanage-reared children showed lower urinary OT response to social interactions,[70] and child maltreatment was related to dysregulated levels of urinary OT following a social stressor.[71] It is also consistent with prior research that compared parental plasma, salivary, and urinary OT and showed that urinary OT was especially sensitive to stress in parenting.[25] Similarly, it was found that maternal touch and vocalizations increased urinary OT in children following a social stressor.[72] OT plays a complex role in urination. Like vasopressin, OT functions as an antidiuretic hormone via the kidney vasopressin type-2 receptor.[73] Moreover, micturition is partially regulated by neurological pathways sending inputs to the limbic system, including preoptic regions, the central nucleus of the amygdala, bed nucleus of the stria terminalis, and hypothalamic nuclei, particularly the PVN where OT is produced.[74] Due to the close connection between micturition and emotion, it is possible that urinary OT acts as a marker for relational stress, albeit much more research is required to determine the associations between components of attachment relationships and their associations with the expression of OT in different fractions.

In addition to maternal depression and negative affect, child psychopathology and social withdrawal had independent and negative effects on the child's OT response. While the prevalence of psychopathology was much greater in children exposed to maternal depression across early childhood, it is possible that by 6 years of age, multiple biological and environmental effects consolidate into a full-blown child disorder and the existence of psychopathology signifies an additional independent risk. Similarly, infant withdrawal, described as a risk factor for later depression,[66] may organize into a stable social style by the time children enter school. Since both withdrawal and OT were tested in the same interaction, it is impossible to address the stability of this biobehavioral pattern or whether these children would be more engaged or exhibit OT increase following interactions with other significant adults. Yet, both child OT and social engagement behavior have been found as stable across time and interacting partners and patterns of mother–child interactions were shown to predict children's social reciprocity and engagement with fathers and friends.[32,75] Such disrupted patterns of behavior during mother–child interactions, therefore, may prevent children from engaging in reciprocal social interactions with agemates, thereby reducing social inputs that can provide alternative pathways for the experience-dependent maturation of the OT system at the preschool stage. Burgdorf and Panksepp[76] suggest that play in juvenile animals provides critical social experiences for maturation of the pulsatile release of OT from hypothalamic neurons and reduction in social play at this stage may negatively impact the development of the OT system during the stage when children move from the home environment to the larger social world.

Slope analysis demonstrated that the direct effect of maternal depression on children's OT response was moderated by maternal OT; when mother baseline OT was high children's OT response was not impacted by chronic depression. These findings have important implications to the study of resilience and highlight the multiple pathways to the maturation of key neurobiological systems. Possibly, the high levels of maternal OT in some depressed mothers, resulting from factors related to maternal genes, physiology, or early experience, may protect against the effects of depression on the child's OT system, perhaps by improving some components of the mother's behavior, perceptions, or ability to create a social support network for their children that can provide alternative pathways for the maturation of the OT system. An earlier study on this cohort found that among children of depressed mothers with the low-risk variant of the *OXTR*rs2254298 allele, prevalence of Axis-I disorders in the child, although higher than among controls, was reduced by half as compared to children of depressed mothers with the high-risk variant.[48] Similarly, Mah and colleages[77] found that OT administration to depressed mothers increased their self-reported perception of the relationship, suggesting that higher levels of OT in depressed mothers may improve aspects of their parenting. While results regarding the effect of exogenous OT and maternal depression are varied and dependent on other maternal characteristics, it appears that this system may account for some of the variability in familial risk for depression.[78] Future research is

TABLE 3. Regression analysis predicting child response OT levels with mother depression, child psychopathology, mother and child baseline OT, child withdrawal behavior, mother sensitivity, mother negative mood, and interactions between them

Predictors		β	R^2 Change	F Change	DF
Block 1:			0.14	7.23***	2.90
	Mother depression	−0.274**			
	Child psychopathology	−0.198+			
Block 2:			0.125	7.422***	4.88
	Mother baseline OT	−0.057			
	Child baseline OT	0.327**			
Block 3:			0.153	7.391***	6.86
	Child withdrawal	−0.324***			
	Mother negative mood	−0.248**			
	Mother sensitivity	0.045			
Block 4:			0.056	1.695	9.83
	Mother depression × mother baseline OT	0.300**			
	Mother depression × child baseline OT	−0.360***			
		R^2 Total = 0.421, $F(9, 82) = 6.63$, $P < 0.001$			

+$P < .1$, *$P < .05$, **$P < .01$, ***$P < .001$.

needed to tease apart biological and behavioral risk elements embedded in the global condition called "maternal depression" and examine each component separately, defining its unique longitudinal effects on the child. From a conceptual perspective, such research can further specify constructs such as "risk" and "resilience," which currently may be too global, by assessing the specific missing element in each child's environment and devising ways to provide personalized intervention to address these deficiencies.[79]

Effects of maternal depression on child's OT response were also moderated by the child's baseline OT, a finding that further suggests a gene-by-environment effect. Children with low baseline OT showed lower OT response, even when not exposed to maternal depression. Baseline OT levels were found to be stable over time,[80] and are longitudinally predicted by both maternal behavior and maternal OT;[48] hence, it is possible that baseline OT levels have a sensitive period for development. It is also possible that children with low baseline OT are constantly exposed to low levels of maternal OT, as seen by the high intercorrelations between maternal and child OT, and this may carry long-term effects on their ability to benefit from mother–child interactions. This hypothesis is consistent with the correlation found between low maternal OT and greater child withdrawal.

Limitations of the study relate to the peripheral measurement of OT. Little is known about the factors affecting diurnal rhythms of OT in peripheral measures, especially regarding OT in urine, and no study to our knowledge has investigated diurnal rhythmicity of OT in children. Moreover, the relationships between peripheral and central measurements of OT have been debated,[81,82]; albeit a study in mice has shown that peripheral administration can elevate both central and peripheral indices of OT.[83] Importantly, recent studies have demonstrated associations between levels of urinary OT and attachment related behaviors such as gaze,[84] maternal care giving,[85] vocalization,[72] and brain reaction to infants,[85,86] further validating the use of this measure in the context of the mother–infant relationship. In addition, it has been found that intranasal OT administration can elevate levels of OT in urine, while simultaneously affecting brain reactivity.[87] Despite these studies, much further methodological human research is required to understand the complex relationships between brain and peripheral OT in humans.

CONCLUSION

As maternal depression has repeatedly shown to exert long-term negative effects on child development,[57] it is important to carefully follow children growing up in the context of maternal depression, specify elements that function as resilience buffers, and formulate interventions that take into account the mother's specific endocrine profile and behavioral repertoire. The current study showed that maternal and child OT are interrelated, exhibit lower response to social contact, and maternal OT moderates the association between maternal depression and child OT functionality. Since functioning of the OT system has been consistently shown to impact the individual's social competencies and ability to form affiliative bonds throughout life,[32,75,88,89] and has been shown as stable across time,[32] our findings may have important implications for the development of early relationship-focused interventions for depressed mothers and their children and highlight the importance of implementing such intervention already in the first months of life. Finally, since our findings are correlational, it is important to remember that direction of effects is unclear and much future research is required to test the long-term effects of maternal postpartum depression on children's biological, social, emotional, and cognitive development in an attempt to tease apart multiple risk and resilience factor in the child's early

environment and their unique and combined effects on the child's biological and social growth.

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