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Maternal depression impacts child psychopathology across the first decade of life: Oxytocin and synchrony as markers of resilience

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Background: While maternal depression is known to carry long-term negative consequences for offspring, very few studies followed children longitudinally to address markers of resilience in the context of maternal depression. We focused on oxytocin (OT) and mother–child synchrony – the biological and behavioral arms of the neurobiology of affiliation – as correlates of resilience among children of depressed mothers. **Method:** A community birth-cohort was recruited on the second postbirth day and repeatedly assessed for maternal depression across the first year. At 6 and 10 years, mothers and children underwent psychiatric diagnosis, mother–child interactions were coded for maternal sensitivity, child social engagement, and mother–child synchrony, children's OT assayed, and externalizing and internalizing problems reported. **Results:** Exposure to maternal depression markedly increased child propensity to develop Axis-I disorder at 6 and 10 years. Child OT showed main effects for both maternal depression and child psychiatric disorder at 6 and 10 years, with maternal or child psychopathology attenuating OT response. In contrast, maternal depression decreased synchrony at 6 years but by 10 years synchrony showed only child disorder effect, highlighting the shift from direct to indirect effects as children grow older. Path analysis linking maternal depression to child externalizing and internalizing problems at 10 years controlling for 6-year variables indicated that depression linked with decreased maternal sensitivity and child OT, which predicted reduced child engagement and synchrony, leading to higher externalizing and internalizing problems. OT and synchrony mediated the effects of maternal depression on child behavior problems and an alternative model without these resilience components provided less adequate fit. **Conclusions:** Maternal depression continues to play a role in children's development beyond infancy. The mediating effects of OT and synchronous, mutually regulated interactions underscore the role of plasticity in resilience. Results emphasize the need to follow children of depressed mothers across middle childhood and construct interventions that bolster age-appropriate synchrony. **Keywords:** Maternal depression; resilience; oxytocin; synchrony; longitudinal studies; child psychopathology.

Introduction

Maternal depression is a major public health concern: In the United States, one in every ten children is exposed to maternal depression at any given year (Ertel, Rich-Edwards, & Koenen, 2011). Although depression is often a life-long disorder, women's most debilitating episodes occur during the childbearing years and the cyclical nature of the disorder renders children susceptible to a condition of typically chronic course (Burcusa & Iacono, 2007). Extant research has pointed to the negative effects of maternal depression on a host of child outcomes, including increased propensity to psychopathology (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013; Goodman & Garber, 2017), more externalizing and internalizing problems (Goodman et al., 2011), pathological stress response (Barry et al., 2015), difficulties in emotion regulation (Harden et al., 2017), and altered neural activations (Pratt, Goldstein, Levy, & Feldman, 2016). By middle childhood, children of depressed mothers exhibit higher rates of mood disorders, internalizing and externalizing problems, and greater emotional difficulties (Apter-Levi et al., 2016; Goodman et al., 2011). Yet, the mechanisms underpinning the cross-generational transfer of vulnerability from depressed mothers to their children are not fully clear.

While millions of young children globally are exposed to maternal depression, there are important lacunas in our knowledge of its long-term effects. First, most studies focused on infancy, the period when maternal depression is most prevalent and carries its most negative effects on caregiving quality and the mother–infant attachment (Beeghly et al., 2017). Very few studies followed children of depressed mothers across middle childhood, a period of unique developmental needs and vulnerabilities. Second, most research on sequalae of maternal depression did not include direct observations and little data are available on how maternal depression impairs children's social behavior or the mother–child relationship beyond infancy. Third, most studies did not separate maternal depression from frequently occurring comorbidities, such as poverty, single parenting, teenage mothering, or premature birth, each carrying independent negative effects on development. Thus, the long-term effects

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of maternal depression as such are unclear, particularly how it affects children as they grow older and their circle of affiliations widens. Finally, most studies focused on risk and vulnerability and very little empirical attention has been directed to resilience. While maternal depression significantly increases child propensity for psychopathology or behavior problems, some children of depressed mothers are more resilient and the biobehavioral correlates of such resilience are still unknown.

Resilience implies successful adaptation in the context of adversity (Masten & Monn, 2015) and determinants of resilience include biological, psychological, social, and cultural factors that jointly determine how one responds to stress (Masten & Monn, 2015; Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014). It has been suggested that resilience is a dynamic processes, linked to the type of stress, developmental stage, and specific outcome measured, with much developmental research focusing on reduced psychopathology or behavior problems in children growing up amidst adversity as key indicator of resilience (Cicchetti, 2013; Reuben & Shaw, 2015; Southwick et al., 2014). Rutter (2013) has argued that while it is critical to discover mechanisms that confer resilience, resilience research must separate one adverse condition from the next, employ longitudinal designs that begin early and span lengthy periods, and include biological markers. As such, the current study followed mothers and children from the second postbirth day and across the first decade of life, repeatedly assessing maternal depression across the first year and again at 6 and 10 years. Our special focus was the neuroendocrine and behavioral arms of the neurobiology of affiliation; oxytocin (OT) and synchrony (Feldman, 2017), as correlates of resilience. Child salivary OT was measured at 6 and 10 years in light of research showing associations between OT and better adjustment in children of that age in various high-risk populations (Apter-Levy et al., 2013; Feldman, Golan, Hirschler-Guttenberg, Ostfeld-Etzion, & Zagoory-Sharon, 2014; Lebowitz et al., 2017; Ulmer-Yaniv et al., 2017). Mother–child synchrony was defined, consistent with several conceptual models (Feldman, 2007; Harrist & Waugh, 2002; Tronick, 2007), as the mutual adaptation of mother and child to each other's social signals in ways that enhance positive affect, sharing, and trust. Our central hypothesis was that child OT and the experience of social synchrony would be associated with lower behavior problems in children of depressed mothers.

Oxytocin, parent–child relationship, and maternal depression

Oxytocin, a nine-amino-acid neuropeptide synthesized in the hypothalamus, provides the foundation for maternal–infant bonding and supports sociality, collaboration, and prosocial behavior in mammals (Feldman, 2012a; Gong et al., 2017). Animal and human studies indicate that the infant's OT system is shaped during early sensitive periods in the context of maternal caregiving and OT is highly open to epigenetic influences (Feldman, 2015; Kappeler & Meaney, 2010). The cross-generational transmission of OT defines a biobehavioral feedback loop: maternal OT supports maternal caregiving, which in turn shapes the infant's OT system through the provision of species-typical parenting behavior (Champagne, 2008). Human studies similarly showed that OT underpins the expression of synchronous parenting and described correlations between parent and child' salivary OT as assessed by baseline levels, OT reactivity patterns, or total OT production measured across several samples. Such parent–child OT fit has been demonstrated in infancy (Feldman, Gordon, & Zagoory, 2010; Weisman, Zagoory-Sharon, & Feldman, 2012), preschool (Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013; Feldman et al., 2014), and middle childhood (Ulmer-Yaniv et al., 2017), mediated by the degree of parent–child synchrony.

Several studies measured children's OT during middle childhood and found associations between OT and prosocial skills, stress reduction, or sensitive parenting as well as attenuation child OT levels when externalizing or internalizing problems are high. For instance, 7–12 year-old girls exhibited OT increase when receiving comfort from their mother following stress (Seltzer, Ziegler, & Pollak, 2010); child plasma OT correlated with theory-of-mind and social communication skills (Parker et al., 2014); and children's OT increased during physiological challenge, highlighting OT's stress-buffering role (Corbett et al., 2016). Furthermore, OT has been associated with resilience in high-risk contexts at this age. Attenuated salivary OT was found in 7–15-year-old children with separation anxiety that increased following sensitive mother–child interaction (Lebowitz et al., 2017); 9–11-year-old children exposed to chronic trauma exhibited lower OT only when their mothers sensitive parenting was low (Ulmer-Yaniv et al., 2017); lower serum OT levels were found in children with ADHD and higher OT correlated with lower impulsivity and aggression and more empathy in these children (Demirci, Ozmen, Kilic, & Oztop, 2016; Demirci, Özmen, & Öztop, 2016); and children's plasma and cerebrospinal fluid OT concentrations predicted lower anxiety (Carson et al., 2015).

Oxytocin has been repeatedly shown to be disrupted in cases of depression, including MDD, elevated depressive symptoms, and postpartum depression. Plasma OT levels were lower in patients with MDD (Frasch, Zetzsche, Steiger & Jirikowski, 1995) and inversely correlated with the severity of depressive symptoms in both patients (Scantamburlo et al., 2007) and healthy adults (Gordon et al., 2008). Plasma OT levels at the third trimester of

pregnancy predicted postpartum depressive symptoms (Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011); lower OT in the first trimester predicted more postpartum depressive symptoms and less maternal attachment behavior (Feldman, 2012b); and depressed mothers exhibited attenuated OT increase after breastfeeding (Stuebe, Grewen, & Meltzer-Brody, 2013). Several studies showed correlations between OT levels in depressed mothers and their children and lower OT in the children. For instance, depressed mothers and their children had lower salivary OT (Apter-Levy et al., 2013) and lower urinary OT response to mother–child interaction (Pratt et al., 2015). These findings may suggest a cross-generational transfer of OT dysfunction or adaptive calibration of the child's OT system to the environment of maternal depression. Furthermore, when depressed mothers carried the *OXTR* allele associated with greater social competencies and less psychopathology or had higher OT levels, the effects of depression on the child's propensity to develop Axis-I disorder or to exhibit attenuated OT response were markedly reduced (Apter-Levy et al., 2013; Pratt et al., 2015). Similar findings emerged in animal research; OT treatment to prenatally stressed newborn rats reduced blood pressure in adulthood (Holst, Uvnäs-Moberg, & Petersson, 2002), suggesting that OT may be associated with better adjustment and greater resilience in the context of early adversity.

Maternal depression and mother–child synchrony

While depression impacts multiple aspects of maternal care and reduces maternal sensitivity (Field, 2010; Goodman & Gotlib, 1999), it specifically impairs the mother's capacity to create the mutual-regulatory dialogue that defines synchrony (Tronick, 2007). Social synchrony, the parent and child's online adaptation to each other's rhythms and signals, is a key component of parenting that confers long-term positive effect on children's social-emotional growth (Feldman, 2007) and predicts less internalizing and externalizing problems in middle childhood (Feldman, 2010). The structure of mother–child synchrony undergoes maturation as children grow. While in infancy, mothers follow the infant's rhythms and affect, in preschool, parents adapt to children's emerging symbolic expression, and during middle childhood, parent and child jointly regulate the interaction to maintain positive affect and involvement and such mutuality promotes children' social competencies (Harrist & Waugh, 2002). Furthermore, during middle childhood, child social engagement, an orientation built on the child's biological dispositions sensitized by attuned parenting (Marshal & Fox, 2006), becomes a key component of social interactions with parents and peers and this social style has been shown to promote resilience and buffers against the development of externalizing and internalizing problems in the context of early adversity by enhancing mother–child synchrony (Halevi, Djalovski, Vengrober, & Feldman, 2016).

Studies point to disruptions in mother–child synchrony in cases of maternal depression in infancy (Beebe et al., 2008; Granat et al., 2016; Weinberg & Tronick, 1996), but we are aware of no study that measured synchrony in relation to maternal depression beyond infancy. Since synchrony is longitudinally linked with children's externalizing and internalizing problems, it is possible that the experience of synchrony may help to promote resilience in the context of maternal depression.

The current study

The current study followed children from birth and across the first decade of life to examine risk and resilience in the context of maternal depression, focusing on middle childhood. While this period has rarely been studied in relation to maternal depression, during these years children make important strides in social abilities susceptible to it (Goodman & Gotlib, 1999). We focused on change trajectories, addressing change in children's externalizing and internalizing problems in relation to change in maternal sensitivity, OT levels, child social engagement, and synchrony from 6 to 10 years.

Three hypotheses were formulated. First, we expected more psychiatric disorders in children of depressed mothers at both 6 and 10 years. While it has been shown that school-aged children of depressed mothers exhibit more psychopathology, our study is the first to assess children of depressed mothers growing in two-parent, low-risk context, and demonstrating more psychopathology in such children may provide further evidence for the long-term negative effect of maternal depression as such, pinpointing directions for intervention. Second, we expected that maternal depression would be associated with lower child OT, reduced maternal sensitivity, lower child social engagement, and decreased synchrony at both ages. The third hypothesis considered the mediating role of OT and social behavior on children's externalizing and internalizing problems in the context of maternal depression. We expected that at each age, lower OT levels, maternal sensitivity, child engagement, and synchrony would link with more behavior problems. Furthermore, to chart a structural model on risk and resilience trajectories, we capitalized on the availability of the exact same variables at 6 and 10 years and addressed the dynamics of change across middle childhood by measuring 10-year variables while controlling for the parallel variables at 6 years, thereby measuring change trajectories in each variable. For the path model, we expected that maternal depression would decrease both maternal sensitivity and child OT, leading to reduced social engagement and synchrony.

Synchrony, in turn, would mediate the links between the decreased sensitivity and attenuated OT and children's behavior problems across middle childhood. This model was expected to provide better fit to the data as compared with two alternatives: (a) model predicting 10-years outcome from 6-year variables, not change trajectories, and (b) model without the two resilience markers: OT and synchrony.

Method

Participants

Birth and first year. The initial cohort included 1983 women recruited on the second postbirth day in three maternity wards who completed measures of anxiety and depression. Only mothers who were healthy, completed high-school, were over 21 years, were married or cohabitating, and above poverty line, and their infants were term, healthy, and singleton were included. Women in the high (BDI>11; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and low (BDI<9) ends of the depressive symptoms continuum completed measures of anxiety and depression at six months ($N = 900$ approached, $N = 680$ responded: 75.5%) and again at nine months ($N = 350$ approached, $N = 254$ responded; 72.5%), excluding high anxiety symptoms (State-Trait Anxiety Inventory Score > 43). Of responding mothers at nine months, 192 (75.5%) were clinically diagnosed and observed.

Six years. Of the 192 families visited at 9 months, 156 (81.2%) were revisited at 6 years (child age 6.33 ± 1.25, mothers' age 38.66 ± 4.4). Of these, 80% of parents had college degree, 91.4% were married, and 89% of mothers were employed. Forty-six mothers (29.6%) were defined as chronically depressed. These mothers showed high depressive symptoms (BDI > 11) at birth, six, and nine months, received MDD diagnosis at 9 m and 6 years and reported being depressed throughout the child's first 6 years. Similarly, 103 mothers (66%) were defined as controls, showed no elevated symptoms at any time-point, and did not receive any Axis-I diagnosis. Seven mothers were excluded due to clinical anxiety ($n = 3$) or subclinical depression ($n = 4$).

10 Years. Of the families visited at 6 years, 125 (81.1%) were located and visited between 9 and 11 years (child age 9.63 ± 0.65, mothers' age 39.06 ± 5.64). Attrition was mainly related to inability to locate families. There were no significant demographic or psychopathologic differences between those who dropped out and those who continued at 6 and 10 years.

Procedure and measures

Families were visited at home in between 4 and 7 PM to control for diurnal hormonal variability and visits included maternal and child psychiatric diagnosis, testing, hormonal collection, and age-appropriate mother–child interactions.

Ethical considerations. Study was approved by the local IRB and all families signed informed consent. Procedures were conducted according to ethical guidelines and explained to participants before study. Participants received a small gift for participation.

Maternal psychiatric diagnosis. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1997). At 10 Years, 15 of the depressed mothers at 6 years (42.8%) were still diagnosed with MDD, while 20 (57.1%) were not. Of the controls, 83 mothers (92.2%) remained without diagnosis, while 7 (7.7%) received MDD diagnosis. We defined the maternal depression group as mothers receiving MDD diagnosis at 6 years, 10 years, or both (42.8%)

Child psychiatric diagnosis. The Development and Well-Being Assessment (DAWBA) is a structured interview and questionnaire that generates ICD-10 and DSM-IV diagnoses in children 4–16 years (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). The DAWBA is well-validated, including large epidemiological study in Israel (Mansbach-Kleinfeld, Apter, Farbstein, Levine, & Poznizovsky, 2010). Diagnoses were conducted by clinical psychologist supervised by child psychiatrist blind to any other information with case conferred every few weeks. The group of "child disorder" included children receiving Axis-I diagnosis at 6 years, 10 years, or both (52.8%), with 31.8% having more than one disorder at either or both times. No difference was found between the number of comorbid disorders at 6 years and 10 years. Diagnoses included: 6 years: affective disorders (25.6%), ADHD (9.6%), conduct disorder/ODD (8.8%), developmental delay/ASD (3.2%), and tic-disorder (0.8%); 10 years: affective disorders (20%), ADHD (19.2%), conduct disorder/ODD (6.4%), developmental delay/ASD (1.6%), and tic-disorder (3.2%). Only the prevalence of ADHD increased from 6 years to 10 years ($p < .01$).

Child behavior problems. The Child Behavior Checklist 4–16 years (CBCL; Achenbach & Edelbrock, 1983) is a parent self-report measure of child behavior problems clustered into internalizing, externalizing, and total scores. The CBCL is the most widely used instrument for assessing behavior problems in children with established reliability and validity (Dutra, Campbell, & Westen, 2004).

Oxytocin collection and determination. At 6 years, only baseline salivary sample was collected. At 10 years, three salivary samples were collected by child putting Salivette (Sarstedt, Rommelsdorft, Germany) in his/her mouth for 1 min; baseline (after 10 min of acquaintance (T1), after testing (T2 80 min from baseline) and after mother–child interactions (T3, 75 min from T2). Participants did not eat for 1 hr and did not drink for 30 min prior to saliva collection. Samples were stored at −20∘C until centrifuged twice at 4°C at 1,500 × *g* for 20 min. Liquid samples were kept at −80 ∘C, lyophilized for 10 days, and stored at −20∘C. On the assay day, the dry samples were reconstituted in water and concentrated ×4 before immunoassay using kit by Enzo®(NY). Measurements were performed in duplicate and the concentrations of samples were calculated using Matlab-7 according to relevant standard curves. The intraassay and interassay coefficients of variability were lower than expected by the kit' insert (12.6% and 20.9%, respectively). We used the average of the three samples for our calculations.

Mother–child interaction. At 6 years, interactions included 10 min of play with age-appropriate toys. At 10 years, mothers and children interacted in two well-validated paradigms for 7 min each: first discussing typical conflict in their relationship, second planning a 'the best day ever' to spend together. Interactions were coded using the Coding Interactive Behavior Manual (CIB; Feldman, 1998). The CIB is a well-validated rating system for social interactions in infants, children, adolescents, and adults that includes multiple scales for parent, child, and dyad, aggregated into theoretically derived composites with good psychometric properties (Feldman, 2012c). Coding was conducted by trained coders, blind to other information, and reliability on 20% of the interactions exceeded 93% and 90% on all codes ($k = 0.84$, range 0.78–95 and $k = 0.82$, range = 0.78–0.96), at 6 and 10 years, respectively. Three constructs were used:

Mother sensitivity – Included mother codes of acknowledging child communication, maintaining positive affect, warm vocalization, adaptation to child signals, supportive presence, and resourcefulness (α = .92, .93 at T1 and T3)
Child social engagement – represents the child's active involvement and initiation of social behavior and included codes related to child's initiation, positive affect, vocal output, trust, and creativity, and social focus (α = .90, .9).
Mother–child synchrony – addressed the goodness-of-fit between maternal and child's behavior, fluency of the interactions, mutual expansion of the interaction, and sense or reciprocity and flow where each partner recognizes the other's signals and gives space to his/her communications (α = .92, .91).

Statistical analysis

Chi-square and two-way ANOVAs compared study variables in children of depressed/nondepressed mothers and those with/without psychiatric disorders. Pearson correlations tested relationships among variables. For a comprehensive model on the direct and mediated paths from maternal depression to children's internalizing and externalizing problems, we conducted path analysis using Lavaan 0.5–23.1097 package (Rosseel, 2012) in R 3.3.2 (R Core Team, 2014; RStudio, 2015). Path analysis was based on maximum likelihood estimations and indicators of model fit were: chi-square values; root mean square error of approximation (RMSEA); comparative fit index (CFI), with Tucker-Lewis index (TLI) values >0.95 considered good fit (Hu & Bentler, 1999). To assess significance of the mediation effects, we used a procedure recommended by Hayes (2013) and calculated the 95% confidence intervals of 5,000 bias-corrected and accelerated bootstrapping analyses (Hayes, 2013; MacKinnon, Lockwood, & Williams, 2004). In cases where the value zero is not included in the confidence interval, this indicates significant effect at $\alpha < .05$. To chart change trajectories, we controlled for t_1 (6 years) variables when predicting t_2 (10 years) mediators and dependent variables; thus, t_2 variables are interpreted as representing change from t_1 to t_2.

Results

Children of depressed mothers were more likely to display a psychiatric disorder at both 6 years [$\chi^2_{(1)} = 10.7$, $p < .01$] and 10 years [$\chi^2_{(1)} = 5.75$, $p < .05$], supporting our first hypothesis. Testing for differences in our main study variables within the depressed group between children exposed to maternal depression at 6 versus 10 years, no significant differences emerged. To maximize the sample size, to address risk and resilience in the context of maternal depression, we combined children exposed to maternal depression at 6 and 10 years into the 'children of depressed mothers' group.

Two-way ANOVAs on study variables with maternal depression and child disorder as independent factors appear in Table 1, partially supporting our second hypothesis. At 6 years, maternal depression main effects included lower sensitivity, reduced synchrony, and attenuated child OT. Child disorder effects included low OT, low child social engagement, and higher externalizing and internalizing problems. Interaction effects were found for internalizing problems; children with disorders to healthy mothers exhibited less internalizing problems. Child engagement also showed interaction effect; children with disorders to depressed mothers were less engaged. At 10 years, maternal depression main effects included low child OT and reduced social engagement. Child disorder main effects included lower OT, lower social engagement, and higher externalizing and internalizing problems, with no interaction effects. Figure 1 presents findings for our resilience markers – OT and synchrony.

To test the third hypothesis, Pearson correlations appear in Table 2 and show associations between lower OT, less maternal sensitivity and synchrony, and lower child engagement with higher behavior problems at 6 and 10 years. Correlations for the depressed and nondepressed group separately appear in Supporting information (Tables S1 and S2) and show similar magnitudes of correlations in the two groups (tested with Fisher *Z*).

To test our conceptual model on the dynamic paths leading from maternal depression to child externalizing and internalizing problems as mediated by maternal and child's relational behavior, OT, and synchrony, we conducted structural model utilizing variables measured at 10 years controlling for the same variables measured at 6 years (Figure 2). The overall model provided good fit to the data: $\chi^2_{(39)} = 43.157$, $p = .298$, RMSEA = 0.029 with lower 90% CI = 0.00 and higher 90% CI = 0.071 PCLOSE = 0.749, CFI = 0.989, TLI = 0.975.

We identified four paths leading from maternal depression to internalizing and externalizing problems at 10 years, controlling for 6-year variables. The first path linked depression to lower maternal sensitivity, which connected with higher internalizing problems. Test of mediation indicates that this indirect path was significant (95% CI = 0.039, 0.693). The second path began similarly with reduced sensitivity, leading to decreased child engagement, linked with lower synchrony, and related to internalizing and externalizing problems and test of mediation proved significant (95% CI = 0.001, 0.024, and 95% CI = 0.001, 0.029, respectively). The third path linked to OT: Depression correlated with low OT, which led to higher internalizing problems (95% CI = 0.075, 0.904). The fourth path began similarly with decreased OT, linked to reduced child engagement, leading to lower synchrony, and converging on the second path. Tests of mediations indicated that the third and fourth indirect paths to internalizing (95% CI = 0.001, 0.006) and externalizing (95% CI =0.001, 0.006) problems were significant.

Finally, to support our conceptual model, we compared it to three alternatives (Figures S1-S3). The first (S1) measured behavior problems at 10 years from variables assessed at 6 years, not change trajectories. This model showed less adequate fit to the data [$\chi^2_{(9)} = 14.092$, $p = .119$, RMSEA = 0.068 with lower 90% CI = 0.00 and higher 90% CI = 0.132, PCLOSE = 0.292,

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Table 1 Means and *SD* for study variables by maternal depression and child disorders

	Mother without depression				Mother with depression						
	Child without diagnoses		Child with diagnoses		Child without diagnoses		Child with diagnoses				
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	Main effect mother	Main effect child	Interaction effect mother–child
Age 6 years											
OT child	6.72_a	3.26	5.06_b	1.64	4.83_a	1.64	4.44_a	1.18	$F_{(1, 92)} = 4.26$, $p < .05$, $\eta_p^2 = .04$	$F_{(1, 92)} = 4.15$, $p < .05$, $\eta_p^2 = .04$	$F_{(1, 92)} = 0.85$, $p > .05$, $\eta_p^2 = .01$
Mother sensitivity	4.59_a	0.59	4.54_a	0.58	4.16_a	0.70	4.15_a	0.92	$F_{(1, 118)} = 8.52$, $p < .01$, $\eta_p^2 = .07$	$F_{(1, 118)} = 0.78$, $p > .05$, $\eta_p^2 = .00$	$F_{(1, 118)} = 0.02$, $p > .05$, $\eta_p^2 = .00$
Child engagement	4.63_a	0.55	4.49_a	0.64	4.85_a	0.24	4.16_b	0.93	$F_{(1, 117)} = 0.21$, $p > .05$, $\eta_p^2 = .00$	$F_{(1, 117)} = 6.27$, $p < .05$, $\eta_p^2 = .05$	$F_{(1, 117)} = 4.16$, $p < .05$, $\eta_p^2 = .03$
Dyadic synchrony	4.34_a	0.72	4.28_a	0.90	4.02_a	1.11	3.76_a	1.23	$F_{(1, 117)} = 4.77$, $p < .05$, $\eta_p^2 = .04$	$F_{(1, 117)} = 0.51$, $p > .05$, $\eta_p^2 = .00$	$F_{(1, 117)} = 0.28$, $p > .05$, $\eta_p^2 = .00$
CBCL											
Internal	3.84_a	2.94	9.55_b	6.05	6.92_a	6.20	8.42_a	4.66	$F_{(1, 104)} = 1.01$, $p > .05$, $\eta_p^2 = .01$	$F_{(1, 104)} = 21.52$, $p < .01$, $\eta_p^2 = .17$	$F_{(1, 104)} = 4.53$, $p < .05$, $\eta_p^2 = .04$
External	4.86_a	4.12	9.75_b	4.36	6.08_a	4.91	9.84_a	5.89	$F_{(1, 104)} = 0.41$, $p > .05$, $\eta_p^2 = .00$	$F_{(1, 104)} = 21.35$, $p < .01$, $\eta_p^2 = .17$	$F_{(1, 104)} = 0.3$, $p > .05$, $\eta_p^2 = .00$
Age 10 years											
OT Child	20.77_a	6.55	15.83_b	5.25	14.92_a	2.61	13.96_a	4.68	$F_{(1, 72)} = 4.78$, $p < .05$, $\eta_p^2 = .06$	$F_{(1, 72)} = 8.69$, $p < .01$, $\eta_p^2 = .11$	$F_{(1, 72)} = 1.58$, $p > .05$, $\eta_p^2 = .02$
Mother sensitivity	4.06_a	0.75	3.95_a	0.66	3.75_a	0.48	3.61_a	0.82	$F_{(1, 103)} = 4.59$, $p < .05$, $\eta_p^2 = .04$	$F_{(1, 103)} = 0.64$, $p > .05$, $\eta_p^2 = .01$	$F_{(1, 103)} = 0.01$, $p > .05$, $\eta_p^2 = .00$
Child engagement	4.15_a	0.44	3.77_b	0.76	3.57_a	0.54	3.56_a	0.31	$F_{(1, 94)} = 5.99$, $p < .05$, $\eta_p^2 = .06$	$F_{(1, 94)} = 6.82$, $p < .05$, $\eta_p^2 = .07$	$F_{(1, 94)} = 1.46$, $p > .05$, $\eta_p^2 = .02$
Dyadic synchrony	4.16_a	0.47	3.74_b	0.87	3.81_a	0.39	3.63_a	0.83	$F_{(1, 105)} = 0.92$, $p > .05$, $\eta_p^2 = .01$	$F_{(1, 105)} = 6.4$, $p < .05$, $\eta_p^2 = .06$	$F_{(1, 105)} = 0.31$, $p > .05$, $\eta_p^2 = .00$
CBCL											
Internal	1.91_a	1.74	3.75_b	3.14	2.75_a	2.26	3.83_a	3.33	$F_{(1, 107)} = 0.51$, $p > .05$, $\eta_p^2 = .00$	$F_{(1, 107)} = 9.83$, $p < .01$, $\eta_p^2 = .08$	$F_{(1, 107)} = 0.46$, $p > .05$, $\eta_p^2 = .00$
External	3.28_a	2.71	5.13_b	2.94	4.92_a	4.61	5.67_a	4.31	$F_{(1, 110)} = 2.09$, $p > .05$, $\eta_p^2 = .02$	$F_{(1, 110)} = 5.26$, $p < .05$, $\eta_p^2 = .05$	$F_{(1, 110)} = 0.61$, $p > .05$, $\eta_p^2 = .01$

For *F*-tests, partial eta squared were calculated as effect sizes. Values in the same row and subtable not sharing the same subscript are significantly different at $p < .05$.

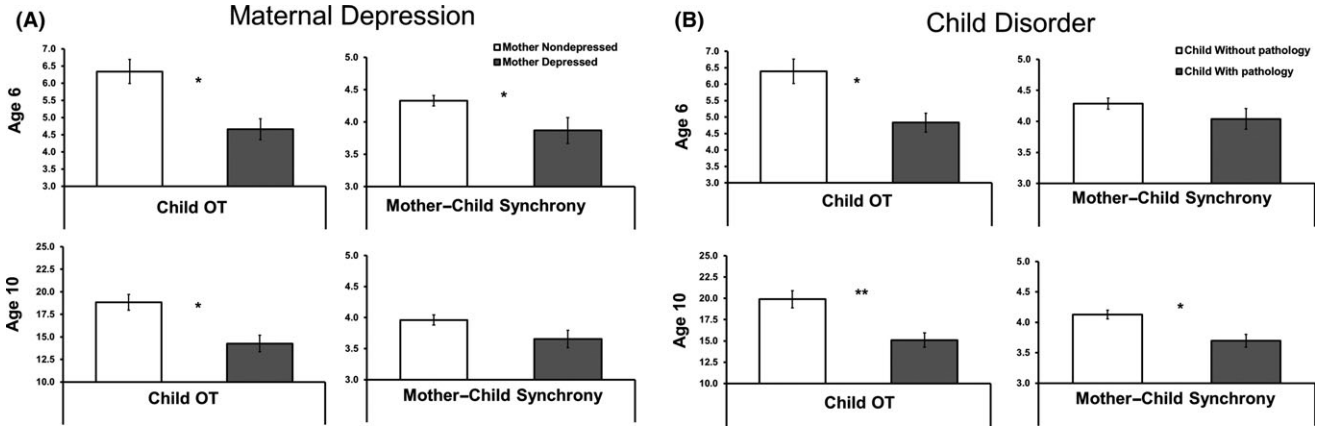

Figure 1 Means and standard errors for oxytocin and synchrony by maternal depression and child disorder at 6 and 10 years. *Note:* * $p < .05$; ** $p < .01$. Significant differences were examined using *F*-tests

CFI = 0.977, TLI = 0.930]. Additionally, some key direct paths were insignificant, including path from synchrony to behavior problems ($p > .05$); path from maternal sensitivity and child OT to behavior problems ($p > .05$), and path from OT to child engagement and synchrony ($p > .05$) and all mediated paths were insignificant. The second alternative model (S2) measured behavior problems at 10 years from variables assessed at 6 years, not change trajectories except for behavior problems. This model also showed inadequate fit [$\chi^2_{(19)} = 34.104$, $p = .018$, RMSEA = 0.08 with lower 90% CI = 0.033 and higher 90% CI = 0.123, PCLOSE = 0.124, CFI = 0.952, TLI = 0.866], with insignificant key paths ($p > .05$) and all mediation paths insignificant. The third alternative model (S3) eliminated the resilience components: OT and synchrony. This model provided less adequate fit [$\chi^2_{(16)} = 28.703$, $p = .026$, RMSEA = 0.08 with lower 90% CI = 0.027 and higher 90% CI = 0.126 PCLOSE = 0.141, CFI = 0.935, TLI = 0.817].

Discussion

Maternal depression, affecting 15% of parturient women in industrial societies (Kessler, 2006), is the most prevalent psychiatric disorder and the only one carrying direct impact not only on the suffering individual but also on her offspring. Yet, very few studies followed children of depressed mothers prospectively from birth and focused on middle childhood, a period of major strides in social-emotional development and when children's own psychiatric disorders begin to express more fully (Colle & Del Giudice, 2011). Here, we addressed the less-researched topic of resilience and focused on two markers of resilience that are related to lower behavior problems in the context of maternal depression; the OT system and social synchrony. Both OT and synchrony are shaped in early infancy within the mother–infant bond and both have been shown to carry long-term effects on children's brain, behavior, and psychopathology (Feldman, 2015). Prior to discussing our findings, it is important to note that the terms 'effects', 'predict' or 'leads to' describe statistically significant paths, not causal effects and the terms 'correlates' or 'markers' of resilience do not imply causality.

Several overall insights emerged from our decade-long study. First, exposure to maternal depression carries measurable consequences for children's well-being beyond infancy. Children of depressed mothers were more susceptible to present a full-blown psychiatric disorder at both 6 and 10 years, even when the family's conditions were low-risk. Second, depression was associated with impairments in the neurobiological and behavioral systems that support participation in social life, including decreased maternal sensitivity, low child social engagement, reduced synchrony, and attenuated OT. Interestingly, while OT at 6 and 10 years showed main effects for both maternal depression and child psychiatric disorder, synchrony shifted from susceptibility to maternal depression at 6 years to main effect for child disorder only by 10 years. These findings underscore the growing indirect effects of maternal depression on children's sociality as they grow older and suggest that preadolescence may be a starting-point for the consolidation of risk and resilience trajectories. Third, our path model pinpointed the process by which deficits in maternal caregiving shape children's social engagement, synchrony, and behavior problems. Our findings that change across middle childhood provided the best fit to the data compared to levels at each 6 or 10 years suggest that change over time may be an important perspective to incorporate into research in developmental social neuroscience.

Maternal depression markedly increased child propensity for psychopathology. Over 60% of children exposed to maternal depression during middle childhood received a full-blown Axis-I diagnosis, with affective disorders being the most prevalent diagnosis at each ages. These numbers should raise concern, particularly as our children were raised in low-risk, middle-class, two-parent families and

Table 2 Pearson correlations of study variables at 6 and 10 years

Variable	1	2	3	4	5	6	7	8	9	10	11
Age 6 years											
1. Child OT											
2. Mother Sensitivity	0.29**										
3. Child Engagement	0.27**	0.53**									
4. Mother–child Synchrony	0.29**	0.72**	0.75**								
CBCL											
5. Internal	−0.20	−0.11	−0.07	−0.10							
6. External	−0.26*	−0.07	−0.20*	−0.10	0.58**						
Age 10 years											
7. Child OT	0.08	0.12	0.02	0.03	−0.16	−0.21					
8. Mother Sensitivity	0.14	0.09	0.11	0.01	−0.22*	−0.27*	0.06				
9. Child Engagement	0.05	0.25*	0.20*	0.14	−0.22*	−0.30**	0.37**	0.23*			
10. Mother–child synchrony	0.06	0.17	0.18	0.16	−0.15	−0.17	0.38**	0.28**	0.54**		
CBCL											
11. Internal	−0.06	−0.12	−0.14	−0.1	0.37**	0.41**	−0.30*	−0.33**	−0.29**	−0.40**	
12. External	−0.06	−0.24*	−0.19	−0.2	0.45**	0.58**	−0.02	−0.19	−0.29**	−0.26*	0.50**

*$p < .05$; **$p < .01$.

maternal depression was the only risk. When maternal depression co-occurs with other contextual risks, child maladaptation may increase. Our findings indicate that children do not 'get used' to their mother being depressed and exposure at any time bears significant effects on their well-being. As the numbers of children exposed to maternal depression are high and increasing, it is important to expand research on its impact beyond infancy and develop targeted interventions.

By 10 years, most effects of maternal depression were linked to child psychiatric disorders. Thus, maternal depression may impact outcome in older children by increasing the prevalence of psychiatric disorders, particularly affective disorders. Possibly, at that age children are already placed on a risk or resilience trajectory, and being on the risky road with a consolidated psychopathological profile charts the pathway to negative outcome. While little theoretical effort and empirical research has focused on resilience in the context of a well-defined early adversity, some authors suggest that resilience is associated with greater neurobiological plasticity and highlighted several resilience-related biomarkers, such as brain glucocorticoids, telomere length, or neural oscillations (Cicchetti & Blender, 2006; Davidson, 2000; Karatoreos & McEwen, 2013), and thus our focus on the OT system and social synchrony are novel and timely. Resilience may suggest that children possess certain skills or better functioning of neurobiological systems that enable plasticity despite adversity. Research on sensitive periods, time-windows when brain plasticity increases (Hensch, 2005), shows wide between-individual variability in the degree of plasticity during sensitive periods that plays a role in later development (Feldman, 2015). In the present context, while maternal depression may close plasticity in offspring, due to toxic stress or limited/rigid caregiving (Cirulli, Berry, & Alleva, 2003; Fagiolini, Jensen, & Champagne, 2009; Love & Williams, 2008), resilience may imply that some children can maintain the window open by either actively engaging a mother with limited resources or seeking other affiliations that provide the missing component, such as fathers, grandparents, or mentors. It has indeed been shown that father involvement in families of depressed mothers reduced children's behavior problems (Chang, Halpern, & Kaufman, 2007) and increased positive family relationships (Vakrat, Apter-Levy, & Feldman, 2017). Child temperamental regulation has similarly shown to buffer the effects of maternal depression (Blandon, Calkins, Keane, & O'Brien, 2008), suggesting that some inborn dispositions foster greater resilience. Furthermore, by focusing on change over time, we highlight another important component of resilience – malleability. During the dynamic period of middle childhood, change trajectories, the dynamic and plastic modulations over time, provided better fit to the data than

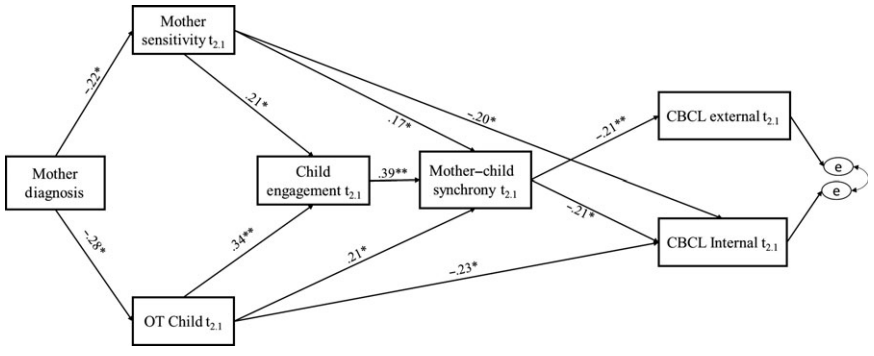

Figure 2 Path analysis linking maternal depression with child behavior problems at 10 years controlling for variables measured at 6 years. *Note:* t_1 stands for measurement at age 6. t_2 stands for measurement at age 10; $t_{2.1}$ stands for measurement at age 10 while controlling for age 6. Coefficients represent standardized regression weights. The overall model provided an adequate fit to the data: $\chi^2_{(39)} = 43.157$, $p = .298$, RMSEA = 0.029 with lower 90% CI = 0.00 and higher 90% CI = 0.071 PCLOSE = 0.749, CFI = 0.989, TLI = 0.975. * $p < .05$, ** $p < .01$

predicting late-childhood end-points from 6-year variables, suggesting that the dynamic maturation of children's social skills and maternal–child coordination is the component that determines the exacerbation or attenuation of children's behavior problems.

We found that OT and social synchrony were correlates of resilience. One possibility is that OT initiates a cascade leading to higher child social engagement and greater synchrony, which lead to reduced internalizing and externalizing problems, mediating the effects of maternal depression on adaptive behavior. OT has been implicated in neural plasticity at both the cellular and network assembly levels and studies in animal models described OT's role in mediating neural plasticity (Dölen, Darvishzadeh, Huang, & Malenka, 2013; Gur, Tendler, & Wagner, 2014; Owen et al., 2013; Zheng et al., 2014), suggesting a possible mechanism for its role in resilience. OT supports growth and healing across the life span and its anti-inflammatory effects support its role in social adaptation and physical well-being (Carter, 2017). Biobehavioral synchrony, the coupling of maternal and child's physiological and behavioral signals during social contact, similarly functions as a plasticity mechanism by which mothers maintain child engagement online, expand their abilities to attend to social cues, and sharpen social understanding (Feldman, 2015, 2017). Furthermore, OT and synchrony are bidirectionally linked; through careful adaptation to the child's signals human mothers, like other mammals, externally regulate the child's OT system and when maternal behavior decreases, for instance in depression, children's OT is impaired (Feldman, 2012a; Pratt et al., 2015). In parallel, parental OT dysfunction, as observed among parents with *OXTR* alleles associated with greater psychopathology, is related to diminished parental synchrony, leading to less optimal child social outcomes and reduced OT (Feldman et al., 2013). Here, we show that these mutually regulated foundations of the neurobiology of affiliation work in concert across middle childhood to mediate the effects of maternal depression on child behavior problems. As seen, OT's resilience-related role was defined via two paths; first, OT directly predicted lower internalizing problems, highlighting the links between affective disorders and OT deficits, and second, OT linked with greater synchrony, which predicted less externalizing and internalizing problems. As OT is a malleable system, highly open to epigenetic effects, interventions that enhance synchrony in age-appropriate ways may help not only infants, but also older children.

Child social engagement mediated the effects of OT and maternal sensitivity on social synchrony and behavior problems. Children's social engagement is an orientation maturing on the basis of biological dispositions integrated with sensitive parenting, shows individual stability over time, and predicts social competencies with peers (Feldman & Masalha, 2010). We found that among children growing in war-zones, social engagement mediated the effects of trauma on child behavior problems at 10 years, similar to the current findings (Halevi et al., 2017). Possibly, by school-age, children's social skills and engaged versus withdrawn style play an important role in resilience, enabling children to draw comfort from their peers and to create meaningful attachments. Interventions that aim to enhance children's social skills may thus be particularly important for promoting resilience at this age.

Our findings have clear implications for intervention and point in three directions to promote resilience in children of depressed mothers. First, interventions should focus on enhancing maternal sensitivity, possibly as early as possible. Improvements in maternal sensitivity may carry effects at all levels, enhance child engagement, and bolster synchrony. Second, our findings emphasize the need to construct interventions for older children, particularly, interventions that promote social engagement, utilizing, for instance, social skills interventions. Finally, interventions that enhance synchrony

in age-appropriate formats may provide important buffer against the development of behavior problems.

Several study limitations should be considered. First, as we focused on the long-term effects of maternal depression apart from other comorbidities, our findings need replications in higher risk samples. Second, as both parents shape their children's well-being, the omission of fathers is an important limitation. Third, while growing research has utilized peripheral OT measurements, the links between central and peripheral OT are still not fully clear and this is a clear study limitation. Yet, studies in animals (Carter et al., 2007; Wotjak et al., 1998) and human's adults and children (Carson et al., 2015) suggest that central and peripheral activity of the OT system is likely to be coordinated. For instance, OT administration, which impacts central OT, is associated with marked increases in salivary OT (Weisman et al., 2012), salivary OT correlates with genetic variability on the *OXTR* (Feldman et al., 2013), parallel increases were found in maternal plasma OT and in fMRI BOLD response in brain areas rich in OT receptors (Strathearn, Fonagy, Amico, & Montague, 2009); and salivary OT measured across multiple ages and laboratories show parallel findings to those observed for central OT in animals. Fourth, at the model, we combined children exposed to maternal depression at 6 and 10 years in order to maximize the sample size. Although there are no differences in major study variables between the two groups, the model may be different to each age group. Therefore, future studies should use larger sample size in order to adequately test developmental differences. Finally, resilience is a controversial construct that requires much further research. Here, we defined resilience, consistent with much developmental research, as lower behavior problems in the context of adversity, but a broader research program on resilience is much in need. Much further research is required to follow children of depressed mothers as they go through other developmental challenges, including the pubertal transition, leaving home, forming pair-bonds, and eventually nurturing their own children and define components of resilience that can help such children enjoy full participation in social life.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Path analysis predicting externalizing and internalizing problems at 10 years from hormones and behavior measured at 6 years.

Figure S2. Path analysis predicting change in children' internalizing and externalizing problems from 6 to 10 years from early childhood variables.

Figure S3. Path analysis without biomarkers of resilience predicting children's internalizing and externalizing problems.

Table S1. Pearson correlations among OT, relational behavior, and child problems at 6 and 10 years for mothers without history of depression and their children.

Table S2. Pearson correlations among OT, relational behavior, and child problems at 6 and 10 years for depressed mothers and their children.

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Key points

- Maternal depression is known to impact children's well-being but no study focused on resilience in children of depressed mothers.
- We followed children of depressed mothers from birth to 10 years, focusing on two resilience markers: oxytocin and synchrony across middle childhood.
- At 6 and 10 years, maternal depression increased child psychiatric disorders.
- At 6 and 10 years, maternal depression and child disorder attenuated child OT.
- OT and synchrony mediated the effects of maternal depression on child externalizing and internalizing problems at 10 years.
- Findings underscore the need to conduct longitudinal follow-ups on children of depressed mothers and construct interventions that bolster age-appropriate social synchrony.

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