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Exposure to early and persistent maternal depression impairs the neural basis of attachment in preadolescence

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ABSTRACT

Maternal depression increases child vulnerability to psychopathology, loneliness, and social maladjustment; yet, its long-term effects on the social brain are unknown. In this prospective longitudinal study we examined the impact of early and persistent maternal depression on the neural basis of attachment in preadolescence. A community cohort was followed in two groups; children exposed to maternal depression from birth to 6 years and healthy controls. At 9 months and 6 years, mother-child interactions were coded for maternal sensitivity and affect synchrony and salivary oxytocin levels were assessed at 6 years. At preadolescence (11–13 years), children underwent magnetoencephalography (MEG) while exposed to own versus unfamiliar mother-child interaction. Own interaction elicited greater response in beta- and gamma-band oscillations across a wide cluster in temporal and insular cortices, including the Superior Temporal Sulcus, Superior Temporal Gyrus, Inferior Temporal Gyrus, and insula. Beta activations were predicted by maternal sensitivity across early childhood and gamma by affect synchrony. Oxytocin was related to beta response to social cues. Maternal depression impacted child's brain response in two ways. First, maternal depression significantly increased the prevalence of child affective disorder and such children showed no neural differentiation between attachment and non-attachment stimuli. Second, maternal depression decreased maternal sensitivity, affect synchrony, and child oxytocin across early childhood and these were longitudinally associated with aberrant neural response to attachment-specific and social-general cues in preadolescence. Our findings are the first to describe mechanisms by which maternal depression impairs the neural basis of attachment at the transition to adolescence and advocate the need for relationship-focused early interventions.

1. Introduction

Although the prevalence of major depressive disorder (MDD) in women of childbearing years is continuously on the rise, rendering maternal depression the most prevalent psychiatric disorder and the only one carrying direct impact not only on the suffering individual but also on her offspring, very few studies followed children of depressed mothers from birth and over lengthy periods. MDD in the months following childbirth is estimated at 7–13% of women in high income countries and up to 30% in the developing world (Parsons et al., 2012a, 2012b); women are twice more likely to suffer MDD than men (Kessler, 2003); over 10% of women aged 18 to 39 years suffer from depression at any given time (QuickStats, 2012); and lifetime prevalence of MDD in women is estimated at over 20% (Kessler et al., 2012). Studies have repeatedly shown that exposure to maternal MDD increases child propensity to psychiatric disorders, behavior problems, and social maladjustment (Feldman et al., 2009; Goodman et al., 2011; Halligan et al., 2007; Rohanachandra et al., 2018; Shaw et al., 2009; Yan and Dix, 2014a). Similarly, maternal depression impairs the quality of caregiving, observed in reduced maternal sensitivity, minimal affect synchrony, and increased maternal negativity and intrusiveness (Cohn and Tronick, 1988; Feldman et al., 2009; Granat et al., 2017) and such disruptions were found to mediate the effects of maternal depression on child psychopathology (Burt et al., 2005; Elgar et al., 2007; Priel et al., 2018). Yet, the effect of maternal MDD on the developing brain has received little empirical attention and the pathways leading from early exposure to maternal depression to impairments in the social brain are largely unknown.

In the current longitudinal study, we targeted the neural basis of attachment in preadolescents followed with their mothers since birth

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and examined the effects of early and persistent maternal depression on functionality of this neural system. We utilized magnetencephalography (MEG) to tap oscillatory processes that are involved in human attachment processes and their cortical generators and how such processes may be impaired by early exposure to maternal depression. A community birth cohort of mothers and newborns was recruited on the second post-birth day and, utilizing an extreme-case design, repeatedly assessed for maternal depression across the first year and again at 6 years to create two matched cohorts: mothers who were continuously depressed from birth to six years and healthy controls. For a fuller biobehavioral assessment we examined the two arms of the neurobiology of attachment as predictors of children's brain response to attachment cues: parent-child synchrony and functionality of the oxytocin system (Feldman, 2017). The central hypothesis guiding our study was that exposure to chronic maternal depression during early sensitive periods would impair the child's neural response to attachment cues and that such impairments would be associated with caregiving over time and oxytocin (OT) levels and would be particularly sensitive to risk factors.

The brain basis of attachment, the “affiliative brain”, has mainly been studied in the context of parenting. Imaging studies have shown that in response to their own infant mammalian mothers activate a distinct subcortical neural network that supports parental care (Insel and Young, 2001; Numan and Young, 2015). In humans, this subcortical mammalian-general maternal network extends to include several human-specific cortical networks implicated in empathy, mentalization, embodied simulation, and emotion regulation (Feldman, 2015a; Young et al., 2017). This global human attachment network underpins the human capacity to form exclusive attachments, empathize with the infant's non-verbal signals, execute parenting in light of cultural meaning systems and long-term parenting goals, and use attachment relationships to foster security, social engagement, and mental health (Feldman, 2016, 2017). The standard paradigm in neuroimaging studies of parental attachment involves exposing parents to their own child stimuli as compared to an unfamiliar infant matched for age, gender, and ethnicity. Overall, this line of research defined the specific regions comprising the neural basis of attachment in humans and addressed their associations with sensitive and synchronous parenting and with the parent and child's oxytocin levels (Abraham et al., 2014; Azil et al., 2011; Feldman, 2015a, 2017; Strathearn et al., 2009).

Although much less research has utilized the same paradigm to test the brain basis of attachment in children, two recent studies lend support to the hypothesis that a similar global attachment network activates in children in response to attachment cues. Both studies utilized MEG and showed a significantly stronger response in the child's brain to own mother-child interaction as compared to unfamiliar interaction and pinpointed the same structures observed in the parental brain in this response, including the Superior Temporal Sulcus (STS), Superior Temporal Gyrus (STG), Fusiform Gyrus (FG), and Insula (Levy et al., 2017; Pratt et al., 2018). Similar to the findings for parents, children's brain response to attachment cues was associated with maternal sensitivity and mother-child affect synchrony - the mother and child's moment-by-moment coordination of affective expressions and level of arousal in ways that promote positive engagement (Feldman, 2007) - experienced in early childhood. These findings indicate that well-adapted caregiving is related to the formation of a comparable attachment network in the child's brain, suggesting that the cross generational transmission of the neural basis of attachment may be mediated, at least partly, by sensitive and synchronous parenting. This hypothesis is consistent with studies in animal models which indicate that the postnatal activation of the maternal brain and the expression of the species-typical maternal behavior tune the child's brain to the social world (Champagne et al., 2001; Francis et al., 2001; Numan and Young, 2016).

Maternal depression impairs the neural basis of attachment in mothers (Laurent and Ablow, 2012, 2013) and is associated with deficits in sensitive and synchronous parenting (Feldman et al., 2009; Granat et al., 2017; Field et al., 1990) and reduced oxytocin production in mother and child (Apter-Levy et al., 2013; Pratt et al., 2015; Yuen et al., 2014). Depressed mothers exhibit blunted neural response to own infant stimuli in key nodes of the affiliative brain, including medial orbitofrontal cortex (mOFC) and insula, areas implicated in reward, empathy, and emotion regulation (Laurent and Ablow, 2012, 2013; Strathearn et al., 2008) and this diminished neural response has been linked with the decrease in maternal sensitivity (Musser et al., 2012). These findings suggest that one pathway for the cross-generational disruptions in the neural basis of attachment in offspring of depressed mothers may relate to the diminished sensitivity and synchrony experienced in early childhood and the decreased OT production (Apter-Levy et al., 2013; Pratt et al., 2015; Priel et al., 2018). A second potential pathway is the higher prevalence of affective disorders in offspring of depressed mothers, which increases as children grow older and has been linked with alterations in the adolescent brain (Barker, 2013; Maughan et al., 2007; Murray et al., 2011; Priel et al., 2018; Trapolini et al., 2007), and are longitudinally predicted by the reduced maternal sensitivity and synchrony experienced in early childhood (Apter-Levy et al., 2013; Morgan et al., 2014; Nicholson et al., 2011). Furthermore, an fMRI study of depressed adolescents showed blunted activations in reward and self-referential networks to videos of their mothers praising them (Silk et al., 2017), suggesting that affective disorder in offspring of depressed mothers may impair their ability to utilize the mother's positive caregiving in the service of brain maturation.

Neural oscillations serve a key role in neuronal activity (Buzsaki, 2004) and afford a unique perspective on the developing brain, particularly on core social functions (Donner and Siegel, 2011). Studies assessing oscillatory response to attachment-related cues pinpointed the involvement of beta and gamma rhythms. For instance, infant faces elicit higher beta oscillations as compared to adult faces in mOFC of non-parents (Kringelbach et al., 2008). Similarly, mothers showed higher beta- and gamma-band activations to infant crying and laughing in temporal-parietal regions (Hernández-González et al., 2016), and infants exhibited greater beta- and gamma-band activity to infant-directed speech compared to singing (Arias and Pena, 2016). The two aforementioned studies exposing children to own versus unfamiliar mother-child interactions highlighted the role of gamma rhythms. The first showed greater gamma activations in both mother and child to own mother-child interactions in the right superior-temporal-sulcus (rSTS); these gamma rhythms were coupled between mother's and child's brains, anchored in moments of affect synchrony, and linked with maternal sensitivity in early childhood (Levy et al., 2017). The second study showed increased beta and gamma oscillations in children to own mother-child interactions in the STS and insula and associations between gamma activity and mother-child synchrony (Pratt et al., 2018). This suggests that beta and gamma rhythms in temporal and insular regions are sensitive to attachment cues and are associated with sensitive and synchronous caregiving.

The current prospective longitudinal study examined the neural basis of attachment in preadolescents exposed to maternal depression from birth to 6 years. We utilized the typical paradigm employed in research on the parental brain and exposed children to own versus unfamiliar mother-child interaction, focusing on beta and gamma rhythms that have been linked with attachment-related stimuli (Arias and Pena, 2016; Hernández-González et al., 2016; Levy et al., 2017). Three global hypotheses were formulated. First, we expected higher gamma and beta activations to attachment cues in temporal and insular cortices, consistent with prior research (Feldman, 2015a; Kringelbach et al., 2008; Pratt et al., 2018; Young et al., 2017) (Hypothesis 1). Second, we expected that these beta and gamma-band activations would be predicted by maternal sensitivity, affect synchrony, and child OT across childhood (Hypothesis 2). Finally, among children exposed to early and chronic maternal depression we expected reductions in

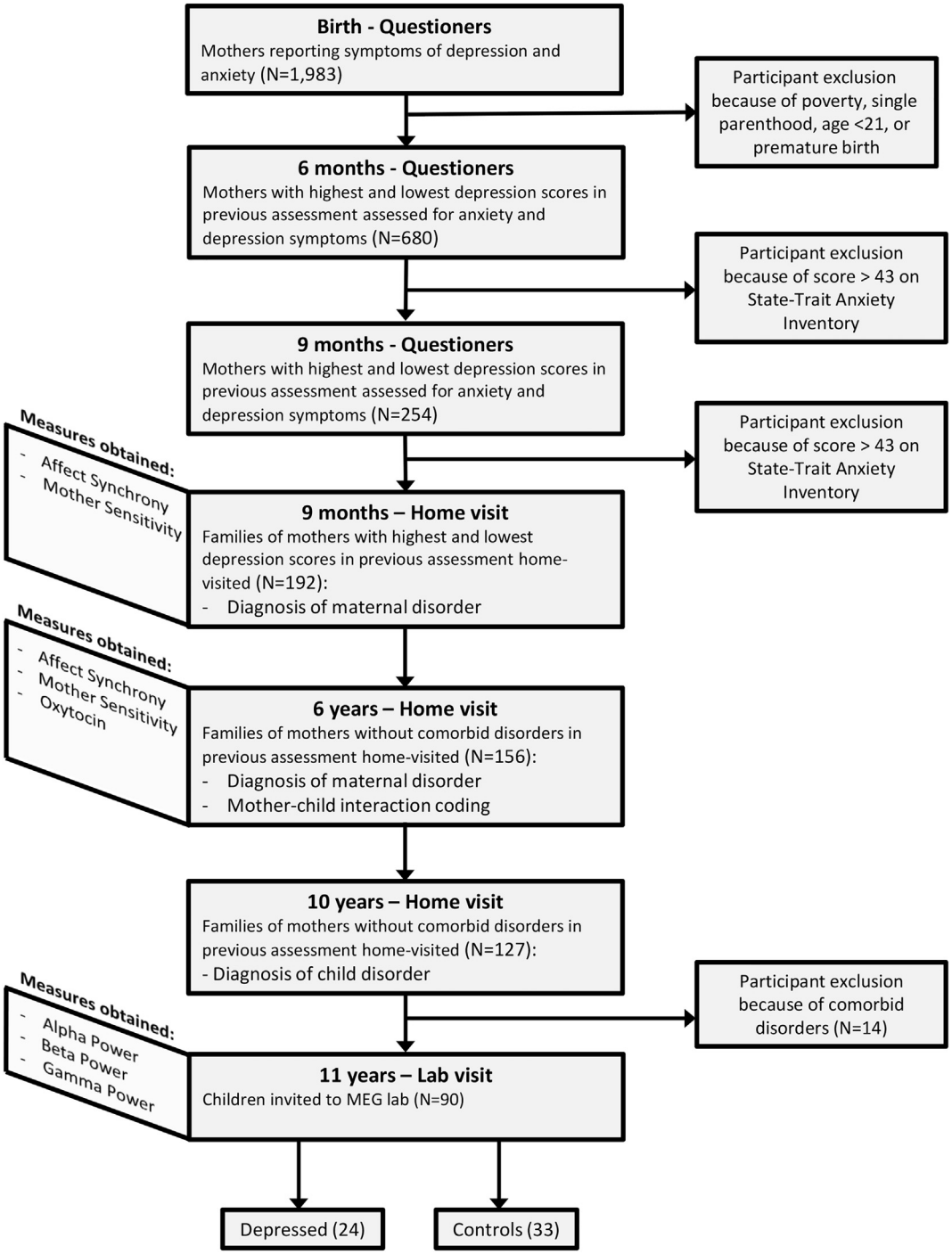

Fig. 1. Consort flow diagram.

maternal sensitivity and synchrony, lower OT, and disruptions to the neural basis of attachment. We have shown that infants of depressed mothers, unlike infants of healthy controls, exhibit no behavioral differentiation when mother and stranger elicited negative and positive emotions (Granat et al., 2017), and thus expected minimal neural differentiation between attachment and non-attachment cues in children of depressed mothers, particularly among those on a risk trajectory who developed affective disorders (Hypothesis 3).

2. Method and materials

2.1. Participants

Participants were recruited in seven waves of data collection and full details of recruitment appear in supplementary material (SM). Fig. 1 presents a consort flow diagram, including measurements collected at each wave of data collection. Our goal was to study the impact of maternal depression *in of itself* and thus, families were of low risk, excluding frequently occurring comorbidities that independently impact infant development, such as poverty, single parenthood, and teenage pregnancy. Similarly, cases with comorbid anxiety were

excluded, as anxiety and depression carry opposite effects on neurobiological systems. On the second post-birth day, 1983 women who were healthy, completed high school, were over 21 years, above poverty cutoff, cohabitating, and whose infants were healthy, full-term, and singleton, were recruited in three maternity wards in large metropolitan area. Mothers were assessed for symptoms of depression and anxiety at 6 m and 9 m post-partum, and those in the highest and lowest quartiles of the Beck Depression Inventory (BDI; Beck et al., 1961), and no elevated anxiety on the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) were home-visited at 9 months and 6 years. At 6y, families were divided into two groups; 46 mothers who reported high depressive symptoms at birth, 6 m, and 9 m, were diagnosed with Axis-I major depression disorder (MDD) at both 9 m and 6y, and reported being depressed throughout much of the child's first 6 years (depressed group), and 103 mothers reporting no elevated symptoms at any time-point and free of psychiatric diagnosis (control group). Families were home-visited, mother-child interaction videotaped, and child OT assayed. At age 10, 127 families were revisited and maternal and child psychopathology diagnosed. At preadolescence, 110 families were contacted to participate in MEG session and 90 participated, excluding children with metals, such as braces. Full MEG data for the attachment paradigm was available for 57 participants, mainly due to video sound problems, muscle artifact, movement, or inability to complete session, including 24 children in the depressed group and 33 controls (mean age 11.25; 33 boys and 24 girls in total). In the depressed group, 13 mothers still received MDD diagnosis while the remaining 13 no longer qualified for full MDD, and no differences emerged between the two sub-groups (SM Table 1). Study was approved by IRB, procedures were explained to the accompanying parent before sessions, and all signed informed consent. Families received small gift for participation.

2.2. Measures

2.2.1. Maternal psychiatric diagnosis

Interviews were conducted by clinical psychologist at 9 m, 6y, and 10y using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997).

2.2.2. Child psychiatric diagnosis

Interviews were conducted by clinical psychologist at 10y using the Development and Well-Being Assessment (DAWBA; Goodman et al., 2000). SCID and DAWBA diagnoses were supervised by a child psychiatrist with reliability exceeding 85% and cases conferred every few weeks (kappa; SCID = 0.85, DAWBA = 0.86).

2.2.3. Oxytocin

Saliva OT was collected by Salivette (Sarstedt, Rommelsdorft, Germany) at age 6y. Children were asked to chew a roll of cotton for 1 min. Saliva samples were kept ice-chilled for up to 1 h before being centrifuged at ˚4C at 1500*g* for 15 min. Liquid samples were stored at 80 ˚C. To concentrate samples by three or four times, liquid samples were lyophilized overnight and kept at 20 ˚C until assayed. Dry samples were reconstructed in the assay buffer immediately before analysis by enzyme immunoassay, consistent with prior research (Feldman et al., 2010a, 2010b). OT level was determined with commercial oxytocin enzyme-linked immunosorbent assay kit. Measurements were performed in duplicate, and concentrations calculated by MatLab7 (MathWorks, Natick, Mass.) according to standard curves. Intra-assay and inter-assay coefficients were 12.4% and 14.5%, respectively.

Table 1
Group differences in mother-child interaction patterns, child OT, and child affective disorder.

	Non-depressed		Depressed		Statistics
	Mean (n)	SD	Mean	SD	T value
Maternal sensitivity	3.76 (33)	0.64	3.37 (24)	0.86	2.65**
Affect synchrony	1.67 (33)	2.85	0.40 (24)	2.40	1.78
Child oxytocin	6.78 (27)	3.26	5.73 (20)	2.37	2.01*
Child affective disorder	(3)		(7)		$\chi^2(1) = 3.87$*
Yes %	9.09%		29.17%		17.54%

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

2.2.4. Mother-child interaction

Ten minutes of mother-child free-play with age-appropriate toys were filmed at both 9 months and 6y (Feldman, 2007). The first two-min segment with least background noise (e.g., phone calls, people talking in the background, etc.) from the 6-year visit were chosen for viewing in the MEG session of own mother-child and of matched unfamiliar mother-child. In light of research on the maternal brain which indicated that interactions marked by high levels of synchrony elicit stronger responses in the maternal brain when contrasted with interaction of a depressed mother with her infant containing minimal synchrony (Atzil et al., 2014), we chose an interaction containing high levels of affective synchrony (ranked 2.87 standard deviations from the mean) between a healthy child and a healthy mother who did not participate in the current study for the unfamiliar mother-child interaction and the same unfamiliar interaction was presented to all participants. Thus, stronger responses to own versus unfamiliar child-mother interaction is not attributed to own-other differences in level of synchrony but to differences attachment status and its key parameter, that is "own-ness" and exclusivity. Order of the two movies (own and other child-mother interaction) was randomized and a 2 s fixation point separated the movies. Movies were presented on a 17″ screen located 60 cm in front of children using e-Prime software (Psychology Software Tools, Inc.).

2.2.5. Behavioral coding

Interactions were coded twice, using global rating scales and micro-analytic coding, as each links with distinct oscillatory pattern (Levy et al., 2017; Pratt et al., 2018).

2.2.6. Micro coding

This coding enables 0.01 s precision, the closest to the temporal resolution of brain activity. Micro-coding was conducted by trained coders on computerized system (Noldus, Wageningen, the Netherlands), consistent with our previous research (Feldman and Eidelman, 2004). Two nonverbal categories were coded for parent utilizing; Affect- positive, neutral, negative, and Physical Proximity-approach, stable, withdraw. Child categories including gaze, affect, vocalizations, and proximity. Inter-rater reliability, conducted for 10% of interactions, averaged 98%. *Affect Synchrony* was calculated as conditional probability indexing total number of mother-child positive affect within approach position.

2.2.7. Global coding

Global coding was conducted for the entire 10 min at both 9 m and 6y using the *Coding Interactive Behavior* (CIB; Feldman, 2012b), reliable system rated from 1(low) to 5(high). Two coders, trained to 85% reliability, coded the interactions with inter-rater reliability computed for 20% of interactions exceeding 87% (intraclass $r = 0.91$, range = 0.87–0.99). *Mother Sensitivity* – this construct was averaged from the following scores derived from the global CIB ratings: parent acknowledging child's communications, parent expressing positive affect, parent resourcefulness in handling the child affect or in navigating the situation, parent warm and appropriate vocalizations, parent praising the child, parent affectionate touch, parent supportive presence, and parent reciprocity. Maternal sensitivity coded from interactions at 9 months and at 6 years were nterrelated ($r = 0.35$, $p < .05$)

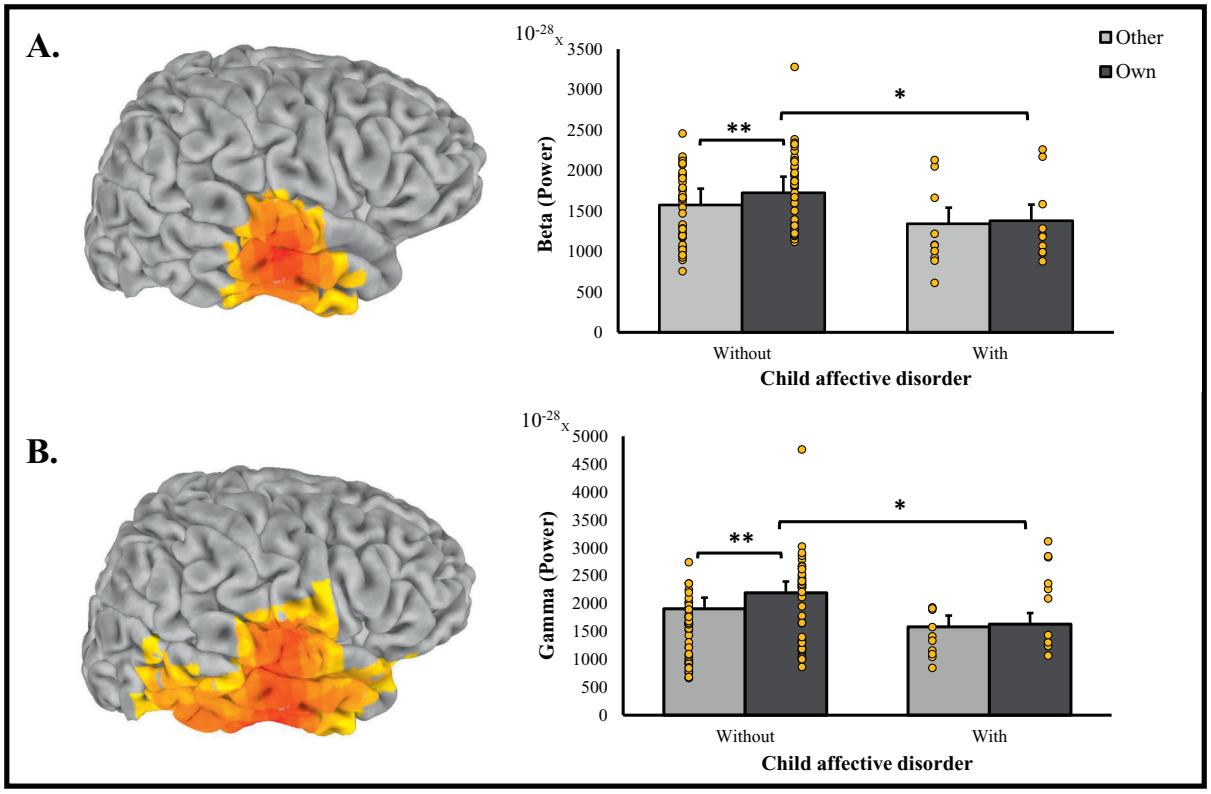

Fig. 2. Source analysis differences between oscillatory power to own versus unfamiliar mother-child interaction in children with and without psychopathology
A. Differences in beta frequency band (14–25). B. Differences in gamma frequency band (30–40).
*$p < .001$. Individual datapoints are marked with yellow circles.

and were averaged into a single *Mother Sensitivity* score.

2.3. Data acquisition and analysis

MEG was recorded with a 248-channel magnetometer array (4-D Neuroimaging) in a magnetically-shielded room with sample rate of 1017 Hz and online 1–400 Hz band-pass filter in supine position. Reference coils located short distance away from the sensor, were used to record environmental noise. Five coils were attached to the participant's scalp for recording of the head position. External noise (power-line, mechanical vibrations) and heartbeat artifacts were removed from the data as previously described (Tal and Abeles, 2013). Signal pre-processing was carried out using MATLAB and the FieldTrip toolbox (Oostenveld et al., 2011). Data were segmented into 1 s epochs with an overlap of 0.5 s (Levy et al., 2017). Segments containing muscle artifacts and power jumps were discarded by visual inspection, resulting in a total mean of 158.21 viable segments (SD = 27.86) per subject, with a mean of 150.76 segments in the "own interaction" (SD = 29.73) and 152.58 segments in the "unfamiliar interaction" (SD = 22.38) in the control group, and 161.25 segments in the "own interaction"(SD = 27.58) and 173.17 segments in the "unfamiliar interaction" (SD = 27.52) in the depressed group. No significant group, condition, or interaction effects for the number of segments emerged. The remaining segments were bandpass filtered in the 1–40 Hz range, and independent component analysis (ICA) was used to remove eye movement and blinks, and other remaining artifacts from the data.

Data were source localized with Synthetic Aperture Magnetometry (SAM) beamformer (Robinson and Vrba, 1999) with a spatial resolution of 0.5 cm in three bands; alpha (8–12), beta (14–25), and low gamma (30-40 Hz). Covariance estimates were calculated using the full dataset and were uniform for both conditions. SAM estimates were noise-normalized via division by the mean square of the active weights. A template MRI (Colin27) was modified to fit each subject's digitized head shape using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, London, UK).

2.4. Statistical analysis

Source level statistics were calculated using the Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni). To estimate whether activation in the three oscillatory bands differed according to condition (own/other) a paired *t*-test was done using AFNI's 3dttest++. To control for multiple comparisons we applied non-parametric permutation approach (Nichols and Holmes, 2002) in which the t-test was repeated 2000 times, with condition randomly assigned within subject at each permutation, calculating the maximal cluster size. The critical cluster size corresponded to the 100th maximal cluster size (5%) in the distribution and contained of 1211 voxels for alpha, 561 voxels for beta, and 881 voxels for gamma. Next, for each subject, the average for each cluster in each condition was used for computing Pearson correlations and ANOVA tests.

3. Results

3.1. Preliminary analyses

Group differences in behavioral and hormonal variables and child psychopathology appear in Table 1. As seen, *Maternal Sensitivity* and child OT were higher in the healthy group and children of depressed mothers showed significantly higher rates of affective disorders. Affective disorders included any type of anxiety disorder (e.g., separation anxiety disorder, general anxiety disorder) and depression.

3.2. The neural basis of attachment; own versus unfamiliar oscillatory activations

Source-level analyses of own versus unfamiliar mother-child interaction revealed one significant cluster for every frequency band. Exact coordinates and sizes of the significant clusters appear in Supplementary Table 2. For alpha (8-12 Hz), differences localized only to visual areas, and thus no further testing were conducted. Alpha power was lower when viewing own interaction, suggesting allocation of greater resources to attachment stimuli. Differences in beta (14-25 Hz) and gamma (30-40 Hz) power were both localized to wide cluster in the right temporal cortex, including the STS/STG, MTG, ITG, and Insula with higher activations to own interaction (see brain images on the left panel in Fig. 2A and B).

3.3. Effects of maternal depression and child psychopathology

Two-way ANOVAs were computed with beta and gamma activations to own interaction as dependent variables, and group and child affective disorder as independent variables. Beta activations showed main effect for affective disorder; $F(1,56) = 4.36$, $p < .05$, $eta^2 = 0.08$; higher beta power was observed in healthy children compared to those with affective disorders, with no maternal depression group or interaction effect (see bar graph in the right panel of Fig. 2A). Similarly, gamma activation showed main effect for child affective disorder; $F(1,56) = 5.12$,$p < .05$, $eta^2 = 0.09$, with higher gamma power among healthy children compared to those diagnosed with an affective disorders and no maternal depression group or interaction effect (see bar graph in the right panel of Fig. 2B). Consistent with our third hypothesis, children with affective disorder showed no differentiation between neural response to own versus unfamiliar interaction in beta ($t(9) = 1.11$,NS) and gamma ($t(9) = 0.70$,NS) power. However, in order to fully ascertain that these brain differences stem from the influence of maternal depression and its effect on increasing the prevalence of child affective disorder, further research must directly compare children of depressed mothers and children of healthy mothers who developed an affective disorder.

3.4. Longitudinal links with caregiving and OT across childhood

Pearson correlations between relational patterns across early childhood and children's affiliative brain at preadolescence appear in Table 2. As seen, *Maternal Sensitivity* across early childhood correlated with beta activation and *Affect Synchrony* at six years correlated with gamma activation to own interaction at preadolescence. Child OT correlated with beta activations to both own and unfamiliar interaction, indicating that levels of OT predict neural response to social cues, regardless of attachment status (Fig. 3).

Following these findings, we tested whether the association between beta activation at preadolescence and maternal sensitivity across childhood is mediated by the child's OT levels at age six. However, the mediation path failed to reach significance and A Sobel test did not show a full mediation in the model ($Z = 1.54$, $p = .12$).

Table 2
Longitudinal associations among neural oscillations, patterns of caregiving, and oxytocin across all participants.

	2	3	4	5	6	7
1. Beta activation to own	0.87***	0.27*	0.20	0.26*	0.09	0.41**
2. Beta activation to other		0.09	0.18	0.23	−0.11	0.39**
3. Gamma activation to own			0.88***	0.03	0.29*	−0.13
4. Gamma activation to other				0.02	0.18	−0.16
5. Maternal sensitivity					0.16	0.31*
6. Affect synchrony						0.14
7. Child oxytocin						

* $p < .05$.
** $p < .01$.
*** $p < .001$.

4. Discussion

While maternal depression is perhaps the most prevalent psychiatric disorder, no study to date has followed children of depressed mothers from birth and over lengthy periods to describe its impact on the neural basis of attachment in offspring of depressed mothers. Overall, our results on children's brain response to attachment cues mirror previous research on mothers' and fathers' neural response to similar attachment-related stimuli (Abraham et al., 2014; Azil et al., 2011; Feldman, 2015a; Levy et al., 2017) and point to parallels in the oscillatory bands and brain structures activated in response to own parent-child interaction in both parent and child. Similarly, the current findings are consistent with longitudinal studies on children's brain (Pratt et al., 2017, 2018; Levy et al., 2017; Zeev-Wolf et al., 2019), which showed that maternal sensitivity and parent-child synchrony experienced across the first decade of life predict various functions of the child's social brain and connectivity of the default mode network. Several overall insights emerged from our decade-long study. First, the neural basis of attachment expressed in children via beta- and gamma-band oscillations localized to temporal and insular cortices, implicating empathy and mentalizing networks in children's affiliative brain comparable to the findings observed in parents (Abraham et al., 2016; Azil et al., 2011; Swain et al., 2014). Second, the long-term effects of maternal depression on child affiliative brain were indirect, related to the increased susceptibility to affective disorders in offspring of depressed mothers and to the reduction in sensitive caregiving during early childhood. Finally, patterns of maternal care across the first years of life and child OT predicted functioning of the affiliative brain in preadolescence. Our findings echo studies in animal models which showed that maturation of neural systems that underpin the capacity to engage socially, pair-bond, and ultimately parent the next generation are shaped by variability in maternal care and the environment-dependent maturation of the OT system (Champagne and Meaney, 2001; Kundakovic and Champagne, 2015).

Own mother-child interaction activated response across a wide cluster in the right temporal cortex and insula. These regions have been shown to activate during emotion understanding (Domes et al., 2010) and social decision making (Paulus et al., 2005) and are central for the neural embodiment of others' emotions (Gallese et al., 2004). The STS plays a key role in understanding others' intentions and theory-of-mind skills (Pelphrey et al., 2004), interpreting social communications (Materna et al., 2008), or reciprocating emotional behaviors (Davidovic et al., 2016). The STS is also involved in attachment processes; it activates when mothers respond to their infants' attachment behaviors (Noriuchi et al., 2008), when fathers respond to their infant's videos (Abraham et al., 2014), or in response to attachment faces (Gobbini et al., 2004). The STS receives projections from primary auditory and visual areas (Kreifelts et al., 2009) and integrates bottom-up processes of social perception (Yang et al., 2015) and biological motion (Jastorff et al., 2012) with top-down mentalization (Dufour et al., 2013). The insula has also been implicated in social and attachment processes; empathy to others' pain through representation of one's own bodily milieu (Singer, 2006), affectionate behavior toward others (Caruana et al., 2011), and maternal attachment behaviors (Gobbini et al., 2004). The insula similarly combines higher-order socio-cognitive processes with lower-level sensory perception (Levens and Phelps, 2010; Singer, 2006), highlighting the involvement of these two integrative areas of bottom-up sensory information with top-down social representations in the neural basis of child attachment.

Children's OT predicted temporal beta response to both own and unfamiliar interaction, suggesting that OT tunes children's brain to social interactions in general but not specifically to attachment-related

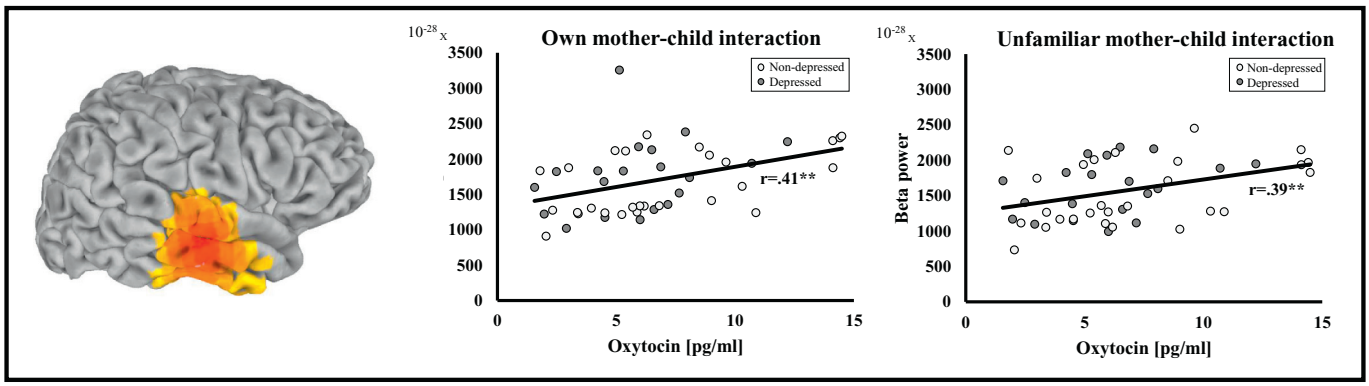

Fig. 3. Overall correlations between beta power to own and unfamiliar mother-child interaction at 11 years and child OT at age 6 years. Different colors indicate group affiliation (children to depressed vs. non-depressed mothers).
$^{**}p < .01$.

contexts. OT is implicated in social competencies, including interactions with parents (Feldman, 2012a, 2012b) and peers (Feldman et al., 2013), empathy to strangers (Apter-Levy et al., 2013), and better social judgement (Wismer Fries et al., 2005), and it has been suggested that the ancient oxytocinergic system increases the salience of social events (Feldman et al., 2016). While OT-system functionality in mammalian young is tuned by the parent-child relationship, as shown in both humans (Feldman et al., 2010b) and animals (Champagne et al., 2001), it is possible that once activated, OT increases attention to general social phenomena. The links between OT and beta are also interesting. According to the predictive coding frame, beta serves as a mechanism of gain control that is involved in the processing of post-synaptic gains through the sensitivity of neurons reporting on predictions and determining information flow toward higher-order targets (Friston et al., 2015). According to this model, OT may sensitize beta mechanisms to social interactions in general, which then undergo fine-tuning to specific attachment-relevant cues.

In contrast to OT, predictions from patterns of maternal care, both micro-analytic and global, were specific to attachment contexts. Maternal sensitivity is the main maternal orientation that supports development, shows stability from infancy to adolescence (Feldman, 2010), and predicts social, emotional, cognitive, and mental health outcomes (Braungart-Rieker et al., 2014; Kiang et al., 2004). Here we show for the first time that maternal sensitivity across early childhood is related to greater neural sensitivity to own mother-child interaction stimuli in *children,* which parallel the same findings described in parents. It has been suggested that the long-term effects of maternal sensitivity rides on its stability over time, which, through mutual influences on the child's inborn self-regulatory dispositions shape long-term outcome (Feldman, 2015b). Our findings similarly show such stability from 9 months to six years and suggest that children's affiliative brain matures in the context of maternal ongoing caregiving and that the degree of sensitive caregiving may chart a pathway for the cross-generational transfer of attachment.

Mother-child synchrony predicted gamma-band power in temporal/insular regions. Gamma is a rhythm that emerges late in development and indexes developmental maturity. Furthermore, gamma implicates bottom-up processing (Fries, 2015) that is shaped by the intensity of perceived stimuli (Hauck et al., 2015) and long-range gamma phase-synchronization supports large-scale integration of neural information (Rodriguez et al., 1999). The second-by-second synchrony of maternal and child affect may afford an environment-depended input to support the post-natal maturation of gamma oscillations (Feldman, 2015b, 2017). In a hyper-scanning study, we found brain-to-brain synchronization in attachment partners, but not in male-female strangers, which expressed in gamma-rhythm coupling localized to temporal cortex (Kinreich et al., 2017). Combined with the current findings and research on mother-child neural synchrony (Levy et al., 2017), temporal gamma may chart a mechanism specifically activated by long-term attachment relationships and distinctly sensitive to dyad-specific patterns of interaction synchrony.

While maternal depression was not directly related to children's affiliative brain, its long-term effects passed through three mechanisms: increasing susceptibility to affective disorders, reducing child OT levels, and decreasing the quality of caregiving. First, children of depressed mothers were three times more likely to develop affective disorder by preadolescence and only those at risk displayed the aberrant neural pattern. Research on risk and resilience trajectories in the context of maternal depression requires much further specification, particularly the components in child physiology or maternal care that bolster resilience. The current findings indicate that across lengthy periods, the impact of maternal depression is observed among those at risk, highlighting the shift from main to interaction effects as children grow older and their social circle widens (Priel et al., 2018). Notably, among children with affective disorders, no differences emerged between brain response to attachment and non-attachment stimuli and this may lead to difficulties in engaging, committing, or drawing reward from close relationships, but this hypothesis requires much further research. Furthermore, as offspring of depressed mothers often suffer from social withdrawal and loneliness at late adolescence and adult life (Pratt et al., 2015; Yan and Dix, 2014b), this finding may offer a novel neural mechanism for early detection. However, this hypothesis requires much further research and should be directly tested in offspring of depressed mothers across intimate relationships.

Second, maternal depression was associated with attenuated child OT response, which predicted blunted neural sensitivity to social cues, both attachment-specific and social-general. Depression has repeatedly been linked with dysfunction of the OT system (Apter-Levy et al., 2013; Yuen et al., 2014) and the current findings emphasize its relevance for the cross-generational transmission of social vulnerability, even among those not developing full-blown disorder. Finally, depressed mothers exhibited lower sensitivity and synchrony across early childhood. Through the coordination of social and physiological signals, mothers sensitize their children to social life and mother-infant synchrony predicts children's emotion-regulation, mental-health, and empathy (Feldman, 2015b, 2016). The current findings indicate that the decrease in social synchrony interferes with gamma activity in the social brain. As gamma oscillations serve as an index of brain maturation (Uhlhaas et al., 2010), such interference may carry long-term consequences for a host of affiliation-related and social functions.

Our results have several important clinical implications. Our findings clearly demonstrate the importance of early interventions for mothers that focus on promoting sensitivity and synchrony in order to prevent the long-lasting effects of maternal depression on the

developing brain. Enhancing children oxytocin levels, whether endogenously through synchrony, touch, and physical contact, or via nasal administration may be another potential avenue for intervention in the context of early and chronic maternal depression.

Several study limitations should be considered. First, our focus was the effects of maternal depression and we thus included only low-risk families and many families were excluded. Thus, findings need replication in higher-risk families. Second, because anxiety and depression often have differential effects on infant development (Feldman et al., 2009) and OT functionality (Weisman et al., 2013), we excluded cases of high anxiety; yet as comorbidity between anxiety and depression is relatively high, this charts an important next step. Third, alongside the advantages of a longitudinal study design that afforded us to draw developmental conclusion, our study could have benefited from measuring all variables at each time point. For example, measuring OT levels again at the time of the MEG scans could have allowed us to link OT levels and brain responses to attachment cues more closely and certainly, repeated brain scans could have been very informative about developmental neural processes. Finally, children's response to attachment stimuli with fathers could shed further light on the affiliative brain. Much further research is needed to prospectively follow children of depressed mothers across childhood, adolescence, and young adulthood focusing specifically on brain and neuroendocrine systems that enable such children to form close relationships and participate fully in social life.

Ethical statement

The study was conducted according to ethical guidelines, it was approved by local IRB, and all participants signed an informed consent.

Drs. Pratt, Zeev-Wolf, Goldstein, Zagoory-Sharon, and Feldman have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2019.03.005.

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