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Specifying the Neurobiological Basis of Human Attachment: Brain, Hormones, and Behavior in Synchronous and Intrusive Mothers

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The mother–infant bond provides the foundation for the infant's future mental health and adaptation and depends on the provision of species-typical maternal behaviors that are supported by neuroendocrine and motivation-affective neural systems. Animal research has demonstrated that natural variations in patterns of maternal care chart discrete profiles of maternal brain–behavior relationships that uniquely shape the infant's lifetime capacities for stress regulation and social affiliation. Such patterns of maternal care are mediated by the neuropeptide Oxytocin and by stress- and reward-related neural systems. Human studies have similarly shown that maternal synchrony—the coordination of maternal behavior with infant signals—and intrusiveness—the excessive expression of maternal behavior—describe distinct and stable maternal styles that bear long-term consequences for infant well-being. To integrate brain, hormones, and behavior in the study of maternal–infant bonding, we examined the fMRI responses of synchronous *vs* intrusive mothers to dynamic, ecologically valid infant videos and their correlations with plasma Oxytocin. In all, 23 mothers were videotaped at home interacting with their infants and plasma OT assayed. Sessions were micro-coded for synchrony and intrusiveness. Mothers were scanned while observing several own and standard infant-related vignettes. Synchronous mothers showed greater activations in the left nucleus accumbens (NAcc) and intrusive mothers exhibited higher activations in the right amygdala. Functional connectivity analysis revealed that among synchronous mothers, left NAcc and right amygdala were functionally correlated with emotion modulation, theory-of-mind, and empathy networks. Among intrusive mothers, left NAcc and right amygdala were functionally correlated with pro-action areas. Sorting points into neighborhood (SPIN) analysis demonstrated that in the synchronous group, left NAcc and right amygdala activations showed clearer organization across time, whereas among intrusive mothers, activations of these nuclei exhibited greater cross-time disorganization. Correlations between Oxytocin with left NAcc and right amygdala activations were found only in the synchronous group. Well-adapted parenting appears to be underlay by reward-related motivational mechanisms, temporal organization, and affiliation hormones, whereas anxious parenting is likely mediated by stress-related mechanisms and greater neural disorganization. Assessing the integration of motivation and social networks into unified neural activity that reflects variations in patterns of parental care may prove useful for the study of optimal *vs* high-risk parenting.

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INTRODUCTION

The mother's attachment to her infant is a complex process involving biological, behavioral, and psychological components that aim to ensure reproductive success and provide the foundation for the infant's well-being and adaptation (Bowlby, 1958; Carter *et al*, 2005). Across mammalian species, infant growth and survival depend on the provision of a unique set of maternal behaviors that appear immediately after birth and function to organize the infant's physiology and behavior (Leckman and Herman, 2002; Meaney, 2001). In humans, the maternal behavioral repertoire includes gaze at infant face, 'motherese' high-pitched vocalizations, expression of positive affect, affectionate touch, and the synchronous adaptation of these behaviors to moments of infant responsiveness (Barrett and Fleming, 2011; Feldman and Eidelman, 2007). Such human maternal behaviors parallel the licking-and-grooming and

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arched-back nursing of other mammals, which have been linked with the affiliation-related neuropeptide Oxytocin and the functioning of motivational and affective neural systems (Champagne *et al*, 2004; Lee *et al*, 2000; Oxley and Fleming, 2000; Shahrokh *et al*, 2010; Strathearn *et al*, 2009; Toscano *et al*, 2009). However, to date, little research examined the integration of brain circuits, affiliative hormones, and maternal behavior in human mothers.

The formation of the mother–infant bond draws on the timely provision of well-adapted maternal behaviors during the early post-partum period (Bowlby, 1969; Feldman *et al*, 2009; Tronick, 1989). Research in rodents indicates that naturally occurring variations in maternal behavior chart distinct patterns of mothering each associated with a specific bio-behavioral profile in mother and child. These patterns of maternal care initiate a cascade of epigenetic processes that uniquely shape gene expression, organize the Oxytocinergic system that supports bond formation in mammals, and determine the infant's lifetime capacity to handle stress (Champagne, 2008; Weaver *et al*, 2004). Studies in humans have similarly shown that optimal mothering involves the synchronous coordination between maternal behavior and the infant's social readiness (Feldman, 2007), and that the degree of interactive synchrony is associated with peripheral measures of Oxytocin in both parent and child (Feldman *et al*, 2010b, 2011). On the other hand, intrusive mothering describes a pattern of care that correlates with maternal anxiety and is expressed in excessive maternal behavior that disregards the child's communications and provides stimulation when the infant signals a need for rest (Kaitz and Maytal, 2005). The human synchronous and intrusive maternal styles, like patterns of maternal care observed in other mammals, are naturally expressed variations in the general population and represent distinct bio-behavioral profiles of parenting. Longitudinal studies have shown that the synchronous and intrusive maternal constellations are individually stable from birth to adolescence, are associated with distinct patterns of maternal and infant HPA and parasympathetic response, and are uniquely predictive of children's social–emotional outcomes across childhood and up to adult life (Feldman, 2010; Feldman *et al*, 2010c; Isabella and Belsky, 1991; Sroufe, 2005).

Maternal–infant bonding is based on the co-activation of motivational mechanisms that index stress, such as heightened vigilance and threat detection, and those associated with reward, which address the high incentive value placed on the infant (Barrett and Fleming, 2011). Such stress- and reward-related mechanisms must integrate to form the parent–infant bond in ways that balance the activity of these two components (Leckman *et al*, 2004). As human attachment develops in the context of the parent–infant relationship during the first months of life (Bowlby, 1969; Sroufe, 2005), describing the mechanisms that link brain and behavior in the formation of affiliative bonds and may reflect underlying neural variations in motivation, vigilance, and reward systems among typical mothers may be of theoretical and clinical importance for the study of healthy and at-risk parenting.

The stress and reward components of maternal attachment are supported by distinct motivational and threat-related networks. The nucleus accumbens (NAcc) and amygdala are limbic structures involved in the 'labeling' of a stimulus with an emotional valance and have shown to play a role in maternal behavior and bond formation in mammals (Cardinal *et al*, 2002). The NAcc, part of the mesolimbic dopaminergic reward circuit, imbues the infant with intuitive reinforcement and provides motivational drive to maternal behavior (Aron *et al*, 2005; Cardinal *et al*, 2002; Leckman and Herman, 2002; Lee *et al*, 2000). Lesions (Champagne *et al*, 2004) and DA manipulation studies (Li and Fleming, 2003) have demonstrated that the NAcc is critical for maternal behavior, particularly for maternal motivation to nest and retrieve pups (Champagne *et al*, 2004; Hansen, 1994; Hansen *et al*, 1991; Keer and Stern, 1999; Li and Fleming, 2003; Vernotica *et al*, 1999). The amygdala, a central node of the limbic affective system, has similarly been implicated in social affiliation and maternal attachment (Fleming and Korsmit, 1996; Lee *et al*, 2000; Oxley and Fleming, 2000). Lesions to the amygdala reduce maternal behavior (Toscano *et al*, 2009) and significant amygdala c-fos changes are observed following mother–pup interaction (Fleming and Korsmit, 1996). However, whereas the NAcc is likely to play a role in the reward-related aspects of mothering, the amygdala, which mediates fear processing and vigilance (Cardinal *et al*, 2002), may be important for the stress-related components. Both the NAcc and amygdala work in concert with several cortical areas, including the medial preoptic area, which integrates infant sensory cues and foster adequate parenting (Insel and Young, 2001; Lee *et al*, 2000; Oxley and Fleming, 2000), the anterior cingulate (ACC), and the dorso-medial prefrontal cortex (dmPFC) (MacLean *et al*, 1990; MacLean and Newman, 1988; Murphy *et al*, 1981; Slotnick, 1967; Stamm, 1955). Some of these cortical areas, particularly the ACC and dmPFC, have been implicated in empathy and 'theory of mind' skills (Assaf *et al*, 2009; Gallagher and Frith, 2003; Vollm *et al*, 2006), and may increase the mother's capacity to read and respond to her infant's signals. As such, the neural basis of mothering is supported by sub-cortical motivational limbic areas as well as by higher-level emotion modulation networks.

Consistent with research in animals, functional imaging studies have underscored the importance of the NAcc and amygdala for human parenting (Barrett and Fleming, 2011; Strathearn *et al*, 2009; Swain *et al*, 2007). Similarly, fMRI studies have demonstrated the involvement of reward dopaminergic circuits, salience areas containing Oxytocin projections (Strathearn *et al*, 2009), the hippocampus (Swain *et al*, 2007), ACC, and insula in human parenting (Bartels and Zeki, 2004; Lorberbaum *et al*, 2002; Noriuchi *et al*, 2008; Swain *et al*, 2007). Yet, to date, most fMRI studies of parenting reported activations in discrete brain areas in response to infant pictures or cries and did not explore the parents' systemic brain response to dynamic infant stimuli or examined the relations between brain activations and naturally occurring variations in maternal behavior.

In light of the above, this study sought to extend knowledge on the neurobiological basis of human parenting. We hypothesized that similar to the findings observed in other mammals (Meaney, 2001), patterns of maternal care in human mothers, specifically synchronous and intrusive maternal behavior, would chart distinct bio-behavioral profiles and would be expressed in unique

patterns of brain–behavior correlations. We videotaped mother–infant interaction and sessions were micro-coded for maternal synchrony and intrusiveness. We then assessed the brain responses in these two groups of mothers to video vignettes of their own infant to provide an individually-tailored ecological trigger to the neural processes that underlie mothering in these two groups. Plasma Oxytocin levels were sampled to examine the integration of maternal behaviors, parenting networks, and affiliation-related neuropeptides. We hypothesized that among synchronous mothers, infant cues would activate networks related to reward circuitry and those would be associated with maternal Oxytocin. Among mothers presenting intrusive behaviors, we expected that the vigilance component of mothering would be more pronounced, resulting in greater amygdala-associated activations.

MATERIALS AND METHODS

Participants

In all, 28 mothers (ages 22–37, 12–21 years of education) were recruited when their infant was 4–6 months old. Mothers were screened for high depression and anxiety symptoms using the Beck Depression Inventory (BDI) (Beck, 1978) and the State-Trait Anxiety Inventory (Spielberger and Lushene, 1970). Five mothers were excluded from the final analysis: two mothers owing to high levels of depressive symptoms (BDI scores of 12 and 14) and three owing to an incomplete imaging procedure. The study was approved by the Institutional Review Board and all participants signed an informed consent.

Procedure

The study included two sessions. In the first, families were visited at home and several sessions of mother–infant interaction and infant solitary play were videotaped. Films were used for both behavioral analysis and as fMRI stimuli. In the second session, mothers participated in brain scanning at the Tel-Aviv Sourasky Medical Center.

fMRI Paradigm

Mothers were presented with a series of infant-related video vignettes while lying in the scanner. Stimuli included a 2-min movie of their own infant during solitary play and a 2-min movie of mother–own–infant interactions (Figure 1, red frame). Control conditions included unfamiliar infants and unfamiliar mother–infant interactions, which were standard across subjects (Figure 1, green frame). Stimuli were counterbalanced and were randomly presented in five different order patterns.

fMRI Acquisition

Imaging was performed on a GE 3T Sigma Horizon echo speed scanner with a resonant gradient echoplanar imaging system. Functional images were acquired using a single-shot echo-planar T2*-weighted sequence. The following parameters were used: 128×128 matrix; field of view of 20×20 cm; 39 slices with 3 mm thickness and no gap; TR/TE 3000/35; and flip angle 90°, acquisition orientation was of the fourth ventricle plane. In addition, each functional scan was accompanied by a three-dimensional anatomical scan using T1-SPGR sequence ($1 \times 1 \times 1\,mm^3$).

fMRI Analysis

BrainVoyager QX version 2.1 (Brain Innovation, Maastricht, the Netherlands) was used to analyze the recorded fMRI data (Goebel *et al*, 2006). The first six functional volumes, before signal stabilization, were excluded from the analysis. Preprocessing included the following operations: 3D motion correction using trilinear interpolation, linear trend removal and high-pass filtering. A 4-mm full-width at half-maximum gaussian smoothing was used to overcome differences in inter-subject localization. Functional 2D data were manually aligned and co-registered with 3D anatomical data, which were normalized into Talairach space. To account for a hemodynamic response, predictors were convolved with 6-s hemodynamic response filter for all participants.

Whole Brain Analysis

Statistical maps were prepared for each subject using a general linear model (GLM), in which the various activation blocks were defined as district predictors. Following, multi-subject analysis was computed (fixed and corrected effect).

Region-of-Interest Analysis

Region-of-interest (ROI) analysis was conducted on bilateral NAcc and amygdala. ROI selection was *a priori* and theory-based. ROI's were defined functionally and anatomically as a box-shaped volume of 7 voxels diameter around the peak of activations in all subjects. This was obtained by a whole brain contrast of all conditions *vs* rest (fixed and corrected effect, $q(\mathrm{FDR}) < 0.05$). Signal values were extracted from each ROI for all conditions and submitted to a descriptive statistical analysis using the 'Statistica' software. Signal change was calculated for each condition as % of baseline. Baseline was considered as the average signal collected at all rest periods throughout the paradigm. A secondary index of 'own infant–stranger infant' was calculated by subtracting the 'stranger infant' signal change from the 'own infant' signal change to assess the ROI activity that is specific to own infant and does not address a general reaction to infants.

Functional Correlation Maps Analysis

The correlation analysis was based on each ROI's time courses (Friston *et al*, 1993; Greicius *et al*, 2003), which were functionally defined for each subject as stated above. Average 'seed' time courses were obtained for each subject by averaging the time series of all voxels in the specific ROI (left NAcc and right amygdala, which differentiated the groups in the ROI analysis). These average time courses were used as a GLM predictor to compute a voxel-by-voxel fit (analogous to linear correlation, fixed and corrected effect) along the entire paradigm (including all standard as well as individually tailored stimuli, see Figure 1). A

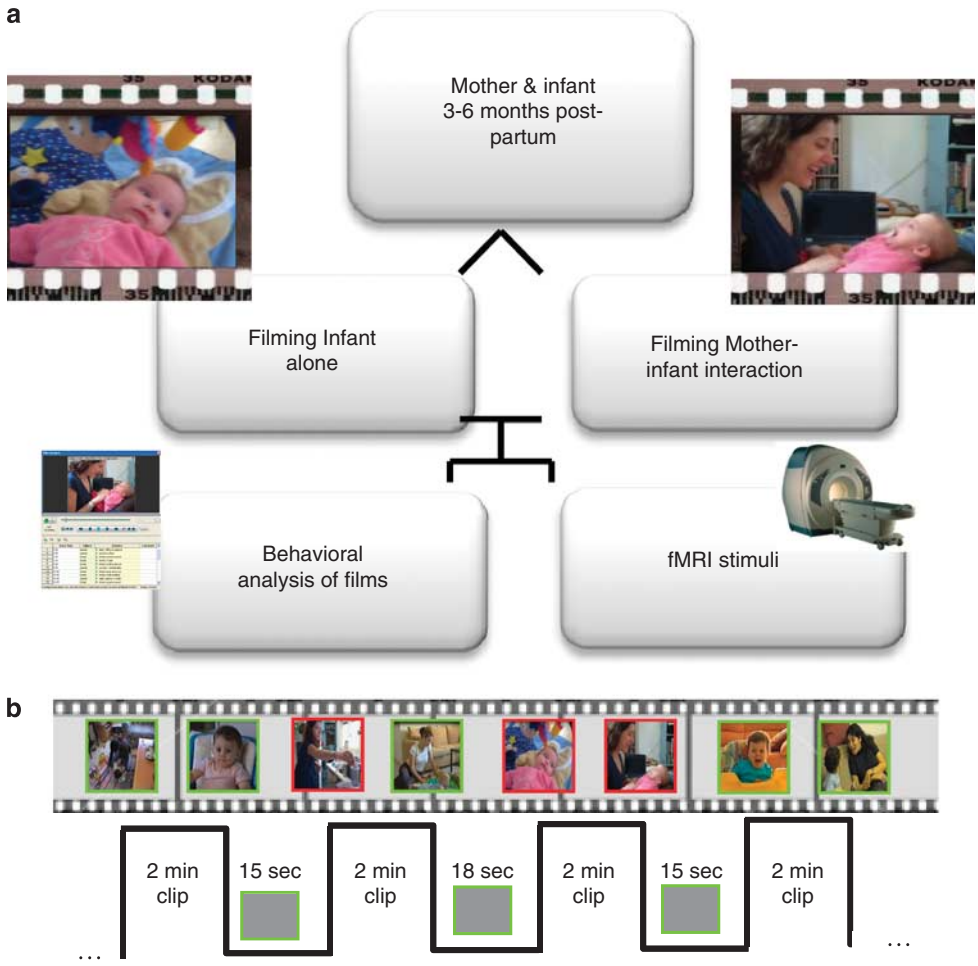

Figure 1 Header: (a) Experimental procedure. Footer: Mothers and infants were recruited 4–6 months post-partum and videotaped during a home visit. Video vignettes of mother–infant interaction were micro-coded for maternal synchrony and intrusiveness. Vignettes of interaction and of infant solitary play were used as functional magnetic resonance imaging (fMRI) stimuli. Header: (b) Experimental paradigm. Footer: Mothers were presented with infant-related vignettes of individually tailored stimuli of own infant and own mother–infant interaction (shown in red). Control stimuli of unfamiliar infants and interactions were fixed for all subjects and included stranger infants, typical mother–infant interaction, and pathological mother–infant interactions (shown in green). Each vignette was presented once and lasted 2 min. Clips were previewed by rest with fixation period of 1 min. Rest with fixation periods of 15–18 s were presented in between the films.

second-level *t*-test was applied to determine the brain areas that showed significant functional connectivity between groups (fixed and uncorrected effect).

Behavioral Coding

To define the mother's synchronous *vs* intrusive style, interactions were micro-coded by trained coders on a computerized system (Noldus, Wageningen, the Netherlands) in 0.01 s frames, consistent with previous research on parent–infant interaction (Feldman and Eidelman, 2004). Four non-verbal categories of parenting behavior were coded and each category included a set of mutually exclusive codes (an 'uncodable' code was added to each category to address moments when codes could not be determined). Categories and codes were as follows: *parent gaze*—to infant, to object or environment, gaze aversion; *parent affect*—positive, neutral, negative; *parent vocalizations*—motherese (high-pitched, sing-song vocalization), adult speech to infant, adult speech to other adult, none; and *parent touch*—affectionate touch (eg, hugging, kissing, stroking), touch of infant extremities, functional touch, proprioceptive touch (ie, changing infant position in space), object presentation, stimulatory touch, and no touch. Infant behavior was coded in a separate viewing for similar categories, including *infant gaze*—to parent, to object or environment, gaze aversion; *infant affect*—negative, neutral, positive; *infant vocalizations*—cry, fuss, neutral vocalizations, positive vocalizations (giggling or laughing), no vocalizations; and *infant exploration*—reaching to a toy, playing with one hand, playing with two hands, mouthing a toy, and no play.

Inter-rater reliability was conducted for 10% of the interactions and averaged 98% ($\kappa = 0.84$). For each behavior, we computed the proportions of time out of the entire interaction this behavior occurred. Maternal synchrony and intrusiveness were defined as conditional probabilities that address the simultaneous behaviors of mother and infant, consistent with previous research (Feldman *et al*, 2011, 2010c). Maternal synchrony was defined as mother coordinating moments of social gaze and affectionate touch with episodes of infant-positive affect,

vocalizations, or social gaze. Maternal intrusiveness was defined as mothers providing stimulatory or proprioceptive touch or presenting objects when infants showed gaze aversion and a need for rest. On the basis of our previous research, maternal intrusiveness was defined as the overall proportion of intrusive behavior observed across the interaction, a measure that has shown to correlate with maternal and infant HPA and parasympathetic responses (Feldman *et al*, 2010c). Synchrony was defined as the mean durations of synchronous episodes—moments in which mother and infant coordinate their positive social engagement—which we found to be associated with plasma and salivary OT (Feldman *et al*, 2011; Weisman *et al*, 2011). The behavioral coding resulted in two groups: synchronous mothers ($N=13$) and intrusive mothers ($N=10$).

Sorting Points into Neighborhood

Sorting points into neighborhood (SPIN) is an unsupervised method for sorting and visualizing multidimensional data (Tsafrir *et al*, 2005). The algorithm iteratively creates an optimal ordering of the objects/signal being studied, such that the distances are small along the diagonal of the pairwise distance matrix and increase as they move away from it. This ordering enables to sort distinct groups of subjects that display similar patterns over several samples (Tsafrir *et al*, 2005).

Oxytocin

Oxytocin data were available for 13 synchronous mothers and six intrusive mothers. Mothers were visited at home during the evening hours (1600–2000 hours) and blood was drawn from the antecubital vein into 9 ml chilled vacutainer tubes containing lithium heparin that were supplemented with 400 KIU of Trasylol (Bayer, Leverkusen, Germany) per 1 ml blood. Oxytocin samples were kept ice-chilled for up to 2 h before being centrifuged at 4 °C at 1000 *g* for 15 min. Supernatants were collected and stored at −80 °C until assayed. Mothers were asked to refrain from food intake 30 min before blood draw. Maternal blood was drawn at least 30 min after nursing and 30 min before nursing. Determination of OT was performed using a commercial OT enzyme-linked immunosorbent assay kit (Assay Design, Ann Arbor, Michigan) as described in earlier studies (Carter, 2007; Feldman *et al*, 2007b; Gordon *et al*, 2008; Levine *et al*, 2007). Measurements were performed in duplicate and the concentrations of samples were calculated by using MATLAB-7 (The MathWorks, Natick, Massachusetts) according to relevant standard curves. The intra- and inter-assay coefficients were less than 7% and 15.8%, respectively.

RESULTS

Behavioral Analysis

To validate our classification of the two groups of mothers, we examined the degree of synchrony and intrusiveness in each group and the findings are presented in Figure 2. As seen, among synchronous mothers, the degree of synchrony was significantly higher than that among the intrusive mothers ($F=4.89$, $p=0.038$). In parallel, among intrusive group, the amount of intrusive behavior was significantly higher than that in the synchronous group ($F=8.98$, $p=0.0069$).

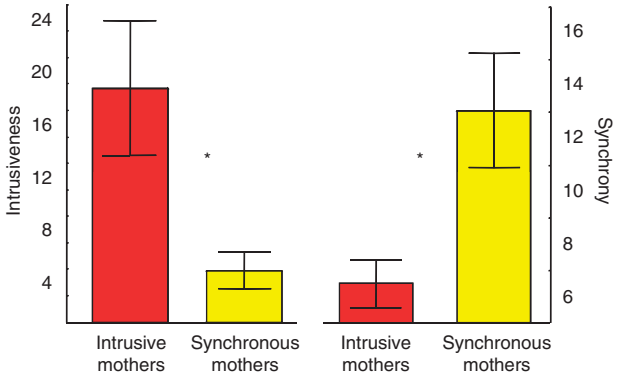

Figure 2 Header: Mean behavioral scores of synchrony and intrusiveness in synchronous and intrusive mothers. Footer: Among the synchronous mothers, the degree of synchrony was significantly higher than among the intrusive mothers ($F=4.89$, $p=0.038$). Among the intrusive mothers, the degree of intrusiveness was significantly higher than that in the synchronous group ($F=8.98$, $p=0.0069$). *$p<0.05$.

Whole Brain GLM

To explore the functional neural networks that are activated when mothers observe their own infants, a whole-brain contrast was performed between own infant vignette and a strange infant vignette. This analysis revealed several areas that are activated while mothers observed their own infant as compared to a strange infant ($p<0.03$, random and uncorrected effect, $N=23$, see Figure 3 and Table 1).

(1) Cortical attention areas oriented to perception–action, including (a) visual association areas and (b) mirror neuron system areas, including superior temporal sulcus, ventral premotor, left inferior parietal cortex, and bilateral inferior frontal gyrus (IFG).
(2) Limbic/paralimbic vigilance areas, including bilateral amygdala, right NAcc, right cingulate cortex, and left insula.

ROI analysis

Signal ANOVA analysis. A contrast index of own–other baby signal was calculated for each mother and each region (see Materials and Methods). A repeated measure 2×4 ANOVA was conducted to bilateral amygdala and NAcc according to the type of maternal care—synchronous ($N=13$) and intrusive ($N=10$) mothering. Analysis revealed a significant two-way interaction effect between ROI and maternal caregiving group ($F_{(3,\ 57)}=3.8048$, $p=0.01480$). *Post hoc* LSD test ($df=74.284$) showed that higher activations in the left NAcc was observed in the synchronous as compared to the intrusive group ($p=0.015$), and significantly higher left NAcc activations than right amygdala activations were observed among the synchronous mothers ($p=0.004939$). The right amygdala also differentiated between the groups and showed a significantly higher signal change in the intrusive mothers group ($p=0.008$) (Figure 4a).

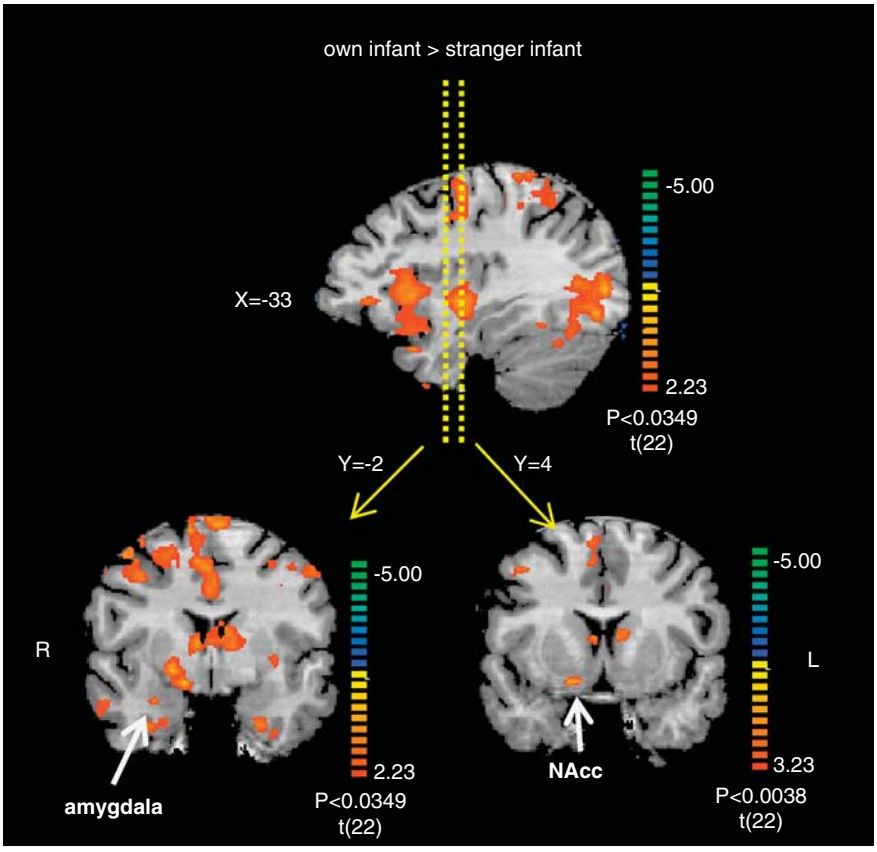

Figure 3 Header: Brain response to own infant video. Footer: Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) statistical maps for 23 mothers presented with the contrast own infant (shown in orange) > stranger infant (shown in blue), showing activation in limbic areas such as the right nucleus accumbens and amygdala, and cortical activations such as the frontal, parietal temporal, and occipital gyri and insula.

Plasma oxytocin levels and correlations of oxytocin with left NAcc and right amygdala. No mean-level differences in Oxytocin levels were found between the synchronous and intrusive groups ($F_{(Pearson,1,18)} = 0.0381$, $p = 0.8474$). However, when considering the correlation between the activation of ROI and Oxytocin, a between-group categorized correlation was found. In the synchronous group, plasma Oxytocin levels were significantly correlated with the left NAcc β-values ($r = 0.7673$, $p = 0.0014$) (Figure 4b). In the intrusive group, on the other hand, there was a negative nonsignificant trend ($r = -0.3877$, $p = 0.4475$). These results should be interpreted with caution owing to the small number of intrusive mothers with Oxytocin data. In addition, among the synchronous group, plasma Oxytocin levels showed a significant positive correlation with right amygdala β-values ($r = 0.6490$, $p = 0.012$) (Figure 4c). Among the intrusive mothers, there was a positive nonsignificant trend of correlation ($r = 0.5863$, $p = 0.2213$), and this may again relate to the low number of intrusive mothers with Oxytocin data. However, no significant correlations were found between the ROI activation and Oxytocin levels when the entire sample was considered (left NAcc: $r = -0.0160$, $p = 0.9331$; right amygdala: $r = 0.2785$, $p = 0.1361$) and correlations emerged only when the synchronous group was examined separately, suggesting that the origin of the correlations lies in the synchronous group.

Correlations between plasma oxytocin levels and maternal behavior. Finally, for a full model of the interrelationship between brain, hormones, and behavior, we examined the correlations between Oxytocin and maternal behavior. Oxytocin correlated with mother–infant synchrony, $r = 0.6107$, $p = 0.0204$, indicating that higher levels of synchrony are associated with higher maternal baseline Oxytocin.

SPIN. This expression matrix is sorted according to correlation in the activity along the corresponding conditions between subjects, with blue denoting low activity and red indicating high activity. This type of data presentation visualizes the activation pattern of the brain regions of interest throughout the time course of the entire paradigm, thus providing additional information beyond the simple analysis of activation/deactivation to a certain condition. As can be seen in the matrix, some mothers show an organized activations pattern, whereas others display disorganized activations. Interestingly, we found that most of the synchronous mothers (10 out of 13) were grouped together and displayed organized left NAcc and right amygdala activity patterns. On the other hand, the majority of intrusive mothers (eight out of nine) displayed a nonorganized pattern of activations of the same limbic nuclei. It is of interest to note that the brain's pattern of organization is more predictive of the mother's caregiving behavior than

Table 1 Brain Regions Showing Significant Activations in the Contrast: Own Infant > Unfamiliar Infant

	x	*y*	*z*	BA	*t* score	*p* score
Confidence threshold min = 3.23						
Right inferior parietal lobule	59	−38	27	40	3.97555	0.00064
Right inferior temporal gyrus	41	−68	−3		5.07622	0.000044
Right precentral gyrus	38	−11	60	6	4.47142	0.000191
Right claustrum	29	19	9		5.15995	0.000036
Right precuneus	23	−56	54	7	4.62824	0.00013
Right precuneus	5	−77	51	7	5.65198	0.000011
Right caudate head	14	16	3		4.39934	0.000227
Right nucleus accumbens	14	−2	−9		4.40801	0.000223
Right medial frontal gyrus	2	−20	48	6	4.92285	0.000064
Right superior frontal gyrus	5	10	57	6	3.85059	0.000868
Right cingulate gyrus	5	19	30	32	4.53295	0.000164
Left medial frontal gyrus	−4	40	33	9	4.26043	0.000319
Left postcentral gyrus	−1	−53	69	7	4.1617	0.000407
Left caudate body	−10	4	15		3.95063	0.00068
Left inferior occipital gyrus	−40	−71	−3	19	5.03215	0.000049
Left ventro-lateral thalamus	−19	−14	18		4.36408	0.000248
Left insula	−37	13	3		4.21708	0.000355
Left supramarginal gyrus	−52	−50	27	40	4.53688	0.000163
Left inferior parietal lobule	−64	−38	27	40	5.41971	0.000019
Confidence threshold min = 2.23						
Left amygdala	−10	−5	−12	34	3.04573	0.00593
Right amygdala	29	1	−18	34	3.49067	0.00207

x, *y* and *z* represent talairach coordinates. $N = 23$, random effect, uncorrected, cluster size > 6, confidence threshold min = 3.2.

the direction of activations to a certain condition. It is possible that intrinsic brain organization may lead to the development of synchronous maternal behavior, whereas disorganized limbic activation may result in intrusive mothering (Figure 4d and e).

Whole brain contrasts of functional connectivity maps. Results of the functional connectivity analysis described two distinct brain networks according to patterns of maternal care—synchrony and intrusiveness. Seed regions were chosen on the basis of the previously described ROI analysis, which demonstrated that the left NAcc and the right amygdala differentiated between the two groups. Following, we computed whole brain functional connectivity maps using these two seed regions to statistically assess the brain areas that correlate with the activity of the left NAcc and right amygdala across the paradigm.

Seed region left NAcc: contrast map of synchronous mothers > intrusive mothers. When comparing the two groups (random effect, *t*-test, $p < 0.016$, uncorrected), it was found that the intrusive mothers group displayed higher correlations in occipital, lateral–frontal, temporal and cerebellar cortices, whereas the synchronous mothers group showed higher cortical correlation in mPFC: BA10 (Figure 5a and Table 2).

Seed region right amygdala: contrast map of synchronous group > intrusive group. Functional connectivity maps with right amygdala as seed region revealed a different pattern. Intrusive mothers, significantly more than synchronous mothers (random effect, *t*-test, $p < 0.047$, uncorrected), displayed higher cortical correlation in mPFC (BA11), cingulate gyrus, superior temporal gyrus (STG), and cerebellum (Figure 5b and Table 3). On the other hand, the synchronous group showed higher amygdala correlations in temporal, occipital, insular, lateral–frontal, and cerebellar cortices.

Focusing on the limbic–mPFC connectivity axis of emotional regulation, it appears that the medial–prefrontal areas are activated in concordance with the left NAcc only among the synchronous group. On the other hand, in the intrusive group, the limbic–mPFC connectivity analysis shows a more extensive functional association with the right amygdala. In addition, several lateral cortex areas were found as differentially associated with the right amygdala. In the synchronous group, we found activation of mirror neuron system (MNS) areas, including insula and STG, which did not appear in the intrusive group (Figure 5b and Table 3).

Finally, we examined whether the synchronous and intrusive patterns of maternal care indeed represent discrete profiles of maternal brain–behavior correlations or whether synchrony and intrusiveness are two poles of the same continuum. For this end, we computed correlations between the degree of synchrony and the degree of intrusiveness in the entire group with left NAcc and right amygdale activations. No significant correlations were found for either structure. Examination of the pattern of correlations showed that the nonsignificant effects were due to opposite patterns of correlations in each group, which led to a nonsignificant overall effect.

DISCUSSION

Results of this study are the first, to our knowledge, to chart the coordinated functioning of neural networks, affiliation hormones, and micro-level maternal behavior in an attempt to further specify the neurobiological basis of mothering. Consistent with methodology developed in animal research and research showing that patterns of maternal care in mammals chart distinct bio-behavioral profiles in mothers, we examined two naturally occurring patterns of human maternal care—synchronous and intrusive mothering—and assessed their brain and neurohormonal correlates. The study is also among the first to assess maternal brain response to ongoing, dynamic, and ecologically valid infant stimuli and describe the neural networks associated with the synchronous and intrusive maternal styles on the basis of functional connectivity analysis. Similar to the analysis of the mother's brain response to an ongoing infant stimulus, our behavioral measures were defined on a temporal continuum and addressed the ongoing coordination between maternal behavior and infant social signals. The findings, therefore, may provide new insights into the interface between the maternal brain response and the moment-by-moment expression of maternal behavior in the formation of maternal–infant bonding in humans.

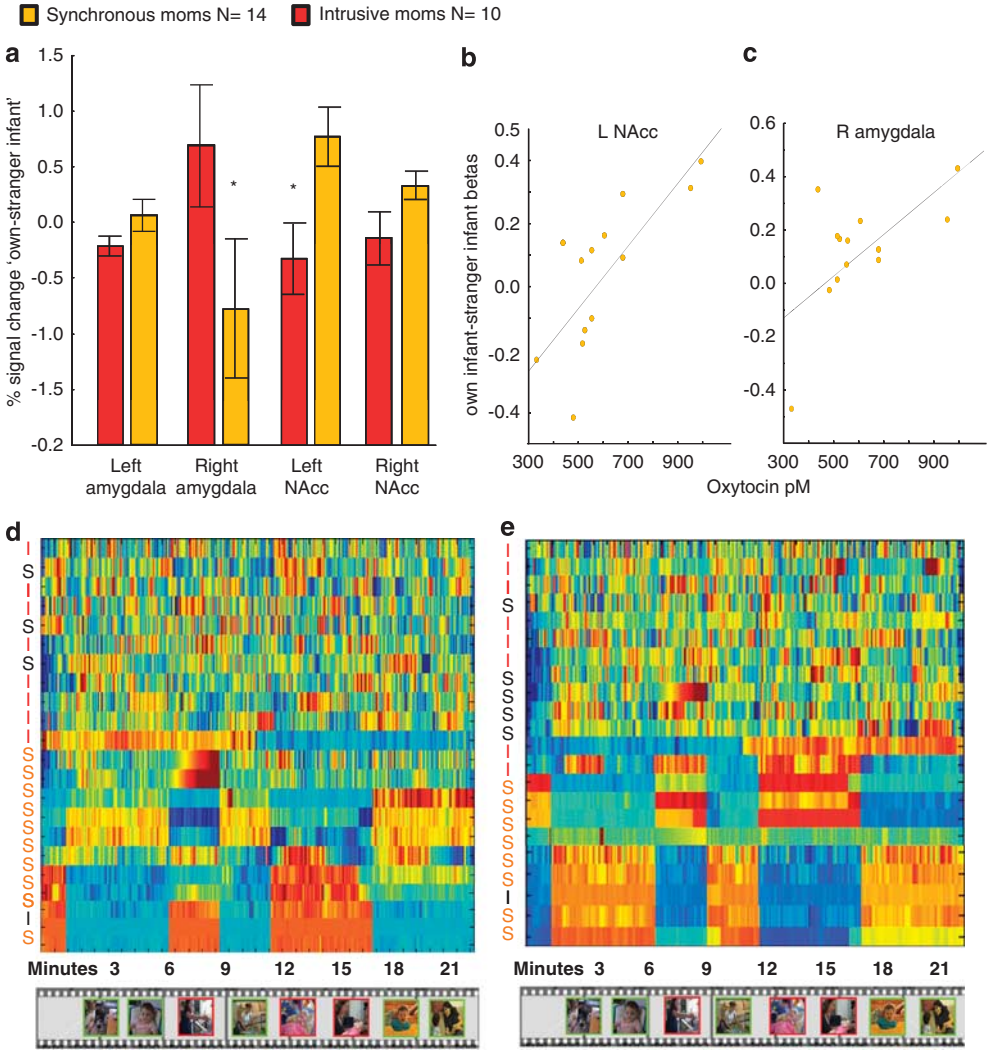

Figure 4 Header: Region-of-Interest (ROI) signal analysis from nucleus accumbens (NAcc) and amygdala in synchronous and intrusive mothers. Footer: (a) Signal change was calculated as % from baseline, and then subtractions of stranger baby from own baby was preformed. A repeated measure 2 × 4 general linear model (GLM) revealed significant interaction effect ($F_{(3, 57)} = 3.8048$, $p = 0.01480$). *Post hoc* least significant difference (LSD) test mark the signal of left NAcc in synchronous moms as significantly higher than intrusive moms ($p = 0.015275$), and also higher than the right amygdala of the same group ($p = 0.004939$). Right amygdala's signal of intrusive moms were significantly higher than right amygdala's signal of synchronous moms ($p = 0.008181$), which are higher than the left NA in the same group (trend, $p = 0.078460$). (b) Correlation between Oxytocin plasma levels and left NAcc β weights in the contrast own infant > stranger infant are evident only in synchronous moms ($N = 14$, $r = 0.7673$, $p = 0.0014$) and intrusive moms ($N = 6$, $r = -0.3877$, $p = 0.4475$). (c) Correlation between Oxytocin plasma levels and right amygdala β weights in the contrast own infant > stranger infant are evident only in synchronous moms ($r = 0.6490$, $p = 0.012$) and intrusive moms ($r = 0.5863$, $p = 0.2213$), not shown. (d) Sorting points into neighborhood (SPIN) analysis. Synchrony clustering according to the activation time course of the left NAcc. (e) SPIN analysis. Synchrony clustering according to the activation time course of the right amygdala. Mothers were presented with infant-related vignettes of individually tailored stimuli of own infant and own mother–infant interaction (shown in red). Control stimuli of unfamiliar infants and interactions were fixed for all subjects and included stranger infants, typical mother–infant interaction, and pathological mother–infant interactions (shown in green). An intrusive mother in the intrusive cluster is marked with red 'I'. A synchronous mother in the synchrony cluster is marked with orange 'S'. Mothers who appear outside of their cluster are marked with a black initial. *$p < 0.05$.

Overall, the results chart three functional neural networks that are activated in response to infant stimuli and may, in combination, describe the brain basis of human mothering. The first refers to a limbic motivational network that includes the NAcc and amygdala (Assaf *et al*, 2009). The second is an attention network (Pessoa *et al*, 2002) oriented at perception–action integration (Dayan *et al*, 2007), which includes the IFG, medial frontal gyrus, associative visual areas, insula, pre-supplementary motor area and parietal cortices that are thought to compose the mirror–neuron network (Iacoboni and Dapretto, 2006; Keysers and Fadiga, 2008). The third network includes the mPFC emotional modulation areas (Bryant *et al*, 2008; Gilboa *et al*, 2004; Liddell *et al*, 2005; Zaretsky *et al*, 2010), which we found to be functionally correlated with the limbic activation of the left NAcc in the synchronous mothers and the right amygdala in the intrusive group. The discrete activations of these structures have been previously associated with maternal response to own infant stimuli (Bartels and Zeki, 2004; Leckman *et al*, 2004; Lorberbaum *et al*, 2002; Swain *et al*, 2007). Here, we describe the coordinated functioning of these three neural networks into a unified time-locked brain activity and suggest that this integration is related to the mother's social behavior. The finding that a unique

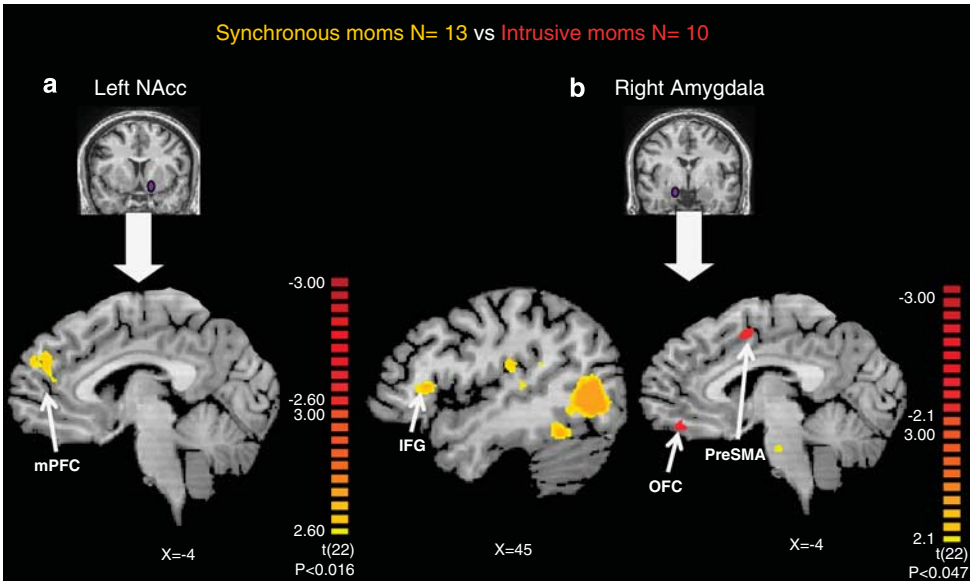

Figure 5 Header: Inter-regional functional connectivity analysis from left nucleus accumbens (NAcc) and right amygdala in synchronous ($N = 13$) and intrusive mothers ($N = 10$), random effect. Footer: (a) A whole brain *t*-test between groups with left NAcc as seed region show significantly higher functional correlation with paracingulate medial prefrontal cortex (PFC) among synchronous moms than among intrusive moms. (b) A whole brain *t*-test between groups with right amygdala as seed region showing significantly higher functional correlation in orbito-frontal cortex (OFC) and pre-supplementary motor area (pre-SMA) among intrusive moms than synchronous moms. Synchronous moms display amygdala correlation to inferior frontal gyrus (IFG), superior temporal gyrus (STG), and insula.

Table 2 Brain Regions Showing Significant Correlations to Left NAcc as Seed Region

	x	*y*	*z*	BA	*t* score	*p* score
Intrusive > synchronous						
Left inferior occipital gyrus	−31	−98	−12	18	−4.342	0.00029
Right middle occipital gyrus	50	−81	6	19	−4.3216	0.0003
Right fusiform	21	−53	−8	19	−4.0954	0.00052
Left cerebellum	−25	−80	−36		−3.8422	0.00095
Left uncus	−25	−5	−39	20	−3.707	0.00131
Right cerebellum	11	−80	−39		−3.6861	0.00137
Left cerebellum	−4	−74	−36		−3.614	0.00163
Right middle frontal gyrus	14	25	39	8	−3.5255	0.00201
Right middle frontal gyrus	26	55	−6	10	−3.4311	0.00251
Left middle occipital gyrus	−28	−95	3	18	−3.0772	0.00572
Synchronous > intrusive						
Right insula	38	1	9	13	2.98469	0.00707
Left caudate head	−10	16	−6		3.00433	0.00676
Left uncus	−16	4	−24	28	3.41192	0.00262
Left temporal pole	−40	23	−30	38	3.49369	0.00216
Left inferior frontal gyrus	−49	31	9	46	3.51655	0.00205
Left medial frontal gyrus	−1	46	27	9	4.1208	0.00049
Right subcallosal gyrus	8	22	−12	25	4.38748	0.00026

x, *y* and *z* represent talairach coordinates. $N = 23$, random effect, uncorrected, cluster size > 6, confidence threshold min = 2.2.

integrative profile of the three neural systems emerged for mothers showing synchronous *vs* intrusive styles of maternal care may suggest that addressing the coordination between various emotional and social brain systems can prove useful in the study of normative *vs* high-risk parenting.

The synchronous maternal style was characterized by four features. At the motivational level, the left NAcc in this group showed greater activations as compared to the right amygdala during the observation of own infant cues. This may suggest that the motivational mechanisms underlying synchronous maternal care are based on the reward components of parenting to a greater extent than on the stress elements. Second, at the connectivity level, the left NAcc in the synchronous group was functionally correlated with the left dmPFC and the right subcallosal ACC. In the context of rodent maternal behavior, these structures were found to control the motivational element of maternal behavior rather than the behavior *per se* (Lorberbaum *et al*, 2002; Slotnick, 1967; Stamm, 1955), whereas human research has implicated these structures in cognitive empathy and 'Theory of Mind' skills (Assaf *et al*, 2009; Gallagher and Frith, 2003; Vollm *et al*, 2006). In addition, in the synchronous maternal care group, functional connectivity was found between the right amygdala and regions included in the so-called MNS, including the STG, insula, and IFG. Such mirror system activations may reflect the mother's ability to better understand the intentions and desires of her infant and to respond with a synchronized conduct. Thirdly, the hormonal analysis revealed that among the synchronous group, plasma Oxytocin levels were correlated with the activation of the left NAcc and the right amygdala. Oxytocin is known to mediate social affiliation in mammals (Insel *et al*, 1997), and thus the connection between Oxytocin and activations of these parenting-related motivational limbic areas may suggest that parenting for these mothers is more closely linked with subcortical motivational mechanisms. Finally, the SPIN analysis indicated that among the synchronous group, the

Table 3 Brain Regions Showing Significant Correlations to Right Amygdala as Seed Region

	x	*y*	*z*	BA	*t* score	*p* score
Intrusive > synchronous						
Left medial frontal gyrus	−4	43	−15	11	−4.1068	0.0005
Left OFC	−13	46	−18	12	−3.943	0.0007
Left supramarginal gyrus	−58	−56	36	40	−3.2628	0.0037
Left superior temporal gyrus	−19	20	−33	38	−3.142	0.0049
Right cerebellum	50	−62	−36		−3.0831	0.0056
Left cyngulate gyrus	−4	4	45	24	−2.8673	0.0092
Right middle frontal gyrus	26	28	33	9	−2.8646	0.0093
Synchronous > intrusive						
Right insula	41	−41	21	28	2.75317	0.0119
Right cuneus V2	23	−86	27	18	3.03171	0.0063
Right inferior frontal gyrus	47	22	9	45	3.05545	0.006
Right cerebellum	44	−50	−18		3.07224	0.0058
Left superior temporal gyrus	−64	−50	15	22	3.11481	0.0052
Left uncus	−16	−17	−31	28	3.22338	0.0041
Right lingual gyrus	11	−95	−3	17	3.35723	0.003
Right postcentral gyrus	50	−26	21	40	3.42512	0.0025
Left uncus	−16	−8	−30	36	3.51478	0.0021
Left superior temporal gyrus	−34	10	−39	38	3.58812	0.0017
Right uncus	17	1	−27	28	3.65478	0.0015
Left fusiform gyrus	−43	−23	−15	20	4.80621	1E-04
Right middle occipital gyrus	47	−71	3	37	5.77649	1E-05

x, *y* and *z* represent talairach coordinates. $N = 23$, random effect, uncorrected, cluster size > 6, confidence threshold min = 2.2.

time course of the left NAcc and right amygdala activations showed a relatively organized pattern across the paradigm, whereas the intrusive group displayed less organized activity of these nuclei. This study is the first to apply SPIN analysis in fMRI research of human attachment, and may thus open new directions for future research. Such analysis focuses on the organization of ROI activity across time, rather than on the direction of effects and underscores the importance of signal organization in the description of maternal care profiles.

In contrast to the synchronous group, the intrusive group was characterized by a different set of features. Among these mothers, right amygdala activations were significantly greater than left NAcc activations, suggesting that the motivational components of fear and anxiety may be more pronounced than those associated with reward and affiliation. In addition, the organizing activity of the dmPFC was missing in this group and wide activations of pro-action areas were observed, including the right premotor cortex and the left OFC. This pattern may point to insufficient behavioral inhibition, which may lead to the excessive, non-modulated maternal behavior typical of the intrusive style. Another feature that reflected intrusive mothering was the lower organization of the left NAcc and right amygdala across time. SPIN analysis revealed that the activity of these motivational nuclei showed lower levels of intrinsic organization in this group and this corresponded with their lower behavioral synchronization. Taken together, the findings chart distinct profiles of limbic and cortical activity and their time-locked integration that differentiated mothers whose caregiving style was characterized by affect synchrony from those whose behaviors were marked by overstimulation, excessive parenting, and miscoordination.

The correlations between the left NAcc and right amygdala activity with plasma Oxytocin in the synchronous group are interesting in light of recent findings on the role of Oxytocin in social affiliation. Oxytocin has been consistently implicated in the onset of maternal behavior in mammals and with more adaptive maternal care in humans (Feldman *et al*, 2010a; Gordon *et al*, 2010a, b; Levine *et al*, 2007; Pedersen *et al*, 1994). Oxytocin has also been linked with social approach behavior (Kosfeld *et al*, 2005) and empathy (Domes *et al*, 2007; Hurlemann *et al*, 2010). Recently, the infusion of Oxytocin directly into rat mothers' ventral tegmental area was found to enhance dopamine signals in the NAcc shell and to increase maternal behavior (Shahrokh *et al*, 2010). The involvement of NAcc dopamine in social reward, including maternal attachment, may be linked with Oxytocin projections. It is possible that social reward relies on different mechanisms than those implicated in other types of reward (eg, food) and that social reward depends to a greater extent on the functioning of the Oxytocinergic system (Strathearn *et al*, 2009). Although the precise nature of such Oxytocin–dopamine interactions in the support of maternal behavior is not fully understood, their combined activity may be central to the formation of affiliative bonds (Douglas, 2010; Strathearn *et al*, 2009). Future endocrine, imaging, and animal studies are required to explore the relations between the Oxytocin and NAcc dopaminergic systems within a model that addresses their combined contribution to human attachment.

Results of this study may provide further insights on the adaptive roles of both the reward and stress components of parenting. The fact that the infant is a powerful reinforcement to its mother (Barrett and Fleming, 2011) serves an important evolutionary role and may be mediated by the NAcc (Champagne *et al*, 2004; Hansen, 1994; Hansen *et al*, 1991; Keer and Stern, 1999; Li and Fleming, 2003; Vernotica *et al*, 1999). However, a certain amount of heightened arousal and vigilance is also required for infant care, which involves some anxious conduct (Barrett and Fleming, 2011; Leckman and Herman, 2002; Leckman and Mayes, 1999; Leckman *et al*, 1999). The amygdala, which processes negative emotions, may participate in directing attention toward the infant and charging the incentive value placed on the infant with acuteness and highly aroused energy. Such finely tuned co-activations of structures within the limbic system are central for the formation of the maternal–infant bond. However, this delicate balance is also highly sensitive to early disruptions and slight deviations from normative functioning may result in non-optimal patterns of maternal care that may bear negative consequences for the infant's future mental health. Indeed, recent studies have shown that up to 29% of mothers and infants suffer from some sort of disruptions to early bonding, due to marked increases in cases of maternal post-partum depression and anxiety, as well as in premature birth (ACOG, 2006; Andersson *et al*, 2006; Silverman *et al*, 2007; Vesga-Lopez *et al*, 2008). Such conditions pose a risk for the infant's adaptation and well-being and may lead to a variety of

epigenetic, behavioral, and mental processes that would compromise the infant's future well-being, health, and adaptation.

The findings demonstrate that the motivational components of stress and affiliation are evident not only at the limbic level, but also at the cortical and mental levels. Synchronous mothers showed higher activations of mirror-neuron and empathy-related cortical systems, which may point to more adaptive theory-of-mind skills and more adequate representations of the infant's needs. Conversely, intrusive mothers consistently activated pro-action areas, which may explain the non-matched excessive maternal behavior and the lack of sufficient mentalizing of the infant's state. These results support the notion that in addition to conserved biological and behavioral aspects, human parenting includes higher-order mental components that involve the capacity to reflect on infant state, differentiate infant signals on the basis of past experience, and plan a course of caregiving actions. Such perception–action systems include primary and associative cortices of different modalities, premotor areas, and mirror neuron areas such as insula, STG, IFG, and parietal cortex that have been associated with empathy (Adolphs *et al*, 2000; Rizzolatti, 2005), theory-of-mind abilities (Gallagher and Frith, 2003), and maternal response to infant cries (Swain *et al*, 2007).

The findings that maternal synchrony and intrusiveness chart two unique profiles of brain–behavior correlations and that these associations did not emerge for the entire group is consistent with the findings for other mammals showing that distinct patterns of maternal care are underpinned by specific biological processes (Meaney, 2001). Future research may extend research from patterns of maternal care observed in the normative population to profiles of brain–behavior correlations in clinical populations. Similarly, future research may integrate other physiological systems with constellations of observed parenting, including the immune system and epigenetic processes.

Two reasons guided our choice to sample plasma Oxytocin at the home and not in the hospital context, where the fMRI data was collected. First, most current knowledge on maternal plasma Oxytocin is based on samples collected in the home and it was important to compare our Oxytocin levels with previously published data. Second, we wished to avoid the potential anxiety-provoking effects of a blood draw on the mother's brain response (if sampled before imaging) or the effects of exposure to infant cues on Oxytocin levels (if sampled after imaging). Plasma Oxytocin levels were found to be highly stable within individuals in several independent samples (Gordon *et al*, 2010a, b; Levine *et al*, 2007) and to be unrelated to demographic conditions, such as parent gender, age, height, weight, body mass index, smoking, use of medications, and time since last meal. Similarly, when not sampled immediately before or after breastfeeding, maternal OT levels are unrelated to menstrual cycle phase, contraceptive intake, mode of delivery (vaginal *vs* c-section), feeding style (breastfeeding *vs* bottle-feeding), post-partum interval (weeks from birth to date of assessment), or the interval from prior breastfeeding (Feldman *et al*, 2010b). Thus, our plasma Oxytocin levels likely reflect baseline levels that are not affected by the situational distress of the fMRI procedure.

Limitations of the study include the small number of intrusive mothers with Oxytocin data and future research with larger samples are required to better describe the hormonal profile of this group and its brain correlates. The father's data would have been important to shed light on the paternal brain and its relation to patterns of paternal care. Attachment patterns in infants were also not tested and this is clearly a study limitation. Assessing infant attachment would have pointed to the relations between bio-behavioral profiles of maternal care and infant attachment security *vs* insecurity. In general, it is important to emphasize that our use of the term 'attachment' was general and does not imply that infant attachment was studied. Such use is consistent with Bowlby's (1958, 1969) description of the mother's attachment to her infant and its biological and behavioral concomitants. Furthermore, as brain, hormonal, and behavioral data were collected concurrently, it is not possible to infer causality, only relationships between variables. Follow-up data would have been important to examine whether maternal brain activations in the post-partum can predict infants' later social–emotional development and assessment of maternal Oxytocin during pregnancy could have shown predictions from hormonal levels to brain activations. Much further research is required to integrate imaging, hormonal analysis, and careful assessments of social behavior with genetic and epigenetic markers to help describe integrative profiles that may later assist in the diagnosis of specific high-risk conditions.

The use of functional magnetic resonance imaging combined with micro-level behavioral analysis and bonding-related hormones may enhance our understanding of typical and high-risk parenting. Our results show that *a priori* categorization of patterns of maternal care that are expressed in the general population can reliably chart different neural networks. Future research is required to apply integrative assessments to various clinical populations that involve risk to the mother–infant bond due to post-partum depression, premature birth, or social adversity. Understanding the motivational basis of healthy and at-risk parenting may open new theoretical vistas and clinical opportunities and may lead to the construction of more specific interventions that can target disruptions to maternal–infant bonding at an earlier stage and in a more accurate manner.

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DISCLOSURE

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)