Dopamine in the medial amygdala network mediates human bonding

Shir Atzil\textsuperscript{a}, Alexandra Touroutoglou\textsuperscript{a}, Tali Rudy\textsuperscript{a,b}, Stephanie Salcedo\textsuperscript{a}, Ruth Feldman\textsuperscript{c,d}, Jacob M. Hooker\textsuperscript{a}, Bradford C. Dickerson\textsuperscript{a,e}, Ciprian Catana\textsuperscript{a,b,1,2}, and Lisa Feldman Barrett\textsuperscript{a,b,1,2}

\textsuperscript{a}Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129; \textsuperscript{b}Department of Psychology, Northeastern University, Boston, MA 02115; \textsuperscript{c}Yale Child Study Center, New Haven, CT 06520; \textsuperscript{d}Gonda Brain Research, Bar Ilan University, Ramat Gan 5290002, Israel; and \textsuperscript{e}Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114

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Research in humans and nonhuman animals indicates that social affiliation, and particularly maternal bonding, depends on reward circuitry. Although numerous mechanistic studies in rodents demonstrated that maternal bonding depends on striatal dopamine transmission, the neurochemistry supporting maternal behavior in humans has not been described so far. In this study, we tested the role of basal dopamine in human bonding. We applied a combined functional MRI-PET scanner to simultaneously probe mothers’ dopamine responses to their infants and the connectivity between the nucleus accumbens (NAcc), the amygdala, and the medial prefrontal cortex (mPFC), which form an intrinsic network (referred to as the “medial amygdala network”) that supports social functioning. We also measured the mothers’ behavioral synchrony with their infants and plasma oxytocin. The results of this study suggest that synchronous maternal behavior is associated with increased dopamine responses to the mother’s infant and stronger intrinsic connectivity within the medial amygdala network. Moreover, stronger network connectivity is associated with increased dopamine responses within the network and decreased plasma oxytocin. Together, these data indicate that dopamine is involved in human bonding. Compared with other mammals, humans have an unusually complex social life. The complexity of human bonding cannot be fully captured in nonhuman animal models, particularly in pathological bonding, such as in autistic spectrum disorder or postpartum depression. Thus, investigations of the neurochemistry of social bonding in humans, for which this study provides initial evidence, are warranted.

Significance

Early social bonding with a primary caregiver is necessary for mental and physical health, whereas the absence of such bonding is a clear risk factor for adult illness (1). However, despite potentially enormous implications, to date the science of mother–infant bonding relies mostly on nonhuman animal models.

Research on nonhuman animals indicates that maternal bonding involves the nucleus accumbens (NAcc), amygdala, and medial prefrontal cortex (mPFC). In rodents, oxytocin and dopamine act in the amygdala and NAcc to regulate maternal appetitive behaviors. In humans, functional MRI (fMRI) studies have verified that NAcc activity increases consistently when mothers gaze at their infants (3). Moreover, the NAcc and amygdala activity have been linked to the quality of maternal behavior (4). Mothers who were sensitive to their infants’ cues for social engagement and who adjusted their own behavior to meet those needs (referred to as “mother–infant synchrony”), showed greater activations in the left NAcc and lower activation in the right amygdala when viewing films of their infants than did nonsynchronous mothers (4). In agreement with the animal studies, oxytocin has been implicated in human maternal behavior, so that synchronous mothers show a stronger link between levels of circulating plasma oxytocin and NAcc fMRI activations when viewing films of their infants (4). Moreover, oxytocin administration increased activations of the ventral tegmental area, which sends dopaminergic projections to the NAcc as part of the mesolimbic system, in response to infant stimuli (5). In this study, we extend our knowledge of the neural basis of bonding by demonstrating that dopamine is associated with human bonding. Bonding behavior was assessed in this study using indices of mother–infant synchrony. We also examined dopamine responses and intrinsic connectivity of the striatum with the broader medial amygdala network (Fig. 1) that connects the NAcc to the medial amygdala, rostral hypothalamus, ventromedial prefrontal cortex (vmPFC), subgenual anterior cingulate cortex (sgACC), and posterior cingulate cortex (PCC). This network’s hubs were consistently linked to human maternal bonding (for review, see ref. 3; also see refs. 4 and 6). Moreover, atypical maternal behavior, as seen in patients with postpartum depression (PPD), is associated with attenuated maternal responses in the striatum (7), rapid striatal attenuation to reward (8), and disrupted connectivity between the right amygdala and the PCC (9). We examined the connectivity within the medial amygdala network using blood oxygenation level-dependent (BOLD) signals acquired during fMRI and examined dopamine function with the radiolabelled ligand \textsuperscript{[11C]}raclopride during PET imaging while a mother watched a film of her own infant and a film of an unfamiliar infant. Whole-brain network investigation during real experiences, using simultaneous probing of PET and fMRI, facilitates the mechanistic understanding of how multifaceted brain function relates to complex human behavior.


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\textsuperscript{C}C. and L.F.B. contributed equally to this work.

To whom correspondence should be addressed. Email: l.barrett@neu.edu.

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Maternal attunement is a broader measure of synchrony that traces how well the mother accommodates her vocal stimulation to the infant’s affect and social engagement. Maternal voice helps regulate the infant’s attention and affect (10). As such, mothers attune their vocal communication not only to the infants’ vocalizations but also to a broader set of affective cues, such as infants’ arousal levels and social engagement. We refer to this broader aspect of synchrony as “maternal attunement.” Maternal attunement measured the time in which mothers provided vocal stimulation while the infant was showing signs of positive affect (the infant is content and socially engaging). In our sample, maternal attunement ranged from 0–27% of the time in the 2-min unconstrained interaction, with a mean of 10.7% and a median of 10.8%. Age, race, or education level did not predict maternal attunement or mother–infant vocalization synchrony.

Imaging Results. Analyses with behavior and PET: Association between mother–infant vocalization synchrony and dopamine response. The imaging paradigm included two scans. Each mother viewed a film of her own infant during one scan (own-infant condition) and a film of an unfamiliar infant during another scan (unfamiliar-infant condition) as a control; the order was counterbalanced. To assess mothers’ endogenous dopamine response in each condition, we injected raclopride to the mothers with \[^{11}\text{C}]\text{raclopride} 10\ min\ into\ each\ film.\ Once\ injected, \[^{11}\text{C}]\text{raclopride}\ binds\ specifically\ to\ free\ D2\ receptors\ that\ are\ not\ occupied\ by\ endogenous\ dopamine\ molecules.\ Our\ primary\ outcome\ measure\ was\ \[^{11}\text{C}]\text{raclopride-nondisplaceable\ binding\ potential (BPnd)} (11). BPnd indirectly indexes the levels of endogenous neural dopamine response: A decrease in \[^{11}\text{C}]\text{raclopride}\ BPnd\ signifies\ a\ proportional\ increase\ in\ endogenous\ dopamine,\ and\ vice\ versa\ (12). Each mother’s relative dopamine response was calculated as the percentage change in endogenous dopamine response in the own-infant condition compared with the unfamiliar-infant condition using the formula $-\frac{\text{raclopride BPnd(own infant) - raclopride BPnd(unfamiliar infant)}}{\text{100/raclopride BPnd(unfamiliar infant)}}$. Our results showed that mother–infant synchrony scores are associated with maternal dopamine responses and that high-synchrony mothers have a dopaminergic preference for their own infants. In a multivariate general linear model, relative dopamine responses in the high vocalization synchrony group were significantly higher in the right hemisphere regions of interest (main effect; $n = 19, F = 4.6, P < 0.02$), with greatest effects in the right pallidum ($F = 11.1, P < 0.004$) and right NAcc ($F = 9.3, P < 0.007$) (Fig. 2A; see Table S1 for a complete list of regions and effects). The left hemisphere contralateral regions did not display such a group difference in \[^{11}\text{C}]\text{raclopride}\ BPnd. In the low-synchrony mothers, most mothers had a stronger dopamine response to the unfamiliar infant (for individual data see Fig. S1; Fig. S2 demonstrates that mothers with a dopaminergic preference in the right pallidum to their own infants are more synchronous). The scatterplots in Fig. 2B and C show the correlation between the individual differences in dopamine responses in the right pallidum and NAcc and vocalization synchrony scores.

Analyses with behavior and fMRI: Association between intrinsic connectivity within the medial amygdala network and maternal attunement. Unlike vocalization synchrony, which was linked to PET dopamine responses, maternal attunement was strongly associated with intrinsic connectivity in the medial amygdala network. Mothers who were more attuned to their infants had a more cohesive medial amygdala network (Fig. 3).

Infants’ ages were correlated with the dopamine responses in the right pallidum ($r = 0.49, P < 0.03$) and right amygdala ($r = 0.5, P < 0.01$) but were not correlated with the connectivity in the medial amygdala network ($r = -0.04, P < 0.8$), vocalization synchrony ($r = 0.3, P < 0.2$), or attunement ($r = 0.2, P < 0.5$). After controlling for infant age, vocalization synchrony was still correlated significantly with dopamine responses in the right pallidum ($r = 0.4, P < 0.03$). We also confirmed that infants’ age
did not mediate the relationship between vocalization synchrony and right pallidum dopamine (Sobel test not significant, $z = 1.03, P < 0.3$). These analyses confirm that mother–infant vocalization synchrony is associated with maternal dopamine responses across infants’ ages.

**Analyses with fMRI and PET: Association between medial amygdala network connectivity and dopamine responses in mothers.** Connectivity within the medial amygdala network was associated with in-network dopamine responses. Mothers with stronger medial amygdala network connectivity showed increased in-network endogenous dopamine responses in the right sgACC, right amygdala, and right NAcc while watching their own infants but not while watching an unfamiliar infant, (Fig. 4). A trend of correlation also was evident for the right PCC ($P < 0.06$). Dopamine responses in the contralateral left regions were not correlated with intrinsic connectivity in the left hemisphere medial amygdala network.

**Analyses with plasma oxytocin levels.** Peripheral oxytocin was measured in circulating plasma because there is still no reliable specific radiotracer for human oxytocin receptors (13). Central oxytocin is secreted as a neurotransmitter via axon terminals in the brain, whereas peripheral oxytocin is secreted via the pituitary gland into the blood circulation as a hormone. Studies in nonhuman animals (14) showed no direct correlation between levels of peripheral and central oxytocin. Nonetheless, numerous studies reported a link between plasma oxytocin and human behavior (for review see ref. 15). In this study peripheral oxytocin and its relations to central dopamine and behavior were evaluated in an exploratory way. Plasma for oxytocin analysis was available for 17 subjects and ranged from 43–370 pg/mL with a mean of 195 pg/mL. Levels of plasma oxytocin predicted medial amygdala network connectivity with a negative correlation coefficient (Fig. 5). Plasma oxytocin was positively correlated with vocalization synchrony ($r = 0.5, P < 0.03$) and showed a trend of correlation with dopamine responses in the left NAcc in the own-infant condition ($r = 0.36, P < 0.07$).

**Discussion**

The results of this study demonstrate that human maternal bonding is associated with dopamine responses in the NAcc and pallidum and with the strength of intrinsic connectivity within the medial amygdala network. Moreover, stronger intrinsic connectivity in the medial amygdala network is associated with increased within-network dopamine levels tested simultaneously and with lower plasma oxytocin levels. Together, these data provide evidence indicating that dopamine is involved in human bonding.

When humans interact, their appetitive behaviors synchronize (1). Synchrony has been shown to improve prosocial behavior in
infant macaques (16, 17), among healthy children (1), and in children with autistic spectrum disorder (18–21). The evidence presented here, which links synchrony to dopamine, provides initial evidence that dopamine is involved in the prosocial effects of synchrony. Behavioral synchronization demands dynamic adjustment of one’s behavior to the dyadic partner. In this study, synchronous mothers had stronger dopamine responses to their own infant in the NAcc and pallidum. In rodents, dopamine in the NAcc regulates appetitive maternal behaviors (2). In response to a salient event, dopamine in the NAcc releases the pallidum from GABA inhibition to disinhibit (or activate) motor pathways that execute appetitive behavior toward the pups (2). The results of this study, linking human behavioral synchronization to dopamine, join the rodent literature and mark dopaminergic function in the NAcc and pallidum as a regulatory pathway of appetitive bonding behavior in humans.

The infants’ films are salient social stimuli that elicit striatal dopamine responses. However, unlike high-synchrony mothers, low-synchrony mothers showed increased dopamine responses in the unfamiliar-infant condition. One possible explanation for this finding could be the novelty of the unfamiliar infant (22). Instead, in synchronous mothers dopamine responses to the mother’s own infant are stronger than those to a novel infant, possibly because the mother’s own infant is extremely salient to her (1). In the clinical realm, such salience-specificity is known as “primary maternal preoccupation” (23), which describes a mother’s complete focus on her infant while disregarding all distractions (23). Low maternal preoccupation is linked to PPD and nonsynchronous parenting (23). In our sample none of the mothers had a psychiatric diagnosis; however, low-synchrony mothers did not show differential dopamine responses that favor their own infants. This lack of a differential response could represent a relative deficit in their infant saliency with regard to other infants. However, beyond increased saliency, the dopaminergic patterns measured here might represent the selectivity of maternal attachment. Primate mothers and sheep show a selective bonding to their own young (24). Additionally, D2 receptors in the NAcc are important for the

![Fig. 3.](image)

Mothers with a stronger medial amygdala network are more attuned to their infants \( (n = 19, r = 0.46, P < 0.02, \text{one-tailed}) \). Medial amygdala network connectivity is represented as Fisher’s \( r \)-to-\( z \) transformed Pearson correlation coefficients between the right medial amygdala seed and the rest of the network’s nodes. Maternal attunement was measured as the percent of time during a 2-min interaction in which mothers provided positive vocal stimulation to their infants while the infants were content and socially engaged.

![Fig. 4.](image)

Stronger intrinsic connectivity in the medial amygdala network is predicted by increased in-network dopamine responses during the own-infant condition. (A–C, Upper) Intrinsic connectivity maps of the medial amygdala network (in red), overlaid with regions of interest for PET analysis (manually illustrated in green, according to FreeSurfer segmentation atlases [34]) in which \( ^{[1]} \text{C} \text{raclopride BPnd} \) is correlated with the network connectivity. (A–C, Lower) The Pearson one-tailed correlation graphs \( (n = 19) \). (A) Right sgACC \( (r = 0.45, P < 0.03) \). (B) Right amygdala \( (r = 0.455, P < 0.02) \). (C) Right NAcc \( (r = 0.38, P < 0.05) \). In the x axes, an increase in dopamine responses during the own-infant condition is indexed by a decrease in \( ^{[1]} \text{C} \text{raclopride BPnd} \). In the y axis, medial amygdala network connectivity is represented as Fisher’s \( r \)-to-\( z \) transformed Pearson correlation coefficients between the right medial amygdala seed and the rest of the network’s nodes.
formation of selective social bonds (2). Accordingly, in humans the increased D2-mediated dopaminergic responses in the NAcc in the own-infant condition as compared with an unfamiliar-infant condition may reflect the involvement of D2 receptors in a mother’s selective attachment to her own child.

This study reports a finding for a second key element in human maternal bonding: the medial amygdala network. Previous studies have shown that the strength of connectivity within the medial amygdala network is a reliable predictor for social affiliation (25). Our results extend those findings by demonstrating that the network is specifically involved in maternal bonding. Moreover, our results extend previous studies on the neural basis of maternal bonding (4, 6) by showing that bonding behavior relies not on the discrete function of the NAcc, amygdala, and mPFC (3) but instead on the synchronous firing in these regions as a network. The medial amygdala network includes the medial–rostral hypothalamus (6), which contains the medial preoptic area (MPOA) (26). The MPOA has a dominant role in maternal behavior in every mammalian species examined experimentally (24). Our study provides evidence for the involvement of this region in human bonding. This evidence helps integrate animal and human studies conceptually and suggests that homologous striatal circuitry has evolved to include broader neural connections with the human cortex. The medial amygdala network possibly supports synchronous affiliation by coordinating two functions: reward and mentalization. Synchrony appeared to be intrinsically rewarding to humans and nonhuman primates and to activate reward circuitry (27, 28). In addition to reward, synchrony relies on mentalization (i.e., the ability to represent the partner’s intentions and anticipate behavior) (4). The medial amygdala network includes subcortical reward regions, such as the NAcc, hypothalamus, and amygdala, which are potentially important for motivating and regulating behavior. The network also includes cortical regions, such as the vmPFC, sgACC, and PCC, which are consistently reported to support mentalization (9). Both the subcortical and cortical regions, and particularly the connectivity between them, promote synchronous bonding by coordinating cortical circuitry that supports mentalization to striatal reward circuitry that supports behavioral regulation. Linking behavior to dopamine in cortical regions of the medial amygdala network extends the contribution of this study beyond the rodent literature because it marks a possible role for dopamine in the higher social cognition needed for human bonding.

Previous findings have suggested a possible mechanistic role for dopamine in intrinsic network function. For example, several studies showed that patients with Parkinson’s disease, who suffer from a dopaminergic deficiency, have abnormal default-mode network connectivity, which is restored after treatment with the dopaminergic precursor L-dopa (29). In healthy humans, L-dopa increased the connectivity in several networks, and the dopaminergic antagonist haloperidol decreased the connectivity in those networks (30). This evidence converges with the results of this report to support a possible role for dopamine in network regulation and thus in human cognition. This finding could have important implications for neuropsychopathologies of the dopaminergic system, including Parkinson’s disease, schizophrenia, addiction (30), and possibly social dysfunction and PPD.

The analysis of plasma oxytocin yielded intriguing results. Oxytocin, which is considered a “prosocial” hormone (2), was negatively correlated to the medial amygdala network, which is considered a prosocial network (25). Animal models revealed that central oxytocin projections from the hypothalamus to the striatum have both inhibitory and excitatory pathways affecting dopaminergic receptors in the NAcc and amygdala (summarized in figure 3 from Human and Young (2)). The negative correlation between oxytocin and the medial amygdala network requires further investigation of the oxytocin–dopamine interplay in humans.

Studying postpartum mothers in a behavioral PET-MRI paradigm involved some limitations. Mothers’ responses to their own infants were compared with their responses to unfamiliar infants and are thus relative. Future studies should administer an additional control condition measuring baseline levels of raclopride BPnd. Moreover, previous studies have observed both left and right NAcc involvement in maternal synchronization, but this study only observed the right NAcc. Recent studies suggest a role for D2 asymmetry in motivation, with D2 receptors in the right hemisphere involved in behavioral regulation, which is important for synchrony. Future mechanistic studies should evaluate a possible lateralization in striatal function. Additionally, animal models do not show that dopamine acts in the pallidum to regulate maternal behavior, but there is strong evidence that dopamine acts on the MPOA to stimulate rodent maternal behavior (31). The human medial–rostral hypothalamus, where the MPOA is located (26), is medially adjacent to the pallidum, so it is possible that the pallidal dopamine observed here actually reflects dopamine transmission into the rostral hypothalamus. Future investigation of the rostral hypothalamus in human bonding, using neuroimaging with improved spatial resolution, is of high importance because of this brain area’s homology to rodents’ MPOA. Importantly, these methods are inherently correlational and cannot provide information about the causal nature of the reported relationships. Moreover, our study focused on positive interactive behavior and did not model maternal dopamine responses to an infant’s distress, a subject for future research. Furthermore, although mother–infant synchrony associated with maternal dopamine responses across ages, age could account for some neural variability and may be an important aspect to consider in future research.

The evidence reported here encourages future research on the neurochemistry of human bonding, including additional neurotransmitters such as central oxytocin and opioids. Moreover, our results may be useful for clinical research testing the involvement of dopamine and the medial amygdala network in PPD and developmental psychopathology. Dopamine within the medial amygdala network potentially promotes human bonding and thus could play a considerable role in optimal human development.

**Materials and Methods**

**Participants.** Nineteen mothers (age range 21–42 y) and their infants (age range 4–24 mo) completed the study. Participants had no psychiatric history and were not breastfeeding or pregnant. The Massachusetts General Hospital Institutional Review Board approved the study, and all mothers signed an informed consent before participating.

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*Fig. 5. Plasma oxytocin negatively predicts connectivity in the medial amygdala network (two-tailed, n = 17, r = −0.415, P < 0.049). In the x axis, medial amygdala network connectivity is represented as Fisher’s r-to-z transformed Pearson correlation coefficient values between the right medial amygdala seed and the rest of the network’s nodes.*
Procedure. During a visit to a subject’s home, study staff collected video recordings of the mother and the infant. Mothers were then invited to participate in fMRI scans during which the mother viewed films of her own infant and an unfamiliar infant, in changing order. While lying in the scanner, mothers passively watched footage of infants playing. The stimuli included a 20-min movie of their own infant during solitary play followed by a 5-min rest and then a 20-min movie of the unfamiliar infant. The radiotracer was injected 10 min into the first film, and PET data collection continued for 90 min. During the second scan, mothers watched the same components of the stimuli with the order of the infants reversed. The initial order of the movies was randomized across participants.

Combined PET-fMRI Scanner. PET data were acquired using the Siemens BrainPET scanner. This prototype device consists of a head-only PET insert (BrainPET) that fits in the bore of the 3-T Total Imaging Matrix Trio MRI scanner (Siemens Healthcare). Each of the 192 BrainPET detector modules consists of a 12 × 12 array of 2.5 × 2.5 mm lutetium oxyorthosilicate (LSO) crystals read out by a 3 × 3 array of magnetic field-intensive avalanche photodiodes. A PET-compatible circularly polarized (CP) transmission coil and an eight-channel receive array coil were used to acquire the MR data simultaneously.

MRI and fMRI. Structural data were acquired using a T1-weighted magnetization-prepared rapid acquisition with a gradient echo (MPRAGE) sequence (repetition time [TR] = 2.530 ms, echo time [TE] = 1.63 ms, inversion time [TI] = 1.200 ms, flip angle = 7°, and 1-mm isotropic voxels). MRI data analysis was performed using FreeSurfer (surfer.nmr.mgh.harvard.edu) and included unpadding, reconstruction, motion correction, intensity normalization, spatial normalization, white matter segmentation, registration, segmentation, and labeling of cortical and subcortical structures. For intrinsic connectivity analysis, whole-brain fMRI data were acquired with an echo-planar sequence during 6-min resting-state periods (TR = 3 s, TE = 30 ms, 3-mm isotropic voxels, 47 slices). To analyze the resting-state fMRI data, a temporal bandpass filter removed frequencies >0.08 Hz. To examine the intrinsic functional connectivity strength of the medial amygdala network, we created spherical volumes around the right medial amygdala seed and the rest of the nodes (25). (For a complete list of the bilateral network coordinates see Table S2.) For each participant, we computed pairwise correlation coefficients between the mean BOLD signal time course of the medial amygdala seed and every target region. The pairwise correlation coefficient values were averaged in each hemisphere to represent a composite measure of connectivity across the network. Then Fisher’s r-to-z transformations were calculated and used to assess the correlations between the strength of intrinsic network connectivity and maternal attunement, central dopamine, and plasma oxytocin.

Behavioral Coding of Mother-Infant Synchrony. To measure bonding behavior, 2-min interaction videos were coded for mother-infant synchrony by trained coders (for a detailed description of the coding scheme, see Table S3) (4). Four categories of behavior (vocalization, gaze, affect, and touch) were coded for each dyadic partner, and then the temporal synchronization of those behaviors was computed. We chose to operationalize synchrony using behavioral contingencies of vocalization because vocalization is an outgoing appetitive behavior central to bonding (10, 32), which relates to dopamine (33), and can be measured accurately in both mothers and infants (1).

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