



Mothers with Substance Addictions Show Reduced Reward Responses When Viewing Their Own Infant's Face

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Abstract: Maternal addiction constitutes a major public health problem affecting children, with high rates of abuse, neglect, and foster care placement. However, little is known about the ways in which substance addiction alters brain function related to maternal behavior. Prior studies have shown that infant face cues activate similar dopamine-associated brain reward regions to substances of abuse. Here, we report on a functional MRI study documenting that mothers with addictions demonstrate reduced activation of reward regions when shown reward-related cues of their own infants. Thirty-six mothers receiving inpatient treatment for substance addiction were scanned at 6 months postpartum, while viewing happy and sad face images of their own infant compared to those of a matched unknown infant. When viewing happy face images of their own infant, mothers with addictions showed a striking pattern of decreased activation in dopamine- and oxytocin-innervated brain

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regions, including the hypothalamus, ventral striatum, and ventromedial prefrontal cortex—regions in which increased activation has previously been observed in mothers without addictions. Our results are the first to demonstrate that mothers with addictions show reduced activation in key reward regions of the brain in response to their own infant's face cues. *Hum Brain Mapp* 38:5421–5439, 2017. © 2017 Wiley Periodicals, Inc.

Key words: maternal; addiction; reward; dopamine; oxytocin; infant

INTRODUCTION

Most mothers find engaging with their infants to be a uniquely rewarding and gratifying experience. With the birth of the infant, many facets of a woman's life that used to take precedence recede, and the infant becomes the center of the mother's attention and affection. Our previous work has shown that an infant's face, particularly when smiling, has unique salience and reward value to new mothers [Strathearn et al., 2008]. This reward experience may underlie and promote mother–infant attachment, motivating mothers to continue to care for their infants in the face of extreme fatigue or other competing needs. However, two decades of animal and human research have shown that this critical bond between the mother and her infant may be compromised as a result of maternal substance-use behaviors, especially substance addictions. Even during intermittent periods of sobriety, mothers with addictions are observed to be less attentive and responsive, while more intrusive and hostile, to their infants [Strathearn and Mayes, 2010]. Compared to mothers without addictions, they find infant cues to be less gratifying and more stressful, which places their infants at increased risk for abuse or neglect [Rutherford and Mayes, 2017; Rutherford et al., 2011].

According to the most recent national survey, 24.6 million Americans aged 12 years or older (9.4% of the population) were active illicit substance users [Substance Abuse and Mental Health Services Administration, 2014]. Binge alcohol use was reported by 60.1 million (22.9%) and 21.6 million (8.2%) qualified for a substance-use disorder as defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [American Psychiatric Association, 2000]. Among women who are substance users, approximately 90% are of reproductive age [Kuczkowski, 2007]. Annually, an estimated 212,000 pregnancies involve illicit drugs, 370,000 involve alcohol, and 606,000 involve tobacco [Martin et al., 2015; Substance Abuse and Mental Health Services Administration, 2014]. While many women abstain from substance use during pregnancy, substance use is often rapidly resumed after child birth, with 30% of mothers drinking, 20% smoking, and 10% binge-drinking within 3 months of their child's birth [Substance Abuse and Mental Health Services Administration, 2009]. Substance use increases the odds of child neglect fourfold and is involved in up to 80% of child maltreatment cases [Barth, 2009] and 60% of infant out-of-home placements [Child Welfare

Information Gateway, 2014; Wulczyn et al., 2011]. The annual public health burden related to substance misuse is estimated to be half a trillion dollars [Centers for Disease Control and Prevention, 2014; National Drug Intelligence Center, 2014; U.S. Department of Health and Human Services, 2014], although adverse consequences associated with maternal substance use extend far beyond this, taking a major toll on the well-being and development of the young children who are affected.

Ultimately, offspring growth and development hinge on maternal neurobiological adaptation during the prepartum and postpartum period (Fig. 1). Rodent models have been instrumental in this line of work and have elucidated the following. Estrogen and progesterone rise steadily during pregnancy until progesterone drops sharply prior to parturition [Brunton and Russell, 2010]. As parturition approaches, there is heightened sensitivity to oxytocin (OT) through increased OT receptor production [Numan and Woodside, 2010; Rilling and Young, 2014]. The medial preoptic area (MPOA) of the hypothalamus, a region rich in OT receptors [Champagne et al., 2001], is thought to monitor changes in hormonal levels over the course of pregnancy and stimulate the onset of maternal behavior at parturition via interaction with the mesolimbic motivational circuitry [Rilling and Young, 2014; Stolzenberg and Numan, 2011]. The MPOA directly projects to the ventral tegmental area (VTA), ventral striatum (VS), and medial prefrontal cortex (mPFC) and induces dopamine (DA) release into the mesocorticolimbic DA pathway [Afonso et al., 2009; Pereira and Morrell, 2011; Stolzenberg and Numan, 2011; Vertes, 2004]. As a key modulatory site of maternal circuitry, the VS integrates corticolimbic inputs and projects to the ventral pallidum [Groenewegen et al., 1999; Pereira and Morrell, 2011; Sesack and Grace, 2010] to direct the mother's responsiveness toward infant cues. The mPFC, with its interconnections with the hypothalamic and mesolimbic structures and its established role in attention allocation, organization, and sequencing [Pereira and Morrell, 2011; Vertes, 2004], is central to the orchestration of a complex array of well-timed and organized maternal behaviors.

The involvement of these regions in the expression of maternal behavior has been studied extensively in rodents. Estrogen, OT, or DA release into the MPOA elicits maternal behavior in virgin rats, which are normally aversive toward rat pups, while lesions of the MPOA abolish many aspects of maternal behavior in postpartum mothers [Bridges et al., 1997; Numan et al., 1977; Pedersen et al., 1994; Stolzenberg

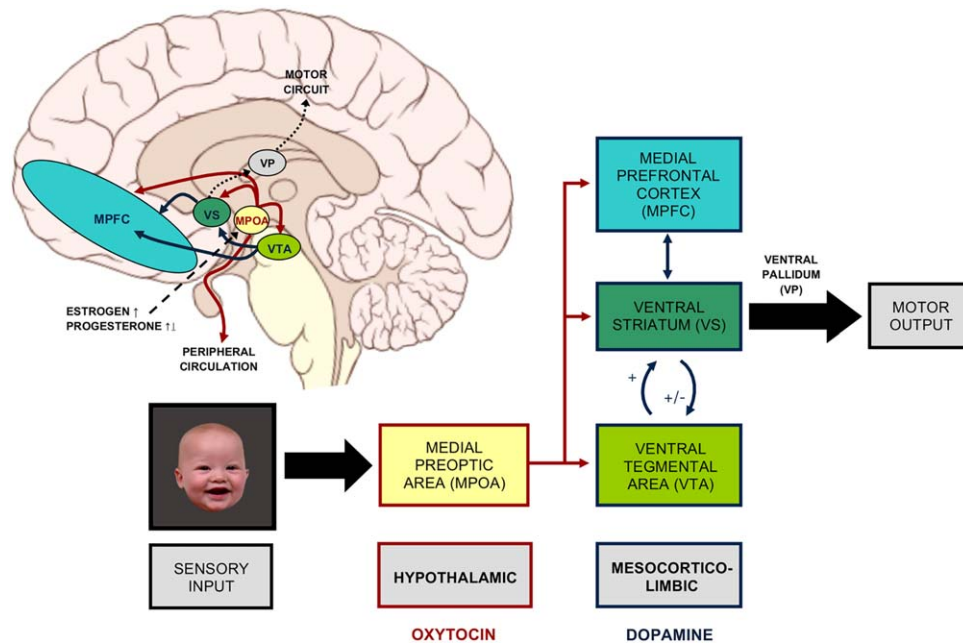


Figure 1.

Hypothalamic and mesocorticolimbic regulation of maternal brain response to infant cues. These OT- and DA-innervated brain regions are critical for the occurrence of maternal behavior. Brain schematic by P. J. Lynch [2006] (CC BY 2.5). [Color figure can be viewed at wileyonlinelibrary.com]

et al., 2007]. VS neurons show increased Fos expression during mother–pup interactions [Stack et al., 2002], and the magnitude of DA release in the VS measured in vivo corresponds with immediately observed levels of maternal behavior [Champagne et al., 2004]. Increased DA input into the VS facilitates maternal responses [Champagne et al., 2004; Stolzenberg et al., 2007], whereas depletion of DA in the VS or lesions of the VS lead to impaired maternal behavior [Li and Fleming, 2003; Numan et al., 2005]. The role of cortical systems has garnered relatively little attention in rodent models of maternal behavior. However, lesions [Afonso et al., 2007] or localized inhibitions [Febo et al., 2010] of the medial aspects of the cortex, including the mPFC, or blockade of OT receptors within the mPFC [Sabihi et al., 2014] have been shown to disrupt the organization and sequential execution of maternal behavior.

Although our understanding of the corresponding neurobiology in humans is limited to broad conclusions drawn from neuroimaging data and may lack the specificity and sophistication of rodent models, recent data suggest that maternal behavior is similarly regulated by a core set of neural circuits and physiological processes across mammals, from rodents to humans [Numan and Woodside, 2010; Rilling and Young, 2014]. A steadily growing body of human neuroimaging studies converges with decades of rodent research pointing to the hypothalamic, mesolimbic, and cortical contributions to maternal behavior. Our previous work has demonstrated activations of OT- and DA-innervated brain regions, including the hypothalamus, VS, and mPFC, in first-time mothers

when they viewed face images, particularly smiling images, of their own infant compared to those of a demographically matched unknown infant [Strathearn and Kim, 2013; Strathearn et al., 2008]. Differential activations of these regions reflected individual differences in maternal attachment and corresponded with the magnitude of maternal peripheral OT response during periods of mother–infant contact [Strathearn et al., 2009]. Although infant cues, particularly smiling cues from one’s own infant, are powerful stimuli evoking widespread activation of the maternal brain, accumulating evidence demonstrates that maternal care is most importantly implicated in two key neural networks in humans: the limbic circuits regulating motivation/salience (e.g., hypothalamus, VTA, VS, amygdala, anterior cingulate cortex) and the cortical circuits subserving social cognition/empathy (e.g., mPFC, insula, orbitofrontal cortex, superior temporal gyrus [STG], inferior parietal lobule [IPL], inferior frontal gyrus) [Atzil et al., 2012; Barrett et al., 2012; Strathearn et al., 2008; Swain et al., 2014]. Increasing attention has been directed to how central components of the maternal circuitry go awry in at-risk mothering and what prevention and intervention efforts may help reverse these abnormalities.

With maternal substance misuse, the DA mesocorticolimbic pathway, which is integral to the establishment of maternal behavior, may be co-opted by addictive behaviors [Strathearn and Mayes, 2010]. DA-regulated reward pathways that are involved in addiction overlap with those that are key to maternal caregiving, including the hypothalamus, VTA, VS, and mPFC [Grant et al., 2006;

Koob and Volkow, 2010; Luscher and Malenka, 2011]. Addictive substances, such as cocaine and amphetamine, induce a surge of DA in the VTA and VS, which may positively reinforce subsequent substance use, and over time may result in multiple neuroadaptations in the mesolimbic DA system [Luscher and Malenka, 2011; Wolf, 2002]. With extended substance use, the DA reward threshold may be recalibrated to a level achieved through use of addictive substances, and a shift is made within the reward system. When such a shift occurs, the reward system may then function to modulate gratification and relief associated with addictive substances rather than to orient the individual to salient natural rewards [Koob and Volkow, 2010; Rutherford et al., 2011].

Strides have been made in empirically delineating this co-opting of the DA mesocorticolimbic pathway in rodent models. These studies have primarily relied on cocaine administration and have documented cocaine-induced deficits in maternal behavior [see Nephew and Febo, 2012 for review], likely via targeted actions on the MPOA, VS, and mPFC [Febo and Ferris, 2007; Mattson and Morrell, 2005; Vernotica et al., 1999]. These actions may be mediated in part by disruptions in the OT system, as cocaine administration suppresses levels of OT, OT neurons, and OT receptors in these regions, particularly in the MPOA where these actions have been studied most [Johns et al., 1997, 2004]. The study of corresponding mechanisms in humans is still in a nascent stage, with only two studies appearing on this topic to date. The first demonstrated reduced plasma OT levels in postpartum mothers reporting gestational cocaine use [Light et al., 2004]. The other is the only existing functional magnetic resonance imaging (fMRI) study of maternal brain responses in substance-using mothers [Landi et al., 2011], documenting reduced prefrontal and limbic activations in response to unfamiliar face images and cries of infants. Perhaps due to the use of generic images of infants rather than images of the mothers' own infants, no findings emerged in this study with respect to the mothers' hypothalamic-mesolimbic activations.

Here, we report on the first human study examining how the mother's brain response to her own infant is modified in the presence of substance addiction. We employed a well-validated fMRI paradigm [Kim et al., 2014a; Strathearn and Kim, 2013; Strathearn et al., 2008, 2009] in which mothers with addictions viewed face images of their own infants in the scanner, interspersed with those of unknown infants. While both happy and sad faces were utilized, the aim of the present study was to examine activations of OT- and DA-innervated brain regions in mothers with addictions in response to what is typically a robust rewarding cue from their own infant—the infant's smiling face. These cues typically form the basis of mother–infant attachment through the intrinsic reward value they hold for mothers and have previously been shown to evoke robust activations of the hypothalamic and mesocorticolimbic brain regions, in comparison to smiling faces of unknown infants, in mothers

without addictions [Strathearn and Kim, 2013; Strathearn et al., 2009]. We predicted that mothers with addictions will demonstrate compromised brain response to their own infant's faces, particularly happy faces, and that this will be most prominently reflected in patterns of activations in OT- and DA-innervated brain regions.

MATERIALS AND METHODS

Participants

Thirty-six postpartum mothers ranging in age from 21 to 47 ($M = 27.8 \pm 5.6$) years were recruited from an inpatient treatment facility¹ for substance-use disorders. All participants were English speaking, met criteria for one or more substance-use disorder within the past year as assessed by the Mini International Neuropsychiatric Interview 6.0 (MINI) [Sheehan et al., 1998], and reported a history of substance use during the most recent pregnancy. Potential participants were excluded if any of the following criteria were met: (a) severe psychiatric symptoms requiring inpatient hospitalization; (b) past or present diagnosis of schizophrenia or other psychotic disorders; (c) pending legal cases (e.g., outstanding arrest warrants or parental rights hearings); (d) insufficient English fluency precluding interview assessments; (e) contraindications for MRI scanning; (f) out-of-home placement of infant for the past month or > 50% of infant's life; or (g) premature birth of infants, clinical evidence of in-utero drug effects, or other infant medical complications. Of the 40 participants who completed the scanning visit, one participant was excluded due to the use of a narcotic drug that compromised her alertness during the visit; the scans of three additional participants were discarded due to motion artifacts and technical problems. Ethics approval for this study was granted by the institutional review board at Baylor College of Medicine. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Study Design

Mothers were screened for study enrollment by licensed chemical dependency counselors and trained research assistants upon admission to the treatment facility. Eligible and

¹The focus of treatment at this inpatient facility centered around cohabitation of mothers and infants, which was integrated into the mothers' treatment program. All mothers cohabitated with at least one child, typically the child from their most recent pregnancy. Additional children, of up to the age of 13, were also encouraged to accompany and reside with mothers during treatment. Mothers placed infants in on-campus childcare for 35 h per week. Infants spent the remainder of the week with their mother in treatment. The standard treatment program was 90 days inpatient, with the option of completing up to 70 additional days of outpatient, which was co-located on the same campus. Mothers returned home at the conclusion of treatment.

enrolled mothers were transported to the Attachment and Neurodevelopment Laboratory for study visits. Infants were approximately 5-month old ($M = 5.0 \pm 2.9$) at the time of the first study visit, at which time infant face images were recorded, and mothers underwent fMRI scanning² at approximately 6 months ($M = 6.0 \pm 3.4$) postpartum, viewing face images of their own and a matched unknown infant. Upon completion of the scan, mothers provided ratings on how they perceived the infant to be feeling in each image (i.e., happy faces: “how happy do you think the baby was feeling?”; sad faces: “how sad do you think the baby was feeling?” and “how distressed do you think the baby was feeling?”) as well as their affective response to viewing each infant face (i.e., happy faces: “how happy did this picture make you feel?”; sad faces: “how sad did this picture make you feel?” and “how distressed did this picture make you feel?”).

Assessment of Substance Use

We used the MINI [Sheehan et al., 1998] to assess the DSM-IV diagnoses of substance-use disorders and the Addiction Severity Index (ASI-Lite) [McLellan et al., 1992] to evaluate the nature and extent of past and present substance use. The Alcohol Use Disorders Identification Test (AUDIT) [Babor et al., 2001] and the Fagerstrom Test for Nicotine Dependence (FTND) [Heatherton et al., 1991] were used to measure the severity of alcohol and tobacco use, respectively. Urine toxicology screens and alcohol breathalyzer tests were performed at the outset of each scanning session.

Stimuli and fMRI Paradigm

Experimental stimuli consisted of 40 infant-face images from four experimental conditions: 10 own-happy (OH), 10 unknown-happy (UH), 10 own-sad (OS), and 10 unknown-sad (US) infant faces (Fig. 2). For each mother, still face images were captured from the videos recorded of her own infant and of a single unknown infant matched on age, race, and affect intensity (and sex, if distinguishable). The video-recording was undertaken at the laboratory approximately 5 months postpartum, while eliciting happy and sad expressions from each infant. Two trained raters with established reliability ($\kappa = 0.954$, $P < 0.001$) classified still face images into one of four affect groups based on valence and intensity [see Cole et al., 1992], which provided the basis for the matching between own and unknown infant faces. The adequacy of classification and matching was confirmed by three independent female raters, who demonstrated that own and unknown infant face images did not differ in terms

²Participants’ average length of stay at the treatment facility prior to the scanning visit was approximately 110 ($M = 109.6 \pm 59.5$) days. Besides the time spent in on-campus childcare (35 h per week), no other mother–infant separation took place prior to the mother’s scanning visit.

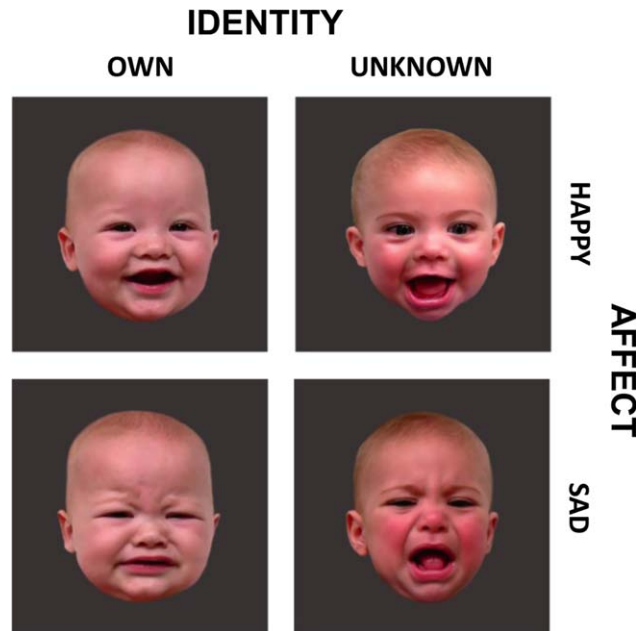


Figure 2.

Infant face images used in the study. [Color figure can be viewed at wileyonlinelibrary.com]

of affect intensity ($M_{OH} = 4.20 \pm 0.03$, $M_{UH} = 4.25 \pm 0.02$, $P = 0.11$; $M_{OS} = 1.50 \pm 0.04$, $M_{US} = 1.55 \pm 0.04$, $P = 0.48$).

Of the 40 total images, 12 own (i.e., 6 OH and 6 OS) and 12 unknown (i.e., 6 UH and 6 US) infant face images were selected for use in each of the two functional runs. Cry stimuli were also randomly interspersed with the face images, but were not the subject of the current paper. The face images were standardized for size (4.5 inches in height), adjusted for luminosity and contrast, displayed against a gray background, and projected onto an overhead mirror display for presentation to mothers during scanning. All images appeared in a pseudorandom sequence with a stimulus duration of 2 s and a random interstimulus interval of 2 to 11 s.

fMRI Data Acquisition

Imaging data were acquired using a 3-Tesla Siemens Trio MRI system (Erlangen, Germany) with a standard 12-channel head coil. Localizer images were acquired for prescribing the functional image volumes parallel to the intercommissural line. Functional images were obtained using a gradient-echo echo-planar imaging (EPI) sequence (32 axial-oblique slices; repetition time [TR], 2,000 ms; echo time [TE], 30 ms; flip angle [FA], 80°; field of view [FOV], 220 mm × 220 mm; matrix, 64 × 64; in-plane resolution, 3.4 mm × 3.4 mm; slice thickness, 4 mm), resulting in 121 images collected per 4:06 min functional run. Two types of anatomical images were acquired: T1 weighted

anatomic scan using a fast low-angle shot (FLASH) sequence (40 sagittal slices; TR, 20 ms; TE, 6.86 ms; FA, 25°; FOV, 240 mm × 240 mm; matrix, 256 × 241; in-plane resolution, 1.0 mm × 0.9 mm; slice thickness, 4 mm) and high-resolution anatomic scan using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (176 sagittal slices; TR, 2,530 ms; TE, 2.43 ms; FA, 7°; FOV, 256 mm × 256 mm; matrix, 256 × 246; in-plane resolution, 1.0 mm × 1.0 mm; slice thickness, 1 mm) for 3D reconstruction.

Data Analysis

fMRI analysis

Preprocessing and analyses of the fMRI data were performed using BrainVoyager QX, version 2.3.1 (Brain Innovation, Maastricht, The Netherlands). Prior to analysis, blood oxygenation level-dependent (BOLD) images were corrected for slice timing and realigned to the first volume for head motion correction. Head motion of <2.0 mm translation or 2.0° rotation was deemed acceptable. Spatial smoothing was performed with a 4 mm full width at half maximum (FWHM) Gaussian kernel, followed by high-pass filtering using a Fourier basis set of two cycles per run to remove low frequency drifts. Functional data were then coregistered with the anatomical data, transformed into 3 × 3 × 3 mm isotropic voxels, and normalized into the Talairach space.

For each run of each subject data, a general linear model (GLM) was specified, modeling the BOLD signal change for each experimental condition (OH, UH, OS, and US) using a double-gamma hemodynamic response function. To adjust for signal magnitude variability and facilitate comparisons with other research [e.g., Atzil et al., 2011; Landi et al., 2011], the resulting regression weights (β) were then percent normalized to reflect percent signal change [Chen et al., 2017; Pernet, 2014; Poldrack et al., 2008] and concatenated across the entire group of 36 subjects for second-level random-effects analyses. Group *t*-maps were generated representing percent BOLD contrasts between own and unknown infant conditions: OH versus UH and OS versus US. Analyses were performed at two levels: first using a whole-brain voxel-wise analysis, followed by a region-of-interest analysis of the bilateral striatum to evaluate within-striatal differences in percent BOLD signals to our contrast of interest. The striatum was selected structurally, based on a mask derived from the subcortical atlas of the Brain Tutor HD, version 2.2 (Brain Innovation, Maastricht, The Netherlands), and comprised 289 and 302 voxels for the left and right, respectively. Post hoc examination of whole-brain analysis results was conducted by extracting percent signal change values for OH and UH from cubes centered at local peaks within the cluster of (de)activation and extending up to ± 10 voxels per dimension, unless limited by the spatial extent of (de)activation. This allowed us to further contrast and visually display patterns of percent BOLD signals for our contrast of interest in our key hypothesized OT- and DA-innervated regions. In all

analyses, statistical threshold of false discovery rate (FDR) corrected $q < 0.05$ and a cluster threshold of ≥ 300 mm³ were used to determine clusters of significant activation. Supra-threshold clusters of active voxels were labeled using a published atlas of the human brain [Mai et al., 2004] and the Talairach Client (Research Imaging Center, TX).

Postscan ratings analysis

Postscan ratings were analyzed with the STATA/SE, version 13.1 XTMIXED procedure. Mothers' ratings of affect, both how they perceived the infant to be feeling in each image and of their own affective responses to the image, were compared for own and unknown infant faces using mixed-effects linear regression analysis that included a subject-level random intercept. Mixed-effects models were also used to probe for the association between mothers' two ratings to examine the degree to which mothers' own affective responses tracked with how they perceived the infant to be feeling. Model building was carried out as follows: (a) the initial model included the fixed main effects of infant identity (i.e., own vs. unknown) and mothers' perceived ratings of infant's affect; (b) a subject-level random intercept was added to model systematic interindividual variability; and (c) interaction terms were added sequentially and retained in the model if they improved model fit. The models were fitted by maximum likelihood estimation, and nested models were contrasted using likelihood-ratio chi-squares.

RESULTS

Participant Characteristics

Participants' sociodemographic and substance-use characteristics are shown in Tables I and II, respectively. Participants were generally of low socioeconomic status, with only 33 percent completing any education beyond high school and 64 percent reporting an annual family income of less than \$15,000. Twenty-two percent of women had been court-mandated to receive substance-use treatment, and 58% had child protective services (CPS) involvement. Sixty-seven percent ($n = 24$) were taking psychotropic medications at the time of the present study, including antipsychotic medications ($n = 8$), mood stabilizers ($n = 2$), medications for depression or anxiety ($n = 13$), and stimulant medication ($n = 1$). Because all women were recruited from an inpatient substance-use treatment facility and the majority remained in treatment at the time of the study, most were not using substances at the time of the scanning visit. All except four women tested negative on a urine toxicology screen on the day of the scan, and none had a positive alcohol breathalyzer test. Results remained unchanged when the four subjects were excluded from the analyses; hence, data reported below include all subjects.

TABLE I. Sociodemographic characteristics of mothers and infants (N = 36)

Maternal age, mean ± SD	27.8 ± 5.6
Infant sex, <i>n</i> (%)	
Male	18 (50.0)
Female	18 (50.0)
Maternal parity, <i>n</i> (%)	
Primiparous	15 (41.7)
Multiparous	21 (58.3)
Maternal ethnicity ^a , <i>n</i> (%)	
Hispanic or Latino	12 (33.3)
Not Hispanic or Latino	23 (63.9)
Maternal race ^a , <i>n</i> (%)	
White	17 (47.2)
Black or African American	11 (30.6)
Other	4 (11.1)
Marital status ^a , <i>n</i> (%)	
Single/never married	17 (47.2)
Living together	11 (30.6)
Separated/divorced/widowed	6 (16.7)
Maternal education ^a , <i>n</i> (%)	
Junior high school (7 to 9th grade)	7 (19.4)
Some high school	9 (25.0)
High school graduate	7 (19.4)
Some college or higher	12 (33.4)
Annual family income ^a , <i>n</i> (%)	
< \$15,000	23 (63.9)
\$15,000 to 30,000	8 (22.2)
\$30,001 to 45,000	3 (8.3)
> \$100,000	1 (2.8)
Breastfeeding status, <i>n</i> (%)	
Still breastfeeding	1 (2.8)
Not breastfeeding	35 (97.2)

^aPercentages do not total 100% due to missing data.

fMRI Findings

Happy faces

As compared to viewing unknown happy infant faces, viewing the happy faces of their own infants induced significant activation in multiple brain regions of mothers with addictions, including the amygdala, hippocampus, thalamus, cingulate, and brainstem structures including the VTA and substantia nigra (Table III), overlapping regions previously reported in normative groups of mothers [Strathearn and Kim, 2013; Strathearn et al., 2008; Swain et al., 2014]. Consistent with the extant literature on maternal brain responses, activations were also seen in the inferior frontal gyrus, ventral premotor cortex, insula, STG, visual association areas, and cerebellum.

However, as hypothesized, maternal brain response was significantly reduced in several key OT- and DA- innervated brain regions in own happy compared to unknown happy infant faces. Our whole-brain analysis yielded a single cluster of deactivation amid clusters of highly significant activations (Fig. 3). The deactivated cluster encompassed the hypothalamus, bilateral VS, and bilateral ventromedial prefrontal regions spanning 258 voxels

(Table IV and Fig. 3a). Figure 3b displays a post hoc examination of local peaks within the deactivated cluster, depicting a negative percent BOLD signal change observed in key OT- and DA-innervated regions in mothers with addictions while viewing their own infant's happy faces, in contrast to the positive change in percent BOLD signals seen in response to an unknown infant's face. Analysis within the striatum region-of-interest revealed that the observed deactivation was specific to the ventral portion of the striatum (Fig. 4).

Sad faces

In our group of mothers with addictions, viewing the sad faces of their own infants relative to unknown infants evoked significant activation in brain regions that largely overlapped with those seen for the happy faces, including the cingulate, thalamus, substantia nigra, parahippocampal gyrus, inferior frontal gyrus, superior frontal gyrus, and cerebellum (Table V). Activations were also present, and more widespread than those observed for happy faces, in the dorsomedial prefrontal cortex, the opercular part of the inferior frontal gyrus, and several parietal-occipital regions, including the precuneus/paracentral lobule and occipital gyri. Our analysis yielded a single cluster of deactivation in the right IPL extending to the STG, spanning 12 voxels (peak Talairach coordinates: 50, -59, 36; $t = -4.62$; $P = 0.000051$). There was no activation or deactivation seen in the hypothalamus, VS, or ventromedial prefrontal regions in either whole-brain or region-of-interest analysis of the striatum.

Postscan Rating Findings

Happy faces

Mothers with addictions reported perceiving happy faces of their own infants as happier than those of unknown infants ($\beta_{\text{identity}} = 0.84$, 95% CI = 0.62 to 1.06, $z = 7.39$, $P < 0.001$; Table VI). Mothers' self-reported affect was also more positive in response to their own infants compared to unknown infants ($\beta_{\text{identity}} = 2.45$, 95% CI = 2.21 to 2.69, $z = 19.69$, $P < 0.001$; Table VI). Mothers' own report of positive affect correlated significantly with how happy they perceived infants to be feeling ($\beta_{\text{infant affect}} = 0.61$, 95% CI = 0.51 to 0.70, $z = 12.47$, $P < 0.001$; Table VII). However, the strength of this association varied as a function of infant identity ($\beta_{\text{identity} \times \text{infant affect}} = -0.33$, 95% CI = -0.50 to -0.16, $z = -3.76$, $P < 0.001$; Table VII). Post hoc probing of the moderation revealed that this association was significantly stronger for unknown infants ($\beta_{\text{unknown}} = 0.61$, 95% CI = 0.51 to 0.70, $z = 12.47$, $P < 0.001$) than for own infants ($\beta_{\text{own}} = 0.28$, 95% CI = 0.13 to 0.42, $z = 3.71$, $P < 0.001$). This indicated that mothers' self-reported positive affect increased more closely in line with their perceived increase in an unknown infant's positive affect than that of their own infant. In other words, mothers' own report of happiness

TABLE II. Substance-use characteristics of mothers (N = 36)

DSM-IV substance-use disorders ^a , <i>n</i> (%)	
Substance dependence	33 (91.7)
Cocaine dependence	16 (44.4)
Opioid dependence	6 (16.7)
Amphetamine dependence	5 (13.9)
Sedative, hypnotic, or anxiolytic dependence	3 (8.3)
Cannabis dependence	3 (8.3)
Substance abuse	3 (8.3)
Cannabis abuse	3 (8.3)
Substance of choice, <i>n</i> (%)	
Cocaine	16 (44.4)
Narcotic	6 (16.7)
Cannabis	6 (16.7)
Stimulants	5 (13.9)
Tranquilizers	3 (8.3)
Substance use during pregnancy, <i>n</i> (%)	
Nicotine	30 (83.3)
Alcohol	21 (58.3)
Cocaine	21 (58.3)
Cannabis	18 (50.0)
Sedatives	13 (36.1)
Opioids	12 (33.3)
Amphetamines	7 (19.4)
Others (Hallucinogens, Inhalants)	3 (8.3)
Alcohol-use severity ^b , <i>n</i> (%)	
Low level	17 (47.2)
Medium level	8 (22.2)
High level/possible dependency	4 (11.2)
Tobacco-use severity ^c , <i>n</i> (%)	
Very low dependence	12 (33.3)
Low dependence	8 (22.2)
High/very high dependence	9 (25.0)
Extent of substance use ^d , mean ± <i>SD</i> (range)	
Last 30 days in controlled environment ^e (days used)	
Illicit substance of choice	0.14 ± 0.68 (0 to 4)
Cocaine	0.07 ± 0.26 (0 to 1)
Narcotic	0.80 ± 1.79 (0 to 4)
Cannabis	0.00 ± 0.00 (0 to 0)
Stimulants	0.00 ± 0.00 (0 to 0)
Tranquilizers	0.00 ± 0.00 (0 to 0)
Any other illicit substance ^f	0.19 ± 1.01 (0 to 6)
Last 30 days prior to admission to controlled environment (days used)	
Illicit substance of choice	15.39 ± 12.73 (0 to 30)
Cocaine	11.33 ± 11.35 (0 to 30)
Narcotic	29.0 ± 2.24 (25 to 30)
Cannabis	19.4 ± 14.72 (0 to 30)
Stimulants	4.67 ± 8.08 (0 to 14)
Tranquilizers	17 ± 14.73 (1 to 30)
Any other illicit substance ^f	9.71 ± 11.08 (0 to 30)
Pregnancy (days used of 270 total days)	
Illicit substance of choice	110.92 ± 107.55 (0 to 270)
Cocaine	97.44 ± 102.90 (0 to 270)
Narcotic	158.33 ± 130.24 (0 to 270)
Cannabis	112.92 ± 106.64 (7.5 to 270)
Stimulants	50.9 ± 48.84 (36 to 270)
Tranquilizers	184.0 ± 148.96 (12 to 270)
Any other illicit substance ^f	73.53 ± 103.85 (0 to 270)
Alcohol	22.21 ± 35.83 (0 to 114)
Tobacco	160.92 ± 114.59 (0 to 270)

TABLE II. (continued).

Lifetime (years used)	
Illicit substance of choice	7.94 ± 5.58 (0 to 29)
Cocaine	9.27 ± 6.85 (1 to 29)
Narcotic	7.0 ± 1.22 (5 to 8)
Cannabis	10.8 ± 11.54 (0 to 30)
Stimulants	6.67 ± 4.93 (1 to 10)
Tranquilizers	6.0 ± 1.0 (5 to 7)
Total illicit substance [§]	10.83 ± 5.75 (0 to 29)
Alcohol	9.31 ± 7.75 (0 to 36)

^aDSM-IV-TR diagnoses of substance use disorders were given using the MINI. No mother received the diagnosis of substance dependence or abuse solely based on alcohol or tobacco use.

^bSeverity of alcohol problems was determined by the AUDIT. An AUDIT score of ≤7 represented a low level, 8 to 15 represented a medium level, and 16 ≤ represented a high level of alcohol problems. The mean AUDIT score was 7.97 (*SD* = 7.24) for the current group of mothers.

^cSeverity of tobacco use was assessed by the FTND. An FTND score of 0 to 2 indicated very low dependence, 3 to 4 indicated low dependence, 5 indicated medium dependence, 6 to 7 indicated high dependence, and 8 to 10 indicated very high dependence on nicotine. The mean FTND score was 3.10 (*SD* = 2.88) for the current group.

^dExtent (frequency) of substance use was assessed using the ASI-Lite. The reported values refer to the number of days or years used during the respective period.

^eControlled environment refers to residential treatment or incarceration.

^fAny other illicit substance refers to any illicit substances other than substance of choice (excluding alcohol and tobacco).

[§]Total illicit substance refers to any combination of illicit substances including substance of choice (excluding alcohol and tobacco).

Note. MINI = Mini International Neuropsychiatric Interview 6.0; ASI = Addiction Severity Index-Lite; AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test for Nicotine Dependence.

increased to a greater degree when perceiving increased happiness in an unknown infant rather than in their own infant.

Sad faces

Consistent with the ratings for happy faces, mothers with addictions reported perceiving their own infants' sad faces as sadder and more distressed than those of unknown infants (sad: $\beta_{\text{identity}} = 0.64$, 95% CI = 0.37 to 0.90, $z = 4.72$, $P < 0.001$; distressed: $\beta_{\text{identity}} = 0.61$, 95% CI = 0.33 to 0.89, $z = 4.26$, $P < 0.001$; Table VI). Mothers' self-reported negative affect was also stronger in response to their own infants compared to unknown infants (sad: $\beta_{\text{identity}} = 2.21$, 95% CI = 1.90 to 2.52, $z = 13.95$, $P < 0.001$; distressed: $\beta_{\text{identity}} = 1.99$, 95% CI = 1.68 to 2.30, $z = 12.59$, $P < 0.001$; Table VI). Mothers' own report of negative affect correlated significantly with how sad and distressed they perceived infants to be feeling (sad: $\beta_{\text{infant affect}} = 0.62$, 95% CI = 0.52 to 0.71, $z = 12.69$, $P < 0.001$; distressed: $\beta_{\text{infant affect}} = 0.56$, 95% CI = 0.47 to 0.65, $z = 12.04$, $P < 0.001$; Table VII). The strength of this association varied as a function of infant identity (sad: $\beta_{\text{identity} \times \text{infant affect}} = 0.23$, 95% CI = 0.10 to 0.37, $z = 3.43$, $P < 0.001$; distressed: $\beta_{\text{identity} \times \text{infant affect}} = 0.27$, 95% CI = 0.14 to 0.39, $z = 4.15$, $P < 0.001$). However, in contrast to the ratings for happy faces, post hoc probing of the moderation revealed that mothers' self-reported negative affect increased more closely in line with their perceived increase in their own infant's negative affect (sad: $\beta_{\text{own}} = 0.85$, 95% CI = 0.74 to 0.96, $z = 15.40$, $P < 0.001$; distressed: $\beta_{\text{own}} = 0.82$, 95% CI = 0.72 to 0.93,

$z = 15.66$, $P < 0.001$) rather than that of an unknown infant (sad: $\beta_{\text{unknown}} = 0.62$, 95% CI = 0.52 to 0.71, $z = 12.69$, $P < 0.001$; distressed: $\beta_{\text{unknown}} = 0.56$, 95% CI = 0.47 to 0.65, $z = 12.04$, $P < 0.001$). In other words, mothers' own report of sadness and distress increased to a greater extent when perceiving an increase in sadness and distress in their own infant rather than in an unknown infant.

DISCUSSION

When mothers are involved in substance addiction, the repercussions extend to their children. Until now, little work has elucidated the underlying neurobiology of this phenomenon. Our results are the first, to our knowledge, to show that mothers with addictions demonstrate reduced hypothalamic and mesocorticolimbic responses to reward-related cues from their own infants. When viewing smiling face images of their own infants as compared to unknown infants, these mothers showed a striking pattern of decreased activation in key OT- and DA-innervated brain regions, including the hypothalamus, VS, and mPFC. Notably, in mothers without addictions, prior research has indicated a robust pattern of activation in these regions [Strathearn and Kim, 2013; Strathearn et al., 2009] (see Fig. 5). As expected, in mothers with addictions, these compromised hypothalamic and mesocorticolimbic activations were seen in response to happy, but not sad, faces of their own infants. Sad faces of own infants instead elicited a decreased activation in a small region of the right IPL and STG in these mothers. These regions form part of the neural network subserving social cognition/empathy [Decety and Lamm, 2007], support maternal responsiveness to an array of

TABLE III. Brain activation in mothers with addictions to the contrast of own happy (OH) versus unknown happy (UH)

	Hemisphere	Talairach coordinates ^a			Peak <i>t</i> value	<i>P</i>	Volume ^b (mm ³)
		<i>x</i>	<i>y</i>	<i>z</i>			
Frontal lobe							
Superior Frontal Gyrus	Right	2	-5	60	7.99	<0.00000001	507
Precentral Gyrus	Right	41	-2	27	7.21	0.00000002	357
Precentral Gyrus/Postcentral Gyrus	Left	-43	-17	45	6.19	0.00000043	469
Parietal lobe							
Precentral Gyrus/Postcentral Gyrus	Right	50	-17	42	9.24	<0.00000001	1,853
Superior Parietal Lobule	Right	23	-59	30	6.14	0.00000051	360
Temporal/Occipital lobe							
Fusiform Gyrus/Inferior Temporal Gyrus/Occipital Gyri	Left	-28	-47	-18	9.37	<0.00000001	8,044
Occipital Gyri	Right	29	-77	0	7.51	0.00000001	2,275
Fusiform Gyrus	Right	32	-44	-15	7.40	0.00000001	2,631
Sublobar regions							
Middle Cingulate Gyrus	Right/Left	-1	-5	33	10.10	<0.00000001	1,395
Limbic ^c							
Dorsal Putamen/Globus Pallidus	Left	-22	-2	-6	8.77	<0.00000001	2,869
Parahippocampal Gyrus	Left	-28	-5	-30	6.59	0.00000013	
Insula/Inferior Frontal Gyrus	Left	-40	4	12	8.04	<0.00000001	946
Parahippocampal Gyrus/ Lateral Amygdala	Right	23	-5	-27	8.02	<0.00000001	1,531
Midbrain/limbic ^c							
Thalamus	Left	-7	-23	6	7.98	<0.00000001	8,895
Substantia Nigra	Right	4	-26	-9	7.26	0.00000002	
Thalamus	Right	2	-14	8	7.01	0.00000004	
Ventral Tegmental Area	Right/Left	-1	-16	-9	6.90	0.00000005	
Hippocampus	Right	23	-23	-6	6.75	0.00000008	
Substantia Nigra	Left	-4	-17	-9	6.48	0.00000018	
Globus Pallidus	Right	17	-5	-6	6.59	0.00000013	324
Posterior Cingulate Gyrus	Left	-4	-53	9	6.36	0.00000026	720
Cerebellum							
Anterior Lobe, Culmen	Right	29	-50	-21	9.38	<0.00000001	4,395
Anterior Lobe, Cerebellar Lingual	Left	-4	-44	-9	7.76	<0.00000001	345
Anterior Lobe, Culmen	Right	14	-59	-18	6.25	0.00000036	602
Posterior Lobe, Cerebellar Tonsil	Left	-7	-50	-30	6.21	0.00000041	494

Note. Data shown are from the activation map for the OH > UH contrast, thresholded at FDR-corrected $q < 0.001$ and a minimum cluster size of 300 mm³. Results are presented at a more stringent threshold of $q < 0.001$ to better delineate specific neuroanatomical locations of activated clusters. Within each lobe, clusters are ordered by decreasing level of significance.

^aTalairach coordinates in millimeters with origin at the anterior commissure, representing peak voxels in each cluster. *x*, *y*, *z* coordinates refer to right (+) to left (-), anterior (+) to posterior(-), and superior (+) to inferior(-), respectively.

^bNumber of contiguously activated voxels within a cluster.

^cNote that where no volume is given for an anatomical region, it forms part of a larger cluster that spans anatomically distinct regions.

affectively nuanced expressions from infants [Lenzi et al., 2009], and show increased activation in response to own compared to unknown, and sad compared to happy, infant cues in mothers without addictions [Lenzi et al., 2009; Noriuchi et al., 2008]. The dysregulated maternal response of mothers with addictions was also evident in their behavioral ratings, which demonstrated that their positive affect tracked more closely with how positive they perceived unknown infants to be feeling compared to their own infants. Of note, this pattern of dysregulation emerged only for happy, but not sad, faces, indicating that reward-related dysregulations may be

particularly relevant for mothers with addictions, manifesting especially in reward-related attachment contexts. Our findings are consistent with the literature from the general population that has underscored the role of diminished salience of natural rewards in addictions [Koob and Volkow, 2010; Lubman et al., 2009; May et al., 2013], while demonstrating for the first time in human mothers how such disruptions may undermine a critical aspect of their responsiveness to their infants.

Rodent models have shown that pup cues are highly reinforcing to postpartum mothers, sufficient to compete with

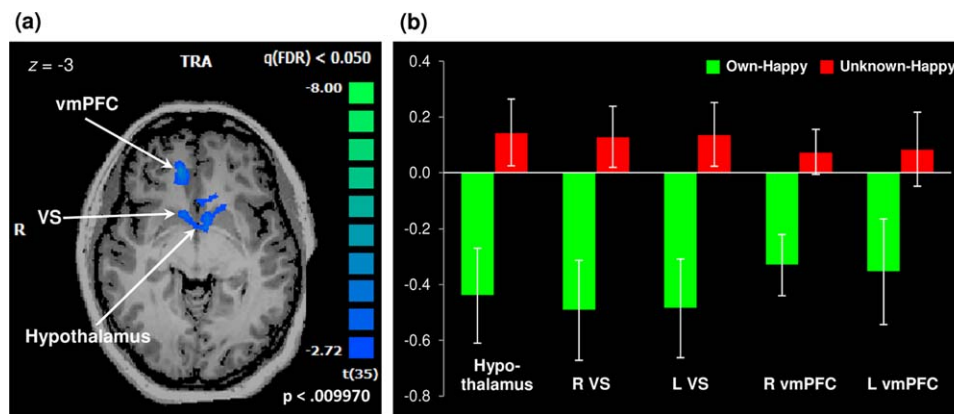


Figure 3.

Reduced maternal brain response in mothers with addictions evidenced by a single cluster of deactivation observed for the own-happy versus unknown-happy contrast, encompassing the hypothalamic, bilateral VS, and bilateral vmPFC regions (258 voxels, $P < 0.01$, FDR-corrected $q < 0.05$; Panel A). Striking deactivation is observed when mothers with addictions view their own infant's smiling faces, compared with unknown infant faces (Panel B). For a post hoc examination of local peaks within the deactivated cluster, percent BOLD signal values were

the hedonic properties of cocaine [Pereira and Morrell, 2011]. Virgin females show activation of the mesocorticolimbic DA pathway upon cocaine administration, while the same pathway is deactivated to cocaine and activated to pup cues in postpartum lactating mothers [Ferris et al., 2005]. This difference preparturition and postparturition reflects a series of neuroadaptations primarily involving, but not limited to, the OT system [Kim and Strathearn, 2016], which occur during the transition to motherhood and ensure the reward salience of pup cues over other hedonic stimuli [Ferris et al., 2005; Numan and Woodside, 2010; Rilling and Young, 2014]. It is in this respect that our findings in mothers

extracted from cubes centered at the peak voxels of each anatomical region and extending up to ± 10 voxels per dimension, unless limited by the spatial extent of activation. Peak Talairach coordinates: hypothalamus, (-2, 1, -3); R VS, (8, 10, -3); L VS, (-13, 19, 3); R vmPFC, (11, 34, 6), L vmPFC, (-16, 37, 3). Error bars represent the standard error of the mean. VS = ventral striatum; vmPFC = ventromedial prefrontal cortex; R: right; L: left. [Color figure can be viewed at wileyonlinelibrary.com]

with addictions are particularly noteworthy. In contrast to the adaptive shifts that help promote mother–infant attachment during the postpartum period, postpartum mothers with addictions in our study showed a pattern of decreased hypothalamic and mesocorticolimbic activation to reward cues from their infants. This is consistent with the notion that substance use compromises maternal behavior by co-opting the mesocorticolimbic DA system and disrupting naturally occurring OT-related neuroadaptations [Rutherford et al., 2011; Strathearn and Mayes, 2010]. Alternatively, dysregulations of the OT- and DA-systems may have already been present in susceptible mothers even prior to the onset

TABLE IV. Brain deactivation in mothers with addictions to the contrast of own happy (OH) versus unknown happy (UH)

	Hemisphere	Talairach coordinates ^a			Peak <i>t</i> value	<i>P</i>	Volume ^b (mm ³)
		<i>x</i>	<i>y</i>	<i>z</i>			
Limbic lobe/Sublobar regions							6970
Ventromedial PFC	Right	11	34	6	-5.78	0.000002	
Ventral Striatum	Left	-13	19	3	-5.41	0.000005	
Ventromedial PFC	Left	-16	37	3	-4.60	0.000054	
Ventral Striatum	Right	8	10	-3	-4.38	0.000104	
Hypothalamus	Right/Left	-2	1	-3	-3.32	0.002102	

Note. Data shown are from the activation map for the OH > UH contrast, thresholded at FDR-corrected $q < 0.05$ and a minimum cluster size of 300 mm³.

^aTalairach coordinates in millimeters with origin at the anterior commissure, representing peak voxels in each cluster. *x*, *y*, *z* coordinates refer to right (+) to left (-), anterior (+) to posterior(-), and superior (+) to inferior(-), respectively.

^bNumber of contiguously activated voxels within a cluster. Volume is not reported for each anatomical region, as each region forms part of a larger cluster that spans anatomically distinct regions.

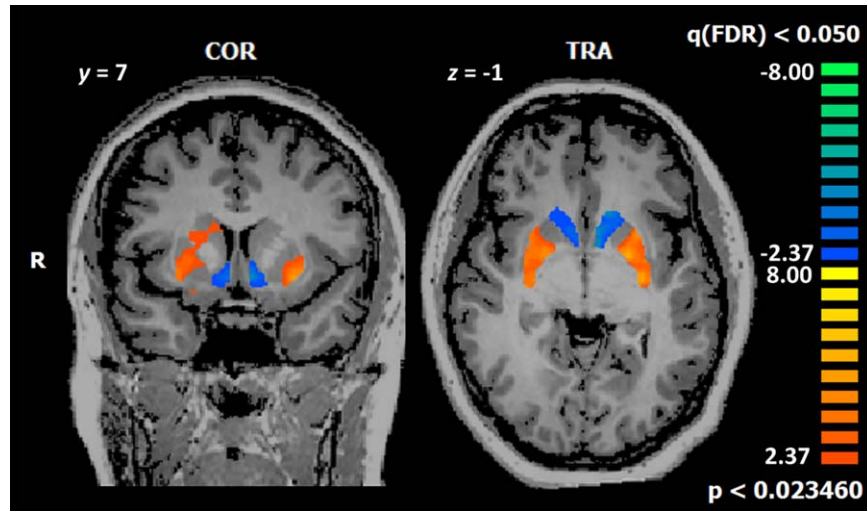


Figure 4.

Striatal activation limited to the *dorsal* striatum, in response to own-happy versus unknown-happy infant faces ($P < 0.02$, FDR-corrected $q < 0.05$). A contrasting pattern of deactivation is seen in the ventral striatum. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE V. Brain activation in mothers with addictions to the contrast of own sad (OS) versus unknown sad (US)

	Hemisphere	Talairach coordinates ^a			Peak t value	P	Volume ^b (mm ³)
		x	y	z			
Frontal lobe							
Precentral Gyrus	Right	50	-17	42	9.22	<0.00000001	3,791
Superior Frontal Gyrus	Right/Left	2	-5	60	8.30	<0.00000001	1,525
Precentral Gyrus/Postcentral Gyrus	Left	-46	-17	39	7.20	0.00000002	899
Inferior Frontal Gyrus	Right	53	7	30	6.72	0.00000009	1,120
Parietal lobe							
Precuneus	Right	17	-71	33	7.96	<0.00000001	1,018
Temporal/Occipital lobe							
Fusiform Gyrus	Left	-28	-47	-18	8.43	<0.00000001	595
Inferior Temporal Gyrus/Middle Temporal Gyrus	Left	-43	-56	-12	7.62	0.00000001	724
Inferior Temporal Gyrus/Middle Temporal Gyrus	Right	41	-47	3	7.26	0.00000002	1,895
Occipital Gyri	Right	41	-77	-3	7.24	0.00000002	404
Middle Temporal Gyrus/Occipital Gyri	Left	-37	-74	18	6.66	0.00000011	1,128
Cuneus	Left	-10	-68	12	6.38	0.00000025	479
Limbic/Sublobar regions							
Substantia Nigra	Right/Left	-4	-23	-21	8.36	<0.00000001	823
Parahippocampal Gyrus/Thalamus	Right	8	-35	3	7.79	<0.00000001	478
Thalamus	Right/Left	-1	-17	6	7.78	<0.00000001	1,017
Posterior Cingulate Gyrus	Left	-16	-53	12	7.65	0.00000001	570
Middle Cingulate Gyrus	Right/Left	-4	7	33	6.81	0.00000007	701
Parahippocampal Gyrus/Thalamus	Left	-19	-38	-3	6.68	0.00000010	434
Anterior Cingulate Gyrus	Left	-4	34	27	6.16	0.00000048	504
Cerebellum							
Anterior Lobe, Culmen/Posterior Lobe, Declive	Right	32	-50	-21	9.08	<0.00000001	1,844
Anterior Lobe, Culmen/Posterior Lobe, Declive	Left	-28	-56	-21	7.96	<0.00000001	1,878
Anterior Lobe, Cerebellar Lingual	Right/Left	-1	-44	-9	7.32	0.00000002	461
Anterior Lobe, Fastigium	Left	-7	-56	-18	6.09	0.00000059	322

Note. Data shown are from the activation map for the OS > US contrast, thresholded at FDR-corrected $q < 0.001$ and a minimum cluster size of 300 mm³. Results are presented at a more stringent threshold of $q < 0.001$ to better delineate specific neuroanatomical locations of activated clusters. Within each lobe, clusters are ordered by decreasing level of significance.

^aTalairach coordinates in millimeters with origin at the anterior commissure, representing peak voxels in each cluster. x , y , z coordinates refer to right (+) to left (-), anterior (+) to posterior(-), and superior (+) to inferior(-), respectively.

^bNumber of contiguously activated voxels within a cluster.

TABLE VI. Mothers' postscan affect ratings of own and unknown infant face images

	Own infant	Unknown infant	Difference (z) ^a
Mothers' perceived ratings of infants' affect ^b			
Happy affect	8.22 ± 0.12	7.39 ± 0.21	7.39**
Sad affect	7.31 ± 0.24	6.70 ± 0.24	4.72**
Distressed affect	7.13 ± 0.25	6.53 ± 0.28	4.26**
Mothers' own affective responses to infants' affect ^c			
Happy affect	8.54 ± 0.11	6.07 ± 0.36	19.69**
Sad affect	6.97 ± 0.28	4.69 ± 0.32	13.95**
Distressed affect	6.56 ± 0.35	4.51 ± 0.31	12.59**

Note. Numbers shown ($M \pm SE$) are mothers' self-reported ratings of affect provided on a Likert scale of 1 to 9. For each given affect, 1 represented "not at all," 5 represented "somewhat," and 9 represented "very."

^az-Statistic comparing own and unknown infant faces for each given affect within the final mixed-effects linear regression model including a subject-level random intercept.

^bMothers' ratings of how they perceived the infant to be feeling in the image. For happy faces, mothers were asked, "how happy do you think the baby was feeling?" For sad faces, mothers were asked to respond to both, "how sad do you think the baby was feeling?" and, "how distressed do you think the baby was feeling?"

^cMothers' ratings of their own affective responses to viewing the infant face image. For happy faces, mothers were asked, "how happy did this picture make you feel?" For sad faces, mothers were asked both, "how sad did this picture make you feel?" and, "how distressed did this picture make you feel?"

** $P < 0.001$.

of addiction [Buisman-Pijlman et al., 2014; Kim et al., 2016]. In this case, the same neurobiological mechanisms that increase the mother's susceptibility to addiction may also undermine her reward response to her infant and may have contributed to the pattern of findings reported here. These hypotheses should be examined and substantiated in future longitudinal research.

Previously, the only other fMRI study of mothers with addictions reported a general pattern of reduced neural responsiveness to unknown infant face and cry stimuli.

Using unknown faces and cries, this prior study observed reduced activations throughout prefrontal, limbic, and occipital regions for happy faces and similarly reduced prefrontal, limbic, posterior parietal, and occipital activations, including the IPL and STG, for sad faces and cries [Landi et al., 2011]. Here, we have compared mothers' neural responsiveness to own and unknown infant faces, documenting markedly reduced activations precisely in key OT- and DA-regions in response to happy faces of own infants, along with reduced activations in a small

TABLE VII. Mixed-effects regression models for mothers' postscan affect ratings

Mothers' affective responses to infants' affect ^c	Wald ^a	Infant affect effect ^b	Identity effect	Infant affect ^b × Identity		
	χ^2 ($df = 3$)	Coefficient ^d (95% CI)	Coefficient ^d (95% CI)	Coefficient ^{d,e} (95% CI)	Simple slope own infant	Simple slope unknown infant
Happy affect	664.63**	0.61** (0.51 to 0.70)	4.64** (3.25 to 6.03)	-0.33** (-0.50 to -0.16)	0.28** (0.13 to 0.42)	0.61** (0.51 to 0.70)
Sad affect	664.53**	0.62** (0.52 to 0.71)	0.10 (-0.87 to 1.08)	0.23** (0.10 to 0.37)	0.85** (0.74 to 0.96)	0.62** (0.52 to 0.71)
Distressed affect	596.22**	0.56** (0.47 to 0.65)	-0.27 (-1.18 to 0.64)	0.27** (0.14 to 0.39)	0.82** (0.72 to 0.93)	0.56** (0.47 to 0.65)

^aWald χ^2 values are those obtained for the best-fitting mixed-effects models for the respective outcome variables.

^bMothers' perceived ratings of infants' affect. For happy faces, ratings were obtained from mothers' responses to the question, "how happy do you think the baby was feeling?" For sad faces, ratings were obtained from the questions, "how sad do you think the baby was feeling?" and, "how distressed do you think the baby was feeling?"

^cMothers' own affective response to infant face images. For happy faces, ratings were obtained from mothers' responses to the question, "how happy did this picture make you feel?" For sad faces, ratings were obtained from the questions, "how sad did this picture make you feel?" and, "how distressed did this picture make you feel?"

^dCoefficients shown are beta weights (i.e., slopes) for the main and interaction effects of infant affect and identity derived from the best-fitting multilevel mixed-effects regression models.

^eSignificance reflects differences in the strengths of associations between infant affect and maternal affective response as a function of infant identity.

** $P < 0.001$.

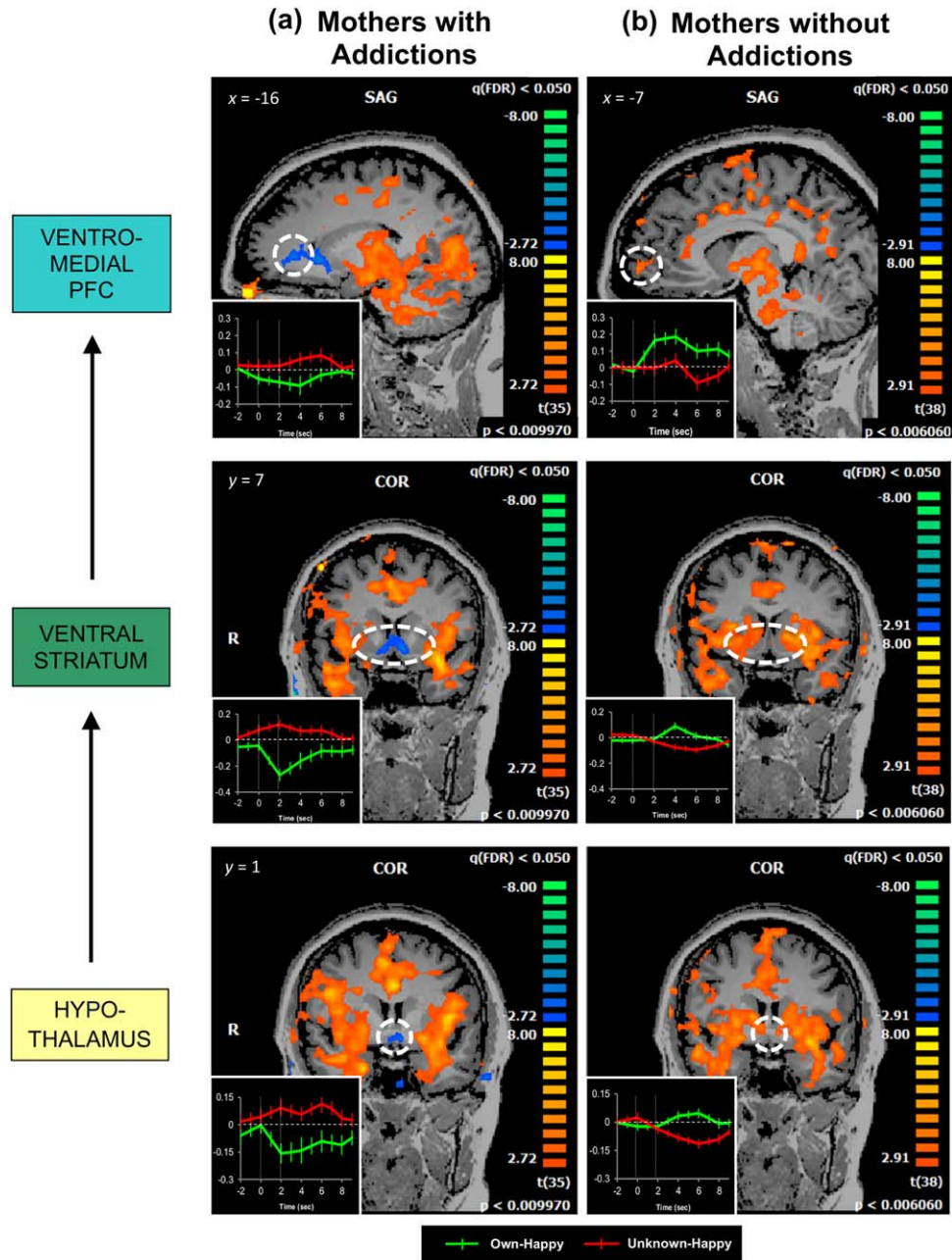


Figure 5.

Mothers with addictions (Panel A; $N = 36$) show decreased activation in the hypothalamus, VS, and vmPFC, which appear different from activations previously observed in mothers without addictions (Panel B; $N = 39$) in corresponding regions. Activation maps for mothers without addictions were generated from our previously published data [Strathearn and Kim, 2013] and are reprinted here for comparison. Both maps are thresholded at FDR-corrected $q < 0.05$. Insets of averaged hemodynamic brain responses to own-happy and unknown-happy infant faces were

obtained from cubes centered at the peak voxels of each anatomical region and extending up to ± 10 voxels per dimension, unless limited by the spatial extent of activation; y axis indicates % BOLD signal change shown with standard error bars; the two vertical lines represent the onset (0 sec) and offset (2 sec) times of the infant-face-stimulus presentation. VS = ventral striatum; vmPFC = ventromedial prefrontal cortex. [Color figure can be viewed at wileyonlinelibrary.com]

region of the IPL and STG in response to sad faces of own infants. The observed deactivations, or robust negative percent BOLD signals, seen in the OT- and DA-innervated regions are particularly noteworthy in two respects: first, they were specific to cues from the mothers' own infants; and second, they were in response to what could arguably be considered the most rewarding cues from infants—their smiling faces. Taken together, these studies indicate that the reward salience of infant cues may be generally reduced in mothers with addictions, but that this pattern may be most pronounced in the case of their own infants.

Why does reward-related disruption become more pronounced with the mother's own infant? Growing evidence suggests that neurobiological systems that underlie reward and attachment functions undergo significant alteration over the course of development via interaction with one's early environment [see Kim et al., 2016 for review]. Consistent with this, some mothers may have developed altered brain reward sensitivities over the course of their upbringing, which may have contributed to both reduced response to natural reward and increased susceptibility to addictive substances. A key contribution of our work lies in demonstrating how these altered brain reward sensitivities, which have received intense scrutiny in the broader addiction literature [Balodis and Potenza, 2015; Kalivas and Volkow, 2005; Lubman et al., 2009; May et al., 2013], may intersect with and undermine the mother's experience of attachment with her own infant, an experience which we essentially conceptualize as that of reward. Furthermore, the broader literature on addictions proposes that, once developed, substance addiction may be maintained via complex interactions between reward and stress neuro-circuitries and their dysregulation [Koob et al., 2014; Rutherford et al., 2011]. As addiction progresses, shifts may occur within the reward circuitry, which may promote addictive behaviors aimed at alleviating stress and discomfort experienced during periods of abstinence [Koob and Volkow, 2010; Koob et al., 2014]. In the face of such shifts, attachment cues (i.e., cues from one's own infant) and the demands for care they signify may no longer be perceived as rewarding but instead evoke stress in mothers with addictions [Rutherford et al., 2011; Suchman et al., 2010]. The negative percent BOLD signals observed in our study specifically for the happy faces of own infants, as well as the affective ratings that were observed to be less 'in-sync' with own infant's happy faces, may be reflections of such dysregulation. Rather than providing a sense of reward and facilitating a mother's approach behavior toward her infant, infant signals may potentially evoke stress and/or intensify cravings for addictive substances that have previously provided mothers with relief from stress. This may be further compounded by heightened stress that these mothers encounter in their roles as mothers, exacerbated by feelings of shame and guilt associated with the perceived repercussions of their addictions on their behavior and competence as mothers. In this manner, in the case of

maternal substance addiction, both substance use and disrupted maternal behavior may form a self-perpetuating feedback loop sustained by dysregulated reward and stress systems.

While the present study focused on reward-system-related dysregulation, it should be noted that stress-related dysregulation is as central to maternal addiction as reward-related dysregulation [Rutherford et al., 2011]. In our sample, sad faces of the mothers' own infants did not yield significant activations or deactivations in key OT- and DA-innervated brain regions, including the hypothalamus, VS, and mPFC. This is consistent with prior research, including our own [Strathearn and Kim, 2013; Strathearn et al., 2008], that similarly documented no activations of these regions in mothers without addictions in response to sad faces of their own infants, although a few studies have observed activations [e.g., Barrett et al., 2012]. While the lack of a control group precludes more conclusive inferences as to whether the absence of responses seen in these regions in mothers with addictions represents deviations from those observed in mothers without addictions, our data are consistent with the notion of the co-optation of the reward circuitry discussed above, which appears to uniquely perturb the processing of happy faces as opposed to sad faces. Despite our findings, we acknowledge that disruptions in maternal responses to an infant's negative affective state are importantly linked to the infant's socio-emotional outcomes [Kim et al., 2014a,b] and may uniquely contribute to compromised maternal behavior seen in maternal addiction. It may be that regions that subserve social cognition/empathy—such as the IPL and STG—which were observed to be deactivated in our sample in response to sad faces, may contribute more to disrupted maternal attunement to infants' negative affective states [Noriuchi et al., 2008] than the reward-related circuitry which has been the focus of this study. This is in line with the recent data in nulliparous women documenting that happy cues of infants tap into an individual's tendency to approach motivationally salient stimuli and activate regions associated with reward, while sad cues of infants tap into an individual's tendency to withdraw from such stimuli and activate regions associated with empathy [Montoya et al., 2012]. Additional research including a control group is warranted for a fuller and more systematic understanding of the neurocircuitry involved in stress-related dysregulation.

Our findings presented here suggest a neurobiological account of why mothers with addictions may find it difficult to contend with the demands of caring for their infants. The transition to motherhood, while rewarding, can also be an inherently stressful period. It is the enhanced perceived appetitive value of infant cues, coupled with the sense of reward and pleasure experienced by the mother, that often help to sustain a mother's attention and responsiveness to her infant during a critical developmental period. When the functions of the OT- and

DA-innervated maternal circuitry go awry, as the data has suggested here in the case of substance addictions, mothers may be compromised in their abilities to care for their infants, and the risk for abuse and neglect may rise.

Several limitations of the study should be recognized. First, we did not include a matched control group of mothers without addictions and were therefore not able to directly examine between-group differences. However, comparisons with the hypothalamic and mesocorticolimbic activations shown by mothers without addictions in previous studies, both from our group [Strathearn and Kim, 2013; Strathearn et al., 2009] and others [Barrett and Fleming, 2011; Noriuchi et al., 2008; Swain et al., 2014], suggest that the observed deactivations are noteworthy abnormalities that may be characteristic of this group. At the same time, without a direct comparison with a control group, we lack information as to whether the size of this effect would translate to a significant group difference. This remains a critical area for future research. Future studies should also examine in further detail differential patterns of (de)activations in the neurocircuitries involved in social cognition/empathy in mothers with and without addictions. Second, our sample showed variability in substance-use characteristics, including the duration and extent of substance use, as well as specific classes of substances used. Our study focused on examining maternal brain responses in the context of a general process of substance addiction, and our small sample size precluded the investigation of potential effects specifically associated with individual substances or substance-use chronicity. Given substantial preclinical and human data underscoring the role of altered reward sensitivities [Balodis and Potenza, 2015; Kalivas and Volkow, 2005], particularly the diminished salience of natural rewards [Koob and Volkow, 2010; Lubman et al., 2009; May et al., 2013], in the process of addiction, we anticipate that abnormalities reported here may be represented to a greater or lesser degree across a range of substances. However, the specific nature of pre-existing OT- and DA-related dysregulations in mothers may have led to differential susceptibility to distinct classes of substances, which, in turn, may have produced unique patterns of neuroadaptations, including those affecting the maternal circuitry, over the course of repeated substance use [Koob and Volkow, 2010]. In future studies with larger samples, it would be of interest to investigate unique and shared effects of individual substances as well as effects associated with the severity and chronicity of substance use. Third, the present study does not examine which aspects of this sample—addiction severity, associated sociodemographic characteristics (e.g., low SES), attachment disturbance, or unresolved trauma prevalent in this population—may account for the findings reported here. Although these factors often co-occur and it is important to document the features associated with this constellation of maternal characteristics, it would be of interest to tease apart associations and interactions

amongst these factors. Fourth, we did not collect systematic information on co-occurring psychiatric disorders. Further studies are warranted to investigate and clarify possible contributions of co-occurring disorders to the findings reported here. Fifth, we did not directly measure the quality of infant-directed maternal behavior and hence acknowledge that the association proposed here between compromised reward-related maternal brain response and disrupted maternal care is only speculative. A larger study with concurrent brain and behavioral measures is necessary to further corroborate this link. In a sufficiently large sample, it would be fruitful to examine whether compromised DA- and OT-related activations relate to aberrant behavioral characteristics in mothers. Finally, additional limitations include a small sample size as well as variability seen in maternal age (27.8 ± 5.6 years), infant age (5.0 ± 2.9 months at the time face images were recorded), and the time elapsed since delivery (6.0 ± 3.4 months at the time of the scan). The maternal brain is understood to undergo structural and functional changes over the course of the postpartum period [Kim et al., 2010, 2016a; Swain et al., 2007] in interaction with the amount of exposure and experience the mother has with her infant. While there may have been developmental variability between younger and older infants (e.g., older infants may have been more expressive in their facial affect), all own and unknown infant face images were matched on infant age and affect intensity, allowing us to reasonably speculate that differences observed in maternal brain responses to own and unknown infant faces were likely a function of infant identity. Furthermore, while maternal age and the amount of maternal contact with the infant may have added to possible interindividual variations in maternal neurobiology among our participants, our findings of striking deactivations in key OT- and DA-innervated brain regions were only seen in response to happy, but not sad, faces of the mothers' own infants. We believe that this corroborates our understanding that findings observed here in mothers with addictions are less likely to be a function of maternal age or postpartum exposure, but can reasonably be interpreted as a reflection of reward-related dysregulations manifesting specifically in reward-related attachment contexts. However, accounting for the role of the amount of maternal exposure, contact, and experience with the infant is critical in the study of maternal postpartum neuroadaptation and would be important to address in future research relating to mothers with addictions.

The present study marks one of the first attempts to delineate neurobiological correlates of disrupted mothering in mothers with addictions. The data suggest that mothers with substance addictions, even during intermittent periods of sobriety, demonstrate markedly reduced response to naturally rewarding cues from their infants. The deactivations observed here may help to explain the link between maternal substance use and impaired maternal caregiving. Our findings point to the mother–infant

relationship as an important element and context for intervention for mothers with addictions, who are often treated in isolation from their infants. Understanding the neurobiological relationship between substance addictions and impaired maternal responses may facilitate earlier and more refined interventions to help support mothers with substance addictions and the infants in their care.

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