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Cocaine addiction in mothers

Potential effects on maternal care and infant development

Lane Strathearn[1,2] and Linda C. Mayes[3]

[1]The Meyer Center for Developmental Pediatrics, Department of Pediatrics, Baylor College of Medicine/Texas Children's Hospital, Houston, Texas, USA. [2]Human Neuroimaging Laboratory, Department of Neuroscience, Baylor College of Medicine, Houston, Texas, USA. [3]Child Study Center, Yale University, New Haven, Connecticut, USA

Address for correspondence: Lane Strathearn, The Meyer Center for Developmental Pediatrics, 6621 Fannin St., CC 1530, Houston TX 77030-2399. Voice: 832-822-3425; fax: 832-825-3399. lanes@bcm.edu

Maternal cocaine addiction is a significant public health issue particularly affecting children, with high rates of reported abuse, neglect, and foster care placement. This review examines both preclinical and clinical evidence for how cocaine abuse may affect maternal care and infant development, exploring brain, behavioral, and neuroendocrine mechanisms. There is evidence that cocaine affects infant development both directly, via *in utero* exposure, and indirectly via alterations in maternal care. Two neural systems known to play an important role in both maternal care and cocaine addiction are the oxytocin and dopamine systems, mediating social and reward-related behaviors and stress reactivity. These same neural mechanisms may also be involved in the infant's development of vulnerability to addiction. Understanding the neuroendocrine pathways involved in maternal behavior and addiction may help facilitate earlier, more effective interventions to help substance-abusing mothers provide adequate care for their infant and perhaps prevent the intergenerational transmission of risk.

Keywords: addiction; cocaine; maternal; dopamine; oxytocin; mother–child bonding; stress

For most mothers, interacting and engaging with one's own infant is a rewarding and pleasurable experience that promotes mother–infant attachment, ensures optimal care for the developing infant, and motivates maternal behavior even in the face of extreme fatigue and competing needs for attention.[1,2] However, animal and human research suggests that mothers who are addicted to substances, particularly cocaine, even when not actively using the drug, may be less able to respond appropriately to their infant's cues, finding these interactions less intrinsically rewarding or more stress invoking.[3,4] This situation may put the infant or child at risk for neglect or abuse.

Cocaine abuse continues to be a significant public health issue in the United States, with 1 million first-time users estimated during 2004. Most significantly, almost 90% of drug-abusing women are of reproductive age, with an estimated 4.6 million female users of cocaine in the United States and 750,000 drug-exposed births annually.[5] This information has long-lasting implications for families, their children, and society, which bears much of the cost for future educational and therapeutic services.

The purpose of this review article is to examine the potential effect of cocaine addiction on maternal care and infant development, exploring brain, behavioral, and neuroendocrine mechanisms (Fig. 1). We focus especially on women with active cocaine dependence because (1) cocaine addiction co-opts neural circuitry that has recently been shown to be key to early parenting, that is, dopaminergically regulated mesocorticolimbic and nigrostriatal brain pathways[6,7]; (2) cocaine abuse is highly correlated with maternal neglect of offspring and poorer maternal–infant interactions in both human and animal models[3,8–10]; and (3) parallel studies of cocaine exposure in the parturient rodent model indicates that cocaine may inhibit both central and peripheral oxytocin (OT) production,[2,11,12] altering maternal sensitivity to offspring's cries, olfactory cues, tactile stimulation, and activity patterns such that mothers are more neglectful of their offspring and more reactive to stress. In particular, these

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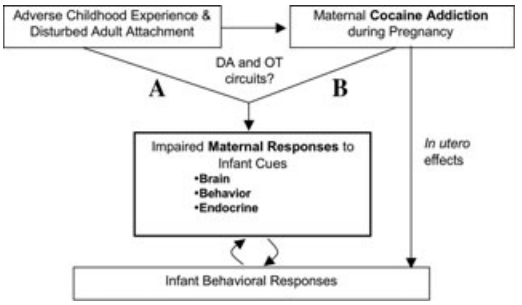

Figure 1. Proposed factors influencing maternal responses and infant development. DA, dopamine; OT, oxytocin.

preclinical studies indicate basic mechanisms by which cocaine abuse may disrupt the earliest and most fundamental aspects of parenting behavior.

In addition, we aim to explore how the mothers' own adverse childhood experience may predispose to addiction behaviors and interact with cocaine exposure to affect maternal responses to infant cues (Fig. 1). Studies have shown a strong graded relationship between stressful or traumatic childhood experiences and subsequent illicit drug use,[13] as well as impaired parenting practices.[14] The lack of responsive, nurturant caregiving in early childhood—which is associated with disturbed patterns of adult attachment—may influence the development of both dopaminergic and OTergic brain systems via epigenetic mechanisms,[15–17] thus making individuals more vulnerable to addiction and adverse parenting responses toward their own infants.

There are also findings from both human and preclinical models that suggest prenatal exposure to cocaine disrupts offspring behavior, as expressed in poor-state lability, decreased social behavior, abnormal activity patterns, and irritability/aggression.[18–22] These behavioral disruptions may, in turn, affect the parenting behaviors of both cocaine-using and non–cocaine-using mothers. Together these observations suggest that, in pregnant women, cocaine abuse impairs parenting both by impairing maternal sensitivity to salient infant cues and by distorting infant cueing behavior.

Although information about the neural circuitry of parenting in humans is still sparse, the few studies available to date suggest concordance with a growing body of work in preclinical rodent models. For example, recent functional neuroimaging studies with a normative sample of first-time mothers responding to visual and auditory infant cues from their own and another baby suggest convergence with preclinical data regarding limbic–hypothalamic–midbrain brain circuits including the amygdala, insula, hypothalamus, ventral tegmental area, striatum, and medial prefrontal cortex.[1,23] Whether these circuits are activated in response to infant cues when parents have abused drugs that affect similar circuitry has to our knowledge never before been studied in humans.

The hope is that understanding the interaction between these factors in cocaine-exposed mothers will inform us on how to most effectively intervene, at primary through tertiary prevention levels. For example, cocaine-exposed mothers with different adult attachment patterns may respond differently to their infants' cues, activating different neural systems, which may require different forms of behavioral or pharmacological intervention. Understanding how maternal responses to infant cues are altered in particular groups may help us to formulate more effective parent–child interaction therapies or home visitation programs, assisting new mothers to recognize and appropriately respond to their infants' cues.[24,25] It may also ultimately lead to improved pharmacotherapy for cocaine-addicted mothers, targeting specific brain regions or neuroendocrine systems important in addiction, such as OT and the amygdala, the ventral striatum, or insula.[26,27]

Understanding the neuroendocrine mechanisms that are critical to parental investment in infants will facilitate more refined and presumably earlier interventions to help substance abusing parents invest in and provide sufficient and necessary care for their infant despite the earlier compromises they may bring to their parenting role. Earlier and more sustained parental care of infants may also diminish the intergenerational effect of substance abuse and neglect on later risk for addiction and related psychopathology among adolescents and young adults, especially those at risk for initiation of drug use and addiction.

Cocaine addiction, maternal care, and infant development

Accumulating evidence from both preclinical and clinical laboratories indicates that early failures in

parental care have a compromising and enduring influence on the stress-regulatory capacities of offspring and on the parenting abilities of those offspring as adults, such that offspring are more vulnerable to stress and hence to a range of psychopathologies, including substance abuse. Further, recent work in both preclinical and clinical settings is delineating a specific neural circuitry that is key to early parenting and attachment to offspring. Substance abuse in general, and cocaine abuse specifically, has long been recognized to be associated with many factors that may compromise an adult's ability to parent, including higher rates of serious psychopathology, such as depression and disorders of attachment, related in part to abuse and neglect experiences in childhood. The mechanism of action for cocaine involves similar dopaminergically regulated reward systems in the brain that overlap with those identified as key to the initiation of parenting behaviors in adults (e.g., amygdala, hippocampus, striatum). These same systems are key to reward and stress/fear regulatory systems, the balance between which is considered critical in models of drug abuse and addiction.[28–30] Thus, it may be that among the many factors affecting a substance-abusing adult's ability to parent, one may be the disruption or co-opting of basic neural circuitry key to infant attachment by drugs of abuse. Although there has been considerable work on the influence of exposure to cocaine during fetal development on long-term child outcome,[22,31–33] there has been far less systematic work on the effect of cocaine on adults' parenting ability. Preclinical studies in models of cocaine abuse suggest that cocaine disrupts basic parenting behaviors, and thus at least a part of the effect of cocaine abuse on child outcome is mediated through disrupted parental care. In the next sections we review work on the effect of parenting behavior on infant development, the effect of substance abuse on parenting behaviors, from both the preclinical and clinical/human perspective, and the emerging work on the neural circuitry of parenting and attachment.

Influence of maternal care on infant development

There has been considerable work characterizing key aspects of maternal behavior in animal models and linking individual variation in these behaviors to offspring development. In general, these findings suggest that maternal behavior in the days and weeks following birth serves to "program" the subsequent maternal behavior of the adult offspring as well as establishing the pups' level of hypothalamic–pituitary–adrenal responsiveness to stress.[34–36] This complex programming also appears to influence aspects of learning and memory. Further, many of the brain regions implicated in these experimental interventions are the same as those identified in the knockout gene and lesioning studies (see the following sections).

Repeated handling of pups in conjunction with brief maternal separations induces more licking and grooming by the rat dams. As adults, the offspring of mothers that exhibited more licking and grooming of pups during the first 10 days of life showed reduced plasma adrenocorticotropic hormone and corticosterone responses to acute restraint stress, as well as increased hippocampal glucocorticoid receptor mRNA expression, and decreased levels of hypothalamic corticotropin-releasing factor (CRF) mRNA.[37] Subsequent studies by the same group of investigators have shown that the offspring of these high-licking and - grooming mothers also show reduced acoustic startle responses, as well as enhanced spatial learning and memory.[38,39] In contrast, repeated handling of pups in conjunction with prolonged maternal separations induces deranged maternal behavior, including a reduction in licking and grooming by the rat dams and reduced maternal aggression.[38] Similarly, the adult offspring show increased neuroendocrine responses to acute restraint stress and air puff startle, including elevated levels of paraventricular nucleus (PVN) CRF mRNA and elevated plasma levels of adrenocorticotropic hormone and corticosterone.[38,40] These animals also show an increased acoustic startle response, as well as enhanced anxiety or fearfulness to novel environments.[38]

Early adoption (3–6 h after birth) has been found to be associated with increased maternal licking behavior[41] and to prevent the prolonged stress-induced secretion of corticosterone evident in early separated offspring that were returned to the nest with their biological mother. Similarly, as adults the early-adopted pups demonstrated lower novelty-induced locomotion and improved recognition performance in a *Y* maze compared to the early separated offspring. However, later adoption at either

5 or 10 days resulted in a prolonged stress-induced corticosterone secretion, increased the locomotor response to novelty, and disrupted cognitive performance in the adult offspring. This finding has been further supported by work on maternal separation of mice, which suggests a role for nerve growth factor to mediate the effects of external manipulations on the developing brain.[42] It also has been shown that the amount of licking and grooming that a female pup receives in infancy is associated with how much licking and grooming she provides to her offspring as a new mother.[35] Low-licking and -grooming dams could be transformed into high-licking and -grooming dams by handling. These changes are also passed on to the next generation—that is, that the female offspring of the low-licking and -grooming dams became high-licking and - grooming mothers if they were either cross-fostered by high-licking and -grooming dams or if they were handled. The converse was also true, namely, that the female offspring of the high-licking and -grooming dams became low-licking and - grooming mothers if they were cross-fostered by low-licking and -grooming dams. These naturally occurring variations in licking, grooming, and arched-back nursing have also been associated with the development of individual differences in behavioral responses to novelty in adult offspring. Adult offspring of the low-licking, -grooming, and -arched back nursing mothers show increased startle responses, decreased open-field exploration, and longer latencies to eat food provided in a novel environment.[35]

Furthermore, Francis *et al.*[35] demonstrated that the influence of maternal care on the development of stress reactivity was mediated by changes in gene expression in regions of the brain that regulate stress responses. For example, adult offspring of high-licking, -grooming, and -arched back nursing dams showed increased hippocampal glucocorticoid receptor mRNA expression and increased expression of *N*-methyl-D-aspartate receptor subunit and brain-derived neurotrophic factor mRNA, as well as increased cholinergic innervation of the hippocampus.[35] In the amygdala there are increased central benzodiazepine receptor levels in the central and basolateral nuclei. In the PVN there is decreased CRF mRNA. These adult pups also show several changes in receptor density in the locus ceruleus, including increased $\alpha 2$ adrenoreceptors, reduced GABA A receptors, and decreased CRF receptors.[43,44] In another recent study, OT receptor binding levels were examined in brain sections from high- and low-licking, -grooming, and -arched back nursing animals killed either as nonlactating virgins or during lactation.[45] Examination of the medial preoptic area (MPOA) and the intermediate and ventral regions of the lateral septum disclosed that OT receptor levels were significantly higher in lactating females than in nonlactating females. Lactation-induced increases in OT receptor binding were greater in high- than in low-licking, -grooming, and -arched back nursing females in the bed nucleus of the stria terminalis (BNST) and ventral region of the septum. Francis *et al.*[45] suggest, therefore, that variations in maternal behavior in the rat may be reflected in, and influenced by, differences in OT receptor levels in the brain.

In sum, the nature of early caregiving experiences can have enduring consequences on individual differences in subsequent maternal behavior, anxiety regulation, and patterns of stress response through specific neuropharmacological mechanisms.[15] Data from animal studies indicate that the interval surrounding birth is a critical period in the life of the offspring that probably has enduring neurobiological and behavioral consequences.

Effect of cocaine addiction on maternal care and infant development: preclinical models

Reports generally agree that all varieties of cocaine exposure (acute, intermittent, and chronic) disrupt some aspects of maternal behavior, the extent dependent on dose and time of testing and exposure.[9,10,46–48] Cocaine has been proposed as mediating maternal behavior/aggression in the early postpartum period in the rat through its effects on the OT system.[49] Only one human study involving mothers who used cocaine during gestation has been published, showing reduced plasma OT levels in cocaine-abusing mothers.[49] The presence of OT seems critical to initiating the onset of maternal behavior in several mammalian species, including the rat and sheep.[50–55] Recently a study by Johns *et al.*[8] examined maternal behavior after treatment with chronic or intermittent cocaine treatment by using cross-fostering of prenatally exposed and non–drug-exposed offspring. Although both drug treatment regimens disrupted maternal behavior toward

all offspring, chronic gestational treatment had the greatest influence on early maternal behavior in the dams regardless of the pups' prenatal condition. Interestingly, however, all dams, both cocaine treated and control subjects including untreated dams, displayed differential maternal behavior to the chronic cocaine-exposed pups. Although the strength of this effect varied depending on the behavior examined, differences were clearly apparent. Differences suggest that rat dams, regardless of treatment condition, detected and responded to cocaine-exposed pups differently. Abnormal behavioral or physical attributes of cocaine-exposed offspring may thus make them more vulnerable to neglect or perhaps unable to elicit normal caretaking, and drug exposure may compromise the adult's ability to care for the pup, especially one with abnormal behavioral or physical characteristics.

Effect of cocaine addiction on maternal care and infant development: human models

Maternal substance abuse, more than most other psychiatric or social problems (except poverty) is the most common factor involved when children are referred to the child welfare system because of suspected parental abuse or neglect.[56,57] Observations of mother–child interactions involving mothers with histories of abuse and/or dependence on illicit drugs (e.g., heroin and cocaine) have indicated poor sensitivity, unresponsiveness to children's emotional cues, and heightened physical provocation and intrusiveness.[58,59] Studies reporting drug-abusing mothers' views about parenting have indicated a lack of understanding about basic child development issues and ambivalent feelings about having and keeping children.[4,60] As a group, drug-dependent mothers fare worse than non–drug-dependent mothers on a wide range of parenting indices and more frequently lose their children to foster care than non–drug-dependent mothers.[61,62] Self-reported behaviors among drug-dependent mothers have also revealed harsh, threatening, overly involved, authoritarian parenting styles juxtaposed with permissiveness, neglect, poor involvement, low tolerance of child demands and misbehavior, and parent–child role reversals.[4,63,64]

To date, fewer than 20 studies have examined the interactions between cocaine-using mothers and their infants and young children. The findings are varied in part because of variations in sample size (from five to 364 mother–child pairs across the studies), use of a comparison or control group, inclusion of the average amount of maternal cocaine use in the analyses and taking into account postnatal changes in amount of use, place of the assessment and age of the child, and the interactive behaviors assessed. With these caveats in mind, findings across the available studies point to a general disengagement, lack of pleasure in the interaction or attention to the infant, and poor attention to the infant's cues. Cocaine-using mothers, whose children were aged 6 months or younger, were found to spend more time passively looking at their infant but were more disengaged from the infant in terms of responding to the infant's cues.[65] They were lacking in social initiative and resourcefulness,[58] showed less flexibility, engagement, and higher noncontingency in interaction,[66] had shorter feeding episodes, and were found less attentive to interaction. Nonattentiveness and tendency to interrupt the interaction also increased toward the 6-month point.[3] With young infants, mothers who relapsed to cocaine use after the birth of the child had more negative interaction behavior as a whole than those who remained drug free after their prenatal use.[67] Infants younger than 6 months of cocaine-using mothers showed longer periods drowsy, asleep, or distressed as newborns[65]; showed less enjoyment during play; and continued to show negative expressions and slow recovery after short interruption of interaction,[68] higher stress to novelty,[66] and less readiness to interact with the mother at 6 months compared with 3 months of age.[3] In their dyadic interactions, there was a notable lack of enthusiasm and mutual enjoyment,[58] less engagement in dyadic interactions,[3] higher dyadic conflict,[66] and less mutual arousal within the dyad.[58]

Cocaine-using mothers of children aged 6 months to 3 years continued to show less enjoyment and pleasure in interaction,[58] showed less emotional engagement,[69] were more intrusive and hostile, showed lower self confidence, and tended to give commands or instructions not appropriate for the child's developmental age.[21] Maternal interaction was found to be most impaired with mothers continuing cocaine use during 3-year postnatal follow-up than with mothers who were drug free.[21] The children of these mothers more often

ignored their mothers' departures,[18] cried less during separation–reunion and showed more avoidance in reunion,[19] showed either lower[69] or higher[22] negative affect in response to stress, less emotional engagement in follow-up play after short interruption,[69] and diminished ability to persist in task.[21]

A few studies have explored issues of attachment between cocaine-using mothers and their children. Sensitive maternal behavior in interaction has been considered the crucial component leading to secure attachment in the child, although adult attachment patterns have not been specifically measured. Insecure attachment is a potent risk factor for a child's later socioaffective and behavioral maladaptation.[70,71] Disorganized attachment pattern is considered most worrisome, because it appears to be associated with higher stress, aggression, externalizing problem behavior, and psychiatric symptomatology in later childhood.[72–74] Findings relating maternal cocaine-use status and child attachment organization have varied. Three studies report insecure and especially disorganized attachment pattern as clearly more prevalent among cocaine-exposed children than in normative samples, measured at 15–18 months of child's age.[75,76]

Thus, although not entirely consistent, what seems clear from these few studies is that the combination of maternal depression, early abuse and neglect, unstable early and current attachments, and continued substance use come together to markedly impair an adult's ability to care for her infant. In turn, the infant and young children may have a biologically conveyed vulnerability to becoming easily overaroused, behaviorally disorganized or withdrawn, more impulsive, and less attentive[32,77,78]—a behavioral profile that would be challenging for the most competent of caregivers and surely stressful for a mother who is herself more fragile and easily disorganized.

Neural circuitry of maternal behavior: oxytocin and dopamine systems

Although the central nervous system events that accompany parental care in humans are largely unknown, it is likely that there is a substantial degree of conservation across mammalian species.[79] Classical lesion studies carried out in rodent model systems (rats, mice, and voles) have implicated the MPOA of the hypothalamus, the ventral part of the BNST, and the lateral septum as regions pivotal for regulation of pup-directed maternal behavior.[80–82] Estrogen, prolactin, and OT can act on the MPOA to promote maternal behavior.[83–85] OT is synthesized primarily in the magnocellular secretory neurons of two hypothalamic nuclei, the PVN and the supraoptic nucleus. The PVN and supraoptic nucleus project to the posterior pituitary gland. Pituitary release of OT into the bloodstream results in milk ejection during nursing and uterine contraction during labor. OT fibers, which arise from parvocellular neurons in the PVN, project to areas of the limbic system, including the amygdala, BNST, and lateral septum.[86]

There are several reports that OT facilitates maternal behavior (sensitization) in estrogen-primed nulliparous female rats. Intracerebroventricular administration of OT in virgin female rats induces full maternal behavior within minutes.[87] Conversely, central injection of an OT antagonist, or a lesion of OT-producing cells in the PVN, suppresses the onset of maternal behavior in postpartum female rats.[53,54] However, these manipulations have no effect on maternal behavior in animals permitted several days of postpartum mothering. This result suggests that OT plays an important role in facilitating the onset, rather than the maintenance, of maternal attachment to pups.[88] Brain areas that may inhibit maternal behavior in rats have been also identified.[89] For example, the vomeronasal and primary olfactory systems have been identified as brain regions that mediate avoidance behavior in virgin female rats exposed to the odor cues of pups.[90]

Ascending dopaminergic and noradrenergic systems associated with reward pathways also appear to play a crucial role in facilitating maternal behavior.[91] For example, rat dams given microinfusions of the neurotoxin 6-hydroxydopamine in the ventral tegmental area to destroy catecholaminergic neurons during lactation showed a persistent deficit in pup retrieval but were not impaired with respect to nursing, nest building, or maternal aggression.[92] There also appears to be an important interaction between dopaminergic neurons and OT pathways.[93] Specifically, pup retrieval and assuming a nursing posture over pups were blocked in parturient dams by infusions of an OT antagonist into either the ventral tegmental area or MPOA.[94]

In summary, the initiation and maintenance of maternal behavior involves a specific neural circuit based in reward, affiliation, and stress response

systems (e.g., striatum, amygdala). With pregnancy or with repeated exposure to pups, structural and molecular changes occur, most of which are not yet completely understood, in specific limbic, hypothalamic, and midbrain regions that reflect, in part, an adaptation to the various homeostatic demands associated with maternal care. Many of the same cell groups implicated in the control of maternal behavior have been implicated in the control of ingestive (eating and drinking) behavior, thermoregulatory (energy homeostasis), and social (defensive and sexual) behaviors, as well as general exploratory or foraging behaviors (with locomotor and orienting components) that are required for obtaining any particular goal object. Many of these same structures are also intimately involved in stress response. Swanson has conceptualized this set of limbic, hypothalamic, and midbrain nuclei as being the "behavioral control column" that is voluntarily regulated by cerebral projections.[95] Consistent with this formulation, it is readily apparent that motherhood presents a major homeostatic challenge within each of these behavioral domains.

Neural circuitry of maternal behavior: human studies using functional brain imaging

Functional brain imaging studies examining brain responses to emotionally charged infant stimuli in healthy parents are just emerging to provide data regarding the neural substrates of normal parenting.[96] Lorberbaum *et al.*[97] provided the first work in this area using baby cries as stimuli and presenting these stimuli to mothers in a functional imaging paradigm. Building on the thalamocingulate theory of maternal behavior in animals developed by MacLean (1990), Lorberbaum predicted that baby cries would selectively activate cingulate, thalamus, medial, and orbitofrontal prefrontal cortex. Mothers who were less than 3.5 months postpartum and were exposed to 30 s of a standard baby cry versus white-noise stimuli[97] showed increased activity in anterior cingulate and right medial prefrontal cortex. In the follow-up study of brain activity in breast-feeding first-time mothers 4–8 weeks postpartum listening to standard baby cry compared with intensity- and pattern-matched white noise,[97] all the regions activated were those known to be important for rodent maternal behavior, including midbrain, hypothalamus, striatum, and septal regions.[80,98] Other groups are now finding similar patterns of activation in thalamocortical-basal ganglia–based circuits in mothers responding to infant cries.[99–101]

In addition to baby cry stimuli, several groups, including our own, are using baby visual stimuli.[2,100–109] We demonstrated that dopaminergic reward pathways are activated when mothers view pictures of their own baby's happy, but not sad, faces.[1] Hypothesizing that reward and OT circuits, which are important for aspects of romantic love, might also be involved in maternal love, and using photographs of familiar and unfamiliar infants, Bartels and Zeki[105] reported activations in anterior cingulate, insula, basal ganglia (striatum), and midbrain (periaqueductal gray) regions potentially mediating the emotionally rewarding aspects of maternal behavior, and a decrease in activity in areas important for negative emotions, avoidance behavior, and social assessment. This finding may suggest a push–pull mechanism for maternal behavior in which child stimuli activate reward and shut down avoidance circuits.[105] A similar study comparing parents and nonparents responding to infant pictures reported bilateral orbitofrontal cortex activations that were correlated with ratings of pleasant mood.[107] Another study, using video of infant images, reported activations in amygdala, temporal pole, and occipital regions.[108]

Thus, it appears that there may be significant differences between parental responses to baby signals across sensory modalities. Preliminary pilot data suggest that these maternal brain responses to infant face cues may differ significantly in mothers with chronic cocaine exposure, particularly within the prefrontal cortex.[110]

Conclusion

Understanding basic neural mechanisms for failure in early parenting in substance-abusing adults facilitates more refined and presumably earlier interventions during pregnancy and in the immediate postpartum period to help substance-abusing parents invest in and provide sufficient and necessary care for their infant despite the earlier compromises they may bring to their parenting role. Elucidating these neural mechanisms in humans also has implications for understanding, first, how early childhood

experience impacts an adult's ability to be a caring and empathic parent, a failure that may be perpetuated across generations, and, second, how these failures in early parental care increase the intergenerational risk especially for depression, disorders of attachment, and addiction.

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Conflicts of interest

The authors declare no conflicts of interest.

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