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Adaptations in reward-related behaviors and mesolimbic dopamine function during motherhood and the postpartum period

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Abstract

Initiation and maintenance of maternal behavior is driven by a complex interaction between the physiology of parturition and offspring stimulation, causing functional changes in maternal brain and behavior. Maternal behaviors are among the most robust and rewarding motivated behaviors. Mesolimbic dopamine (DA) system alterations during pregnancy and the postpartum enable enhanced reward-related responses to offspring stimuli. Here, we review behavioral evidence demonstrating postpartum rodents exhibit a bias towards pups and pup-related stimuli in reward-related tasks. Next, we provide an overview of normative adaptations in the mesolimbic DA system induced by parturition and the postpartum, which likely mediate shifts in offspring valence. We also discuss a causal link between dopaminergic dysfunction and disrupted maternal behaviors, which are recapitulated in postpartum depression (PPD) and relevant rodent models. In sum, mesolimbic DA system activation drives infant-seeking behavior and strengthens the mother-infant bond, potentially representing a therapeutic target for reward-related deficits in PPD.

Keywords

Maternal; postpartum; dopamine; VTA; reward; motivation; humans; rodents; postpartum depression

1. Introduction

In both humans and rodents, pregnancy and motherhood bring about a wide variety of changes in behavior as well as in brain structure, function, and connectivity, including adaptations within the brain's reward system- the mesolimbic dopamine (DA) pathway [1; 2; 3; 4]. In humans, pregnancy is associated with pronounced and long lasting structural (i.e.

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Declaration of Interest

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grey matter volume) and functional (i.e. connectivity) changes across several regions associated with reward-related and social processes [2; 5; 6; 7]. Many of these neurobehavioral modifications are also recapitulated in postpartum rodents [8; 9; 10]. Importantly, these alterations are thought to be adaptive since they prepare maternal mammals for the new role as a mother and facilitate the onset and maintenance of maternal behavior, which is fundamental to the survival of the offspring [11; 12].

The immediate onset of maternal behavior at the time of delivery is due to the hormonal changes that are characteristic of pregnancy and parturition [10; 13; 14; 15]. However, from postpartum days (PD) 4–20, the maintenance of maternal behavior is more strongly influenced by learning and the tactile and odor stimuli coming from the pups. Thus, the initiation of maternal behavior in rodents is a complex interaction, which is initially mediated by hormones and sustained by recent sensory experiences through interacting with pups [16; 17]. Interestingly, the onset of maternal behavior can be mimicked in ovariectomized virgin rodents by treating the female with hormones (e.g. estrogen, progesterone, oxytocin) normally associated with elevated maternal responsiveness at parturition and providing them with pups or in intact females via continuous presentation of pups (i.e. sensitization) [18; 19; 20; 21; 22; 23].

Hormones, such as progesterone, estradiol, prolactin and oxytocin, can exert stimulatory effects and cause functional changes across several brain regions, which together comprise the maternal brain circuit, to facilitate the rapid induction of maternal behaviors in rats, such as sniffing and licking pups, retrieving and huddling pups together, crouching over pups and nursing [24; 25; 26], by reducing the initial neophobic responses to pups commonly seen in virgin females [27; 28]. The maternal brain circuit is comprised of an output projection pathway from the medial preoptic area (mPOA) to the ventral tegmental area (VTA), which has reciprocal connections with the nucleus accumbens (NAc), and hindbrain; an input projection pathway to the mPOA directly from the medial amygdala, bed nucleus of the stria terminalis (BNST); and, indirect inputs from multiple sensory systems, especially the olfactory system [29; 30; 31; 32; 33] (see Figure 1). These brain regions are known to interact in order to mediate the expression of maternal behavior [30; 31; 32; 33]. For example, the mPOA mediates maternal pup retrieval, nursing and nest-building in postpartum rodents through a downstream projection to the VTA [30; 34], and lesions of the mPOA disrupt a variety of maternal behaviors [35; 36]. Moreover, activation of the mesolimbic DA system (i.e. reward pathway) is part of a central mechanism contributing to the reinforcing property of pups [37], and functional integrity of this system is required for the expression of maternal behavior, as pharmacological inactivation of the VTA- the origin of mesolimbic DA-disrupts nursing and pup retrieval [38].

Importantly, both the mPOA and the VTA are sensitive to hormonal effects, which can influence their function in the regulation of maternal behavior. One of these hormones is oxytocin, a neuropeptide released during parturition and lactation that is necessary for the onset of maternal behavior, mother-infant bonding, and affiliative behaviors [39; 40; 41]. Infusions of an oxytocin antagonist into the mPOA or VTA block pup retrieval and crouching (i.e. nursing posture over pups) in early postpartum rodents [42], suggesting that these maternal behaviors are mediated via oxytocinergic modulation of the mPOA and VTA.

Indeed, oxytocin neurons within the mPOA project directly to the VTA [43] and oxytocin release enhances the activity of VTA DA neurons [44]. Thus, the mesolimbic DA system is a downstream target for oxytocin regulation, and along with other components of the maternal circuit (i.e. mPOA, NAc), is implicated in the expression of rewarding aspects of maternal behavior and preference for pups [45; 46].

The mesolimbic DA system consists of a neuronal pathway in which dopaminergic neurons in the VTA project to the NAc, which is part of the ventral striatum, as well as the amygdala, and prefrontal cortex (PFC) [47; 48]. Thus, the VTA is the major source of dopaminergic innervation to major components of the mesolimbic DA system, which plays a well-established role in processing rewards and motivated behavior [49; 50], including maternal behavior [29; 32]. Indeed, activation of the mesolimbic DA system is thought to drive pup-seeking behavior and strengthen the dam-pup bond. Here we review alterations in reward-related processes in postpartum rodents, which exhibit a shift towards pup interaction and pup-stimuli. Next, we review evidence that these behavioral alterations are likely mediated by normative adaptations in the maternal mesolimbic DA system induced by parturition and the postpartum in humans and rodents. We also discuss causal evidence demonstrating that interfering with (i.e. blocking) mesolimbic DA function gives rise to disrupted maternal behaviors. Lastly, we review clinical evidence indicating mesolimbic DA dysregulation in mothers with PPD and preclinical evidence showing that similar effects are induced by environmental and/or genetic manipulations that negatively impact maternal behavior and mesolimbic DA system function, which are used to model postpartum depression (PPD).

2. Alterations in reward-related behaviors induced by motherhood: Bias towards offspring

While virgin female rats generally display avoidant or aversive reactions to pup odors, for maternal animals these represent a strongly rewarding stimulus and potent reinforcer [37; 51]. In rats, maternal behaviors including nursing/crouching, nest-building, pup retrieval and licking, develop during late pregnancy, peak at parturition and slowly decline after delivery [52]. Enhanced maternal motivation during the postpartum period is highly adaptive, since the strong drive to seek out and interact with pups shortly after birth stimulates the expression of maternal behaviors essential for the development and survival of the offspring [53]. Thus, pup interaction is one of the most highly motivating behaviors in maternal mammals. Although virgin rodents initially lack maternal behavior or display incomplete behavior, they actively care for their own pups soon after parturition, indicating that the response to pups is qualitatively different before and after giving birth [17]. Furthermore, as reviewed above, virgin animals can be rendered maternal through hormonal manipulations mimicking the changes occurring during pregnancy and the postpartum or through continuous pup exposure (i.e. sensitization) [17; 22; 23; 54; 55; 56]. Indeed, behavioral evidence suggests that postpartum rodents, as well as maternally primed virgin rodents, exhibit a bias towards pups and offspring-related stimuli in variety of reward-related tasks.

2.1 T-Maze.

The T-maze test takes place within an apparatus that is shaped like a T and is based on the innate tendency of rodents to explore their environment and obtain natural rewards with minimum effort [53; 57]. In this test, the animal is placed at the base end of the T, allowed to explore the maze and make a choice to enter the right or left arm. A reward may be placed in one arm, or different rewards may be placed in each arm. The rewarded arm can be distinguished from the non-rewarded arm by its spatial location, local cues associated with the maze itself, or by the direction in which the animal turns to approach the goal arm [57]. The T-maze can be used to study preference for different rewards, including social rewards, by allowing experimental animals to interact with a social stimulus located in one arm, while the other arm is empty or with different stimuli (social vs nonsocial) located in each arm.

T-maze tasks have been used to study maternal approach responses to pups since the 1970s. When tested in the T-maze, postpartum dams (i.e. rats, mice) retrieve more pups than sensitized virgins (i.e. rendered maternal via pup exposure) and prefer to retrieve pups over other objects [58; 59]. Compared with virgin females, rat and mice dams exhibited enhanced pup retrieval performance in the T-maze. It is worth noting that the home-cage maternal behavior of virgin animals that become maternal after daily pup exposure is comparable to that of postpartum dams [22]. Nonetheless, these 2 groups differed in their willingness to retrieve pups in the T-maze, suggesting differential maternal motivation and responsiveness within a novel environment in postpartum dams. Stern and Mackinnon investigated the contribution of hormonal factors to the observed differences in T-maze performance in sensitized virgins (via hormonal exposure or pup exposure) and postpartum dams. Postpartum dams that could not suckle due to nipple removal (i.e. thelectomy) had pup retrieval performances that were similar to control (suckling) dams and virgin females that were rendered maternal via hormonal exposure [60]. However, only a small percentage of the virgin animals rendered maternal via pup exposure retrieved pups from the T-maze. These results suggest that the hormonal factors associated with pregnancy and/or parturition, but not suckling stimulation, promote enhanced pup retrieval in the T-maze.

2.2 Operant Responding for Pup Reinforcement.

In operant conditioning tasks, animals are trained to perform an arbitrary act, such as pressing a bar or a lever, in order to obtain a reward. After pressing the lever, the animal obtains a reward and learns the contingency between lever pressing and reward delivery so that the next time it is placed in a box it is likely to press the lever again to obtain the reward [61]. Responses are reinforced, or not, according to some programmed schedules that consist of rules that govern the contingency between responses and outcomes, such as rewards or cues associated with the reward. Since operant responding can be maintained by drugs of abuse, food, and social rewards [53; 62], these type of studies have provided major insights to the understanding of brain rewarded mechanisms.

Operant tasks have been used to study the rewarding properties of pups in female rodents of varying reproductive conditions (e.g. virgin, pregnant, postpartum) by training animals to press a bar or lever. Indeed, virgin rodents, pregnant and postpartum rats can be trained to bar press for pups, and readily pick them up and retrieve them into the nest, although the

operant response rate for pups varies with reproductive and hormonal states [63; 64; 65; 66]. Postpartum rodents perform significantly more pup-reinforced lever presses than intact or ovariectomized virgins, and ovarian hormones play a critical role in the facilitation of pup-reinforced lever pressing that occurs during this period [63]. Pup-reinforced bar presses require the functional integrity of the mPOA: dams sustaining lesions of the mPOA show deficits in maternal behavior within the home cage as well as in bar-press responses for pups, as indexed by a reduction in the number of bar presses compared to sham-lesioned animals [66]. This suggests that mPOA-lesioned animals do not find pups reinforcing and therefore do not engage in instrumental behaviors necessary to obtain access to pups. Thus, the mPOA plays an important role in both stereotyped maternal responses and in instrumental responses for pup-reinforcement. In postpartum animals, amygdala lesions also produced a bar-press deficit [66], suggesting a potential role for mesolimbic DA system dysregulation in this hedonic deficit.

2.3 CPP.

Conditioned place preference (CPP) is one of the most commonly used experimental approaches to study natural and drug rewards in rodents [67; 68; 69]. CPP experiments are based on the principles of classical (Pavlovian) conditioning in which neutral environmental cues (i.e. contexts) can gain the capacity of evoking approach behaviors after being repeatedly paired with a rewarding stimulus (e.g. drugs, food, pups). Thus, the rewarding properties of a certain drug or event serve as an unconditioned stimulus (US), whereas neutral environmental cues can function as a conditioned stimulus (CS) through their association with the US, acquire motivational value, and induce approach behaviors [70]. Most CPP test apparatus consist of at least 2 compartments that are characterized by distinct visual, olfactory or tactile cues, which enables the animal to distinguish between the compartments. A standard CPP experiment involves several conditioning sessions where the animal is presented with a certain US (i.e. pups) within a distinct compartment of the apparatus. Similarly, animals also get exposed to the other compartment without the US. The environmental context paired with the US acquires motivational value through repeated association, which is then tested by letting the animal roam around freely in the whole apparatus (i.e. both contexts) in the absence of the US and using the amount of time spent in the compartment previously associated with the US as an indicator of CPP.

Fleming and colleagues were the first to compare CPP with food vs pup-interaction in rat dams and virgin females. Pup interaction produced CPP in postpartum dams, but not in virgin rats with a similar amount of pup exposure [37]. The majority of virgin rats developed a strong preference for the food-associated compartment, and this effect was reduced in postpartum dams. These results indicate that virgin and postpartum rats differ in the salience and reinforcing value attributed to environments associated with food vs pups. However, pup CPP can be induced in virgin rats by either hormonal manipulations mimicking the physiological changes occurring in the dams at the end of pregnancy and after parturition or by prolonged pup exposure [37; 56]. Importantly, pup-associated CPP requires physical interaction with pups during conditioning as well as access to pups' olfactory and somatosensory cues [56; 71].

CPP experiments have also been used to compare conditioned responses to cocaine- and pup-associated compartments at different postpartum time-points, which have identified time-dependent changes in pup-induced CPP [72; 73]. In the early postpartum period, postpartum day (PD) 8, the majority of dams showed preference for the pup-associated compartment and spent more time there [72; 73]. However, by PD 16, the majority of dams showed preference for the cocaine-associated compartment [72; 73]. These data suggest that the rewarding properties of pups during the early postpartum period are so strong that they can compete with food and drug reward, and that the preference for the pup-associated compartment is higher in the early versus late postpartum period. Thus, early postpartum dams may be in a unique state of reward responsivity in which pups are more rewarding than food and cocaine, which is consistent with a prior studies showing differential operant responses for cocaine throughout the reproductive cycle in female rodents [74] as well as differential activation of mesolimbic DA targets (i.e. PFC, amygdala) following the expression of pup-induced vs cocaine-induced CPP [75]. Moreover, these data also suggest that the rewarding value of pups decreases, at least compared to cocaine, as the postpartum period progresses. This normative decline in pup reward during the postpartum has been shown to be dependent on two factors: changes in the dynamics of mother-pup interaction due to hormonal fluctuations in the postpartum dam, and changes in the needs of the pups due to their development, which alter their salience to the dam [76]. Finally, it appears that both the mPOA and the mesolimbic DA system are required for the expression of pup-induced CPP, as place preference for pups is disrupted following mPOA/VTA inactivation or by systemic DA blockade [37; 77; 78].

Taken together, these findings demonstrate that parturition and the postpartum induce a switch in the valence of pup stimuli, which predisposes the animal to a behavioral shift in reward-related tasks, resulting from inhibition of avoidance and activation of approach neural systems in response to infant stimuli [29; 79]. As discussed above, postpartum rodents will readily navigate a maze to retrieve pups, perform bar or lever presses to obtain access to pups, and develop a place preference for pups and/or pup-related cues. Notably, many of these effects can be mimicked in virgin rodents via hormonal stimulation or prolonged pup exposure, which indicates roles for both hormones as well as experience-dependent modifications in giving rise to maternal motivation. The reinforcing property of pups appears to be highest between PD1–7 but declines dramatically by PD 10 and beyond, which provides evidence that the dam’s appetitive motivation changes over time; and, is consistent with the notion that the dam’s maternal behavior declines slowly after parturition. Collectively, these data suggest that resistance against competing hedonic stimuli during the early postpartum may be an adaptive, evolutionary mechanism that assures the salience of pup seeking over other rewards, thereby enhancing species survival.

3. Alterations in reward-related brain activity during motherhood and the postpartum

As reviewed above, maternal care is a rewarding motivated behavior for the dam [37; 53]. Alterations in the mesolimbic DA system enable maternal females to respond to offspring as rewarding [32; 80]. Because of this, numerous studies have provided evidence of functional

changes within the maternal mesolimbic DA system at baseline and in response to mother-infant interactions and offspring-related cues. As discussed below, there are multiple lines of evidence (e.g. immunohistochemistry, neurochemistry, electrophysiology, neuroimaging) showing adaptations in the maternal mesolimbic DA system in rodents and, when the data are available, humans.

3.1 Immunohistochemistry.

Immunostaining procedures employing immediate early genes (i.e. c-Fos, FosB) as indirect markers of neural activity have been used to examine the cellular circuitry involved in dam responses to pup stimuli and across reproductive states [81; 82]. Physical interaction with pups, with or without suckling, elicits high levels of Fos-immunoreactivity in numerous sites implicated in maternal behavior, such as the mPOA and the NAc, as well as in somatosensory cortices and the paraventricular thalamic nucleus (PVT)[83; 84]. Specifically, pup suckling induces extensive activation in the mPOA and across cortical areas responsive to sensory stimuli including the somatosensory, auditory and olfactory cortices, subcortical areas that are part of sensory pathways, as well as in the striatum, amygdala and the periaqueductal gray (PAG) [83; 85; 86]. Fleming and colleagues used the pattern of nuclear Fos-like immunoreactivity (Fos-lir) to map the functional pathways in the brain that mediate the onset and retention of maternal behavior and showed that presentation of pups increases levels of Fos-lir in the mPOA, NAc and the amygdala in PD 1 dams [87]. PD 1 dams with pups also exhibited increased Fos-lir within the amygdala and mPOA compared to PD 1 dams without pup exposure or exposure to nonsocial stimuli (i.e. food)[88]. Similar results have been obtained in early postpartum mice: pup presentation induced greater increases in Fos immunoreactivity within the VTA, NAc in lactating dams at PD3–5 than in virgin females, and increased the number of Fos positive cells in the mPOA in both virgins and dams [82].

3.2 Microdialysis/Voltammetry.

These electrochemical techniques enable the monitoring of neurotransmitters and other molecules in the extracellular environment [89; 90; 91]. Using these methods, several groups have demonstrated that pup exposure and interaction (i.e. pup licking and nursing) increase extracellular concentrations of DA levels within the ventral striatum of rat dams during PD1–10 [92; 93; 94; 95; 96]. Moreover, increases in DA release within the NAc shell are correlated with the duration of licking/grooming bouts displayed by the dam [93]. Interestingly, similar increases in pup-elicited NAc DA release have also been observed in virgin rats rendered maternal via hormone treatment and pup exposure [94; 96]. This is significant because, compared to cycling virgin rats, dams exhibit reduced basal DA release within the NAc at PD1 and PD5 [94], which suggests reduced mesolimbic DA responsivity (i.e. activation) at baseline, and this effect is also observed in hormonally-primed virgins rendered maternal through pup exposure [96]. This is consistent with an electrophysiological study showing reduced tonic activity within VTA DA neurons in dams at PD1 and PD3 compared to cycling virgins rats [97] and a recent study showing reduced intracellular DA levels within the prelimbic PFC and NAc shell in early postpartum rats (PD7–8) compared to virgins [98]. Taken together, these findings demonstrate alterations in basal and pup-induced DA release within the NAc as a function of reproductive condition or hormonal

status in which both postpartum and virgin rodents rendered maternal exhibit basal DA suppression and enhanced NAc DA release in response to pup stimuli.

3.3 Electrophysiology.

The activity of VTA DA neurons undergoes significant changes across reproductive conditions, which are also time-dependent throughout the postpartum. Compared to virgin rats, early postpartum (PD1–3) dams exhibit reduced numbers of spontaneously active DA neurons within the VTA [97], which is defined as attenuated VTA population activity (i.e. DA downregulation) and is proposed to make the DA system less responsive to stimuli such as reward-related events, which we propose to be a basis for anhedonia [99].This difference was not observed when comparing virgin and 1-week postpartum (PD7–8) rats or when comparing virgins and late postpartum (PD22–23) rats, suggesting that these alterations are transient and limited to the first couple of days postpartum. Interestingly, reduced DA neuron activity in early postpartum rats was driven by a selective attenuation in the medial tracks of the VTA [97]. Because the majority of VTA DA neurons in the medial VTA project to the ventromedial NAc, reducing the active number would be expected to decrease the response selectively of NAc projecting neurons to reward-related stimuli. In accordance, prior reports have shown reduced basal DA release in the NAc of early postpartum rats (PD1–8) compared with virgin rats [94; 98], which is consistent with reduced tonic activity of DA neurons within the medial VTA [97].

Virgin and postpartum rodents also exhibit differential electrophysiological responses within the mesolimbic DA system during active maternal behaviors and pup-related stimuli. For example, the absolute power of the 8–11 Hz band in the PFC showed a significant increase during pup retrieval compared to during walking and a significant increase in all three frequency bands examined (6–7, 8–11, 12–21 Hz) in the VTA during pup licking when compared to forepaw licking [100]. These data show differential responses within components of the mesolimbic DA system as a function of active versus passive maternal behavior. Moreover, smelling of the nest increased relative power of the 6–7 Hz band in the mPFC and a higher relative power of the 8–11 Hz band in postpartum rats compared to proestrus/estrous virgins [101], suggesting enhanced pup-induced electrophysiological responses within these components of the mesolimbic DA system. Postpartum rodents also showed the highest frequency and duration of smelling the nest bedding, which is likely to be related to the increased motivation of postpartum rats to seek out and engage in maternal behaviors.

3.4 Neuroimaging.

Magnetic resonance imaging (MRI) studies in humans and rodents have provided evidence that motherhood induces structural and functional alterations within the brain reward pathway- the mesolimbic DA system [2; 5; 7; 102]. Structural MRI methods are used to examine gray matter (GM) and white matter (WM) morphometry. Common methods for examining GM volume include manual measurement of specific regions of interest (ROI) and voxel-based morphometry (VBM), which is a hypothesis-free approach to examine GM differences among groups across the entire brain [103]. These approaches have been used to examine structural changes during pregnancy and the postpartum. Using VBM, Hoekzema et

al. showed that pregnancy is associated with pronounced and long-lasting GM volume reductions across a wide variety of brain regions, including components of the mesolimbic DA system; significant pre- to post-pregnancy (up to 2 years) reductions in GM volume were found for subregions of the PFC and the hippocampus [5]. Using ROI delineation, similar pre- and post-pregnancy reductions in GM volume have also been found for the ventral striatum [6]. Changes in GM volume have also been found across the postpartum period. For example, Kim et al. reported increases in GM volume of the PFC, amygdala and midbrain structures across the postpartum period (from 2–4 weeks postpartum to 3–4 months postpartum) that were associated with maternal positive perception of her baby [104].

Functional MRI (f-MRI) is a technique sensitive to the oxygenation status of hemoglobin that is used produce images that reflect changes in cerebral blood flow and volume in distinct and separate brain regions occurring in response to changes in neural activity during a task or at rest [105]. For example, enhanced synaptic and neural activity is associated with a compensatory increase in blood flow and oxygenated hemoglobin, which causes a positive blood-oxygen-dependent (BOLD) change in the magnetic resonance signal [4; 106]. A number of neuroimaging studies in postpartum women have identified normative changes in mesolimbic DA system activation in response to their own infant [107]. For example, healthy mothers display increased BOLD activation to visual (i.e. pictures, videos) and auditory (i.e. cries) cues of their own infant, but not an unknown infant, in reward-related areas such as the VTA, ventral striatum, and the PFC [108; 109; 110; 111; 112; 113]. Moreover, human studies have shown that maternal synchrony- the coordination of maternal behavior with infant signals- is associated with differential activation of reward-related circuitry [114]. For example, synchronous mothers showed greater activation in the NAc when viewing video vignettes of their own infant. Moreover, maternal bonding behavior relies on synchronous firing within nodes of the mesolimbic DA system, such as the NAc, amygdala and PFC, as a network, and stronger connectivity within this network has been linked to greater in-network DA responses in synchronous mothers [114; 115]. Thus, human neuroimaging studies have established a link between motherhood, the mother-infant relationship and adaptations within mesolimbic DA (i.e. reward) system function.

Pup stimulation increases BOLD signal intensity in early postpartum dams (PD4–8) within reward-related brain areas that receive prominent inputs from the VTA, including the dorsal and ventral striatum and the PFC, and are activated by cocaine administration in virgin females [116]. When exposed to cocaine instead of pups, early postpartum dams exhibited a robust negative BOLD signal change was observed throughout the mesolimbic DA system, reflecting suppression of neural activity within these same brain regions. These data suggest that reproductive condition in females is a critical determinant in the effects of different rewards (e.g. drugs, pups) on mesolimbic dopamine system activation, and that this pathway is more sensitive to pups than cocaine during the early postpartum period. A follow up study conducted in PD 4–8 dams revealed overlapping changes in brain activation in response to pup suckling closely and oxytocin administration in areas including the PFC, NAc, VTA, amygdala, and several hypothalamic nuclei [117]. Moreover, systemic blockade of oxytocin receptors attenuated pup-induced activation in these regions. Collectively, these data suggest that early postpartum rats favor interaction with pups at the expense of other rewarding

activities due to pup-evoked increases in oxytocin release, which promote mother-infant bond formation partly by acting through areas involved in regulating affect and reward (i.e. the mesolimbic DA system) [102; 117]. Thus, the enhanced release of oxytocin during nursing may function to promote bond formation between mother and pup while reducing the sensitivity of the mesolimbic DA system to the stimulatory and rewarding effects of cocaine.

As reviewed above, a comprehensive body of basic research has shown broad changes within components of the maternal brain circuit, particularly in the mesolimbic DA system, following parturition and during the postpartum. Using a wide variety of techniques, multiple groups have demonstrated that the expression of motivated maternal behaviors (i.e. preference, approach, licking, retrieval) is linked with increased mesolimbic DA system activation and neurotransmission in response to the offspring. Moreover, these changes appear to be more robust during the early postpartum period. Importantly, a recent study identified decreased mesolimbic DA signaling as a mechanism contributing to the decline in maternal behaviors across the late to early postpartum period in rodents [118]. Grieb and colleagues administered DA D1 and DA D2 receptor agonists (i.e. SKF38393 and quinpirole) to dams from PD9–15 and found that combined treatment of SKF38393 and quinpirole increased the proportion of dams exhibiting full repertoire of maternal behaviors throughout PD12–15 [118]. Thus, it appears that mesolimbic DA system changes not only stimulate maternal behavior during the early postpartum period, but also contribute to the characteristic waning of maternal behaviors as the postpartum period progresses. In sum, these findings underscore the importance of dopaminergic brain reward regions in positive maternal caregiving and maternal attachment while also raising the possibility that reduced mesolimbic DA function can negatively impact multiple aspects of mothering.

4. Mesolimbic dysfunction is associated with disrupted maternal behaviors

The mesolimbic DA system plays a critical role in maternal behavior and is potently activated by pup interaction and pup-related stimuli. Thus, dysfunction within the mesolimbic DA system has been repeatedly shown to disrupt maternal behaviors. For example, rat dams with electrical lesions of the VTA exhibit reductions in nest-building and nursing, as well as increases in pup cannibalization [119]. Temporary inactivation of the VTA via bilateral infusion of muscimol or baclofen (i.e. GABA receptor agonists) also disrupted maternal behavior: muscimol disrupted both retrieval of pups and nursing behaviors, whereas baclofen disrupted pup retrieval without affecting nursing behavior [38]. Moreover, DA depletion via 6-OHDA, a selective DA neurotoxic compound, infused into the NAc or DA cell bodies in the VTA impair pup retrieval by the dam [120; 121; 122].

Systemic administration of DA D1-like (i.e. SCH23390) and D2-like (i.e. clebopride) receptor antagonists both result in significant attenuation of maternal care immediately postpartum (e.g. within 3 hours of parturition) [123]. Specifically, dams receiving high doses (1mg/kg) of either antagonist exhibited longer latencies to retrieve and crouch over pups compared to vehicle-treated dams on PD1 [123]. When tested for retention of maternal

behavior 7 days later, only the dams that were injected with the D2 receptor antagonist (clebopride) displayed a delayed onset of full maternal behavior, as indexed by longer latencies of retrieving, grouping and crouching, towards donor pups, suggesting that pharmacological disruption of D2-like receptors interferes with the retention of maternal behavior [123]. Collectively, these results may suggest that while both DA receptor subtypes appear necessary for the full and rapid expression of maternal behavior during the early postpartum period, only the D2 receptor subtype appears to be involved in the retention of maternal behavior. Furthermore, systemic administration of D2 receptor antagonists (i.e. raclopride, haloperidol) inhibit pup retrieval and nest-building in a dose-dependent manner [121; 124; 125; 126], although effects of D2 receptor antagonism on maternal licking of pups have yielded mixed findings, with some researchers reporting reduced pup licking by the dam [125] and others finding no effect on pup licking and nursing [124]. Furthermore, infusions of mixed D1/D2 or D1 DA receptor antagonists cis-flupenthixol or SCH 23390, respectively, directly into the NAc of PD7–9 dams impair pup retrieval and reduce maternal licking of pups [127; 128]. Taken together, these data demonstrate a causal role for mesolimbic DA neurotransmission in the onset and maintenance of a variety of motivated maternal behaviors during the postpartum, which is consistent with the VTA's role as part of the maternal caregiving network.

5. Dysregulation of the mesolimbic DA system in PPD

Depression and postpartum depression are mediated by deficiencies in the brain's reward pathway (i.e. mesolimbic DA system)[3; 129], and these represent substantial risks for the health 18 of the offspring [130; 131; 132; 133; 134] as depressed mothers lose interest in their babies, provide less stimulation and are less responsive to the baby's needs [135; 136; 137; 138]. In humans, dysregulation of mesolimbic DA function and altered responses to infant-related cues are hallmark features of PPD [3; 139; 140]. Neuroimaging studies of mothers with PPD have identified reduced activation within components of the mesolimbic DA system in response to rewarding as well as infant-related stimuli. For example, atypical striatal function has been reported in mothers with PPD in response to monetary rewards, in which depressed mothers' BOLD responses rapidly attenuated to baseline whereas healthy mothers exhibited a sustained response to reward receipt [141]. Another fMRI study identified blunted striatal activation in response to positive words as well as blunted amygdala activation in response to negative (i.e. threatening) words, which were associated with greater PPD symptomatology in mothers [142; 143]. These results were supported by other fMRI studies showing decreased activity in the PFC and amygdala in response to negative emotional faces as well as decreased PFC-amygdala resting state connectivity in mothers with PPD [144; 145; 146]. Importantly, these data indicate that the striatal response to rewards and amygdala response to threat are altered in PPD and could contribute to decreased motivation and caregiving deficits in PPD. In accordance, additional fMRI studies have shown decreased striatal and amygdala activation to positive (i.e. happy) adult faces as well as to their own infant's happy faces in mothers with higher depressive symptoms [147; 148; 149]. For mothers with higher depressive symptoms, greater striatal response to positive faces was associated with more positive caregiving, whereas the opposite pattern was found in mothers with lower symptoms [147]. Moreover, poorer quality of maternal

experience was associated with reduced amygdala response to pictures of their own infant [149]. Taken together, these data suggest a link between aberrant striatal and amygdala function and impaired caregiving in mothers with high depressive symptoms.

Alterations in mesolimbic DA function have also been observed in women with PPD in response to their own infant's cry [137; 150]. Compared to non-depressed mothers, depressed 19 mothers failed to show the striatal (i.e. caudate, NAc) fMRI activation in response to their baby's cry [137]. Depressed mothers also show reduced functional connectivity between the NAc and the extended amygdala in response to their baby's cry, whereas healthy mothers showed an increase in functional connectivity between these two areas [150]. Notably, human infants elicit parental attention, proximity and solicitude by crying [151; 152; 153] and activation of the mesolimbic DA system, including the striatum, is thought to underlie reward and motivational process needed to engage in a sensitive parental response. Within this context, healthy mothers are able to better activate their NAc, and associated reward pathways, during baby cry distress, to promote caring behaviors for the baby. In contrast, depressed mothers may be less able to respond to their own infant because they experience it as less rewarding, as suggested by the blunted striatal response and attenuated NAc-amygdala connectivity data in women with PPD, which could then underlie diminished maternal responses. Consistent with this notion, a recent systematic review aimed at integrating findings from studies of neural responses to infant stimuli in healthy mothers and in mothers with mood disorders identified that the most consistent results were that healthy mothers exhibit stronger and faster neural responses to infant stimuli than non-mothers in key emotional processing regions including the amygdala and the PFC, which is accentuated for own infants, whereas depressed mothers display blunted neural responses within these regions which correlates with greater depression severity [154]. Finally, there is also evidence indicating that mothers with greater mesolimbic DA system function are able to establish and maintain warm and nurturing relationships with their infants despite psychiatric symptoms [147].

In sum, these findings highlight the importance of mesolimbic DA system function in positive maternal attachment and caregiving, but also raise the possibility that impaired mothering in PPD results from lower mesolimbic DA system activation [3]. Interestingly, a PPD study conducted in humans using positron emission tomography (PET), identified higher levels of monoamine oxidase-A (MAO-A), an enzyme that is involved in monoamine catabolism that is proposed to lead to DA deficiency, in the striatum [155]. Indeed, elevated levels of MAO-A are observed across a wide variety of brain regions, including the striatum, in depressed patients [156; 157]. Genetic studies of PPD have further implicated MAO-A as well as catechol-O-methyltransferase (COMT)- an enzyme that also inactivates DA- in depressive symptoms [158; 159; 160].

6. Mesolimbic dysfunction in animal models relevant for the study of PPD

Environmental and/or genetic manipulations known to alter mesolimbic DA function, such as exposure to chronic stress during pregnancy and/or the postpartum, induce impairments in maternal behavior to similar to those observed following blockade or inactivation of mesolimbic DA signaling (reviewed in section 4)[161; 162; 163; 164]. Thus, animal models

are useful tools to study how known risk factors in PPD influence maternal behaviors and the mesolimbic DA system, while providing for the opportunity to examine mechanisms as well as potential treatment/interventions. Although there are many different rodent models relevant for the study of PPD [165; 166], here we focus on studies using stress-based and genetic models that examined mesolimbic DA structure and/or function.

6.1 Stress-based models.

Chronic stress during pregnancy or shortly after giving birth is one of the strongest predictors for the emergence of PPD in humans [167; 168] and a translational risk factor employed in rodent models of PPD [165; 166; 169; 170; 171]. For example, multiple groups have shown that gestational restraint stress alters maternal care behaviors in rats, including reductions in arch-back nursing and more time spent away from the nest, and increases passive coping (i.e. immobility behavior) in the forced swim test (FST), which was interpreted as depressive-like behavior, at both early (PD7) and late (PD21) postpartum timepoints [172; 173; 174; 175; 176]. Moreover, exposure to gestational stress is associated with compromised structural plasticity within the mesolimbic DA system during the postpartum period [174; 175]. For example, dams exposed to chronic gestational stress exhibit reduced dendritic spine density on mPFC pyramidal neurons and altered spine morphology [175]. In addition, dendritic length, branching and spine density on medium spiny neurons in the NAc, specifically the NAc shell, were diminished in dams that experienced gestational stress, although stress-induced reductions in spine density were only observed in early/mid postpartum females [174]. Thus, gestational stress induces structural modifications in both the mPFC and the NAc that co-exist with disrupted maternal care and increased depressive-like behavior. A subsequent study tested whether these stress-induced neurobehavioral alterations were sensitive to antidepressant (i.e. SSRI) treatment, which would be consistent with the notion that these alterations represent a PPD-like phenotype in rodents [176]. To this end, control and stress-exposed dams were implanted with an osmotic minipump on PD1 and received either citalopram or vehicle (i.e. saline) over 22 days. Chronic administration of citalopram during the postpartum reversed the increase in immobility behavior, or passive coping, in dams exposed to chronic gestational stress as they displayed reduced percent immobility compared with saline-treated dams that were exposed to gestational stress [176]. Furthermore, chronic postpartum administration of citalopram also reversed stress-induced decreases in total dendritic length, number of branch points and dendritic spine density on MSNs in the NAc shell as well as reduced dendritic spine density in the mPFC [176]. Thus, postpartum females that were administered citalopram did not exhibit the stress-induced behavioral alterations in the FST or the structural modifications in the NAc and mPFC, indicating that these alterations reflect a depressive-like state. Finally, preliminary results suggest that gestational stress decreases DA levels in the striatum and diminishes oxytocinergic inputs and oxytocin receptor expression in the VTA [3], which would suggest less oxytocin availability within the reward system and provide initial evidence for aberrant oxytocin-DA interactions in a rodent model of PPD.

The influence of postpartum stress exposure on maternal behavior and DA-related brain activity has been modeled in rodents using chronic social stress (CSS). This model is based on clinical literature indicating that chronic exposure to psychosocial stress is common in

human mothers and that social conflict is one of the strongest predictors of depression in mothers [177; 178; 179; 180; 181]. In this paradigm, dams are exposed to a novel male intruder within the home cage for 1 hour daily from PD 2–16, which elicits robust behavioral and neuroendocrine stress responses and impairs maternal care as indexed by longer latencies to initiate nursing and lower durations of pup nursing and grooming on PD 9 [161; 182]. Importantly, the adult female offspring of dams exposed to CSS also exhibit long-term changes in maternal behaviors towards their own offspring, such as depressed maternal care and impaired lactation (i.e. reduced pup grooming, increased latency to nurse, shorter nursing durations), as well as a persistent increase in stress hormone (i.e. corticosterone) levels [183]. Furthermore, analyses of resting state functional connectivity (R-fMRI), which measures the temporal correlation of spontaneous BOLD signal among spatially distributed brain regions, in adult females that were reared with a CSS-exposed mother rat revealed broad changes in limbic and reward-related systems, including the NAc and PFC, among others [184]. A follow-up study conducted in adult postpartum rats that had been reared with a CSS-exposed dam showed decreased functional connectivity between the anterior cingulate cortex (ACC)-a subregion of the PFC- the mPOA, and the mPFC during the early postpartum (PD 3–6) [185]. This finding is consistent with neuroimaging studies indicating depressed mothers exhibit decreases in the ACC [145], and it is postulated that this hypoactivity may be accompanied by reduced communication between this structure and other downstream regions critical to responding to infant sensory cues [185]. In sum, the CSS procedure induces maladaptive effects across multiple levels (i.e. behavioral, hormonal, functional) on both the mother and the female offspring that are consistent with the effects of PPD in humans [186].

6.2 Endogenous genetic models.

The Flinders Sensitive Line (FSL), which was selectively bred from Sprague Dawley (SD) rats, and Wistar Kyoto (WKY) strain, which was selectively bred from Wistar rats, are considered genetic animal models relevant for the study of endogenous depression and PPD [187; 188; 189]. In accordance, FSL dams exhibit increases in immobility in response to an acute inescapable stressor (i.e. FST)- a common behavioral outcome in rodent models relevant for the study of depression [190]- as well as less frequent pup licking and non-nursing contact with pups compared to SD dams [191; 192]. FSL dams also show stress-induced alterations in a subset of maternal behaviors when compared to SD dams: FSL dams had longer latencies to retrieve pups and initiate nursing following a 15-minute FST exposure [192]. With regard to reward- and DA-related responses to pups, FSL dams show reduced preference to the pup-associated box in the CPP paradigm at PD6, and failed to show the pup-induced increase in extracellular DA levels and DA turnover within the NAc from PD5–7 compared to SD dams [193]. Collectively, these data suggest that FSL dams show enhanced depressive-like behavior, deficits in maternal behavior and attenuated pup-elicited reward at both behavioral and neurochemical levels- all of which are consistent with an animal model relevant for the study of PPD.

Although little is known about depression-related abnormalities and DA function in WKY females and dams [189], a recent study comparing a variety maternal behaviors in WKY and SD dam at both early and late postpartum time points found severe parenting deficits and

altered DA levels in WKY dams [98]. Following a 20-min mom-litter separation, WKY dams consistently exhibited fewer active maternal responses, including lower numbers of pup retrievals, corporal and anogenital lickings, longer latencies to retrieve and reunite pups, and less time spent with pups compared with SD rats; and, these differences were more pronounced in the early postpartum (PD7–8)[98]. Similar reductions were found during undisrupted home-cage observations: WKY dams displayed reduced active caregiving behaviors and more time spent off pups at PD1–8 and PD9–16 compared with SD dams; WKY dams also spent less time nursing their pups during PD1–8 [98]. These data are in agreement with a prior report indicating increased time away from pups and reduced pup licking in WKY dams during both light and dark cycle phases across PD1–21 [194]. Furthermore, WKY dams showed altered DA levels and turnover within several structures, including the striatum, the NAc core and the mPOA. Specifically, WKY dams exhibited lower DA levels within the dorsolateral, dorsomedial and ventrolateral striatum, the NAc core and the mPOA, as well as higher DA turnover rates in these structures [98]. Taken together, these data suggest that deficits in maternal behaviors in WKY rats are associated with reduced DA levels within various regions of the mesolimbic DA system, thereby raising the possibility that deficits in mesolimbic DA might underlie the deficits in active caregiving observed in WKY dams.

In sum, these preclinical studies demonstrate that compromised activity of mesolimbic DA structure and function induced by chronic stress during pregnancy or the postpartum and/or genetics interfere with reward-related processes necessary for maternal motivation and are associated with increased depression-related outcomes, suggesting that interventions and/or treatments aimed at addressing maternal reward deficits in animal models of PPD, and perhaps depressed mothers, may improve the formation of the maternal infant bond and enhance maternal care.

7. Conclusions

In this review, we summarized the literature addressing normative changes in reward-related processes, with a focus on mother-infant dyad, and the mesolimbic DA system occurring during the postpartum. Alterations in mesolimbic DA function induced by the hormonal events of motherhood and the postpartum promote the valence bias towards offspring and give rise to motivated maternal behaviors. A causal link between the integrity of the mesolimbic DA system and maternal behaviors/responsiveness was established, as dopaminergic dysfunction leads to disrupted maternal behaviors and is a core feature in PPD and animal models for the study of PPD. Since, the DA system provides a link between pup stimuli and rewarding events, deficits in DA system function may prevent the normal association between pup and reinforcement. For this reason, manipulations and/or procedures that interfere with DA system activity could prevent a strong association between the infant and the motivation of the mother. In sum, these findings underscore the importance of the dopaminergic brain reward regions in positive maternal attachment and caregiving while also providing support for the possibility that may be represent a therapeutic target for ameliorating reward-related deficits observed in PPD.

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Highlights

- Maternal mammals exhibit increased reward-related responses to offspring
- Motherhood induces adaptations in mesolimbic dopamine (DA) function
- Mesolimbic DA system activation plays a causal role in maternal motivation
- DAergic dysfunction leads to disrupted maternal behaviors
- Postpartum depression involves deficits in reward and mesolimbic DA function

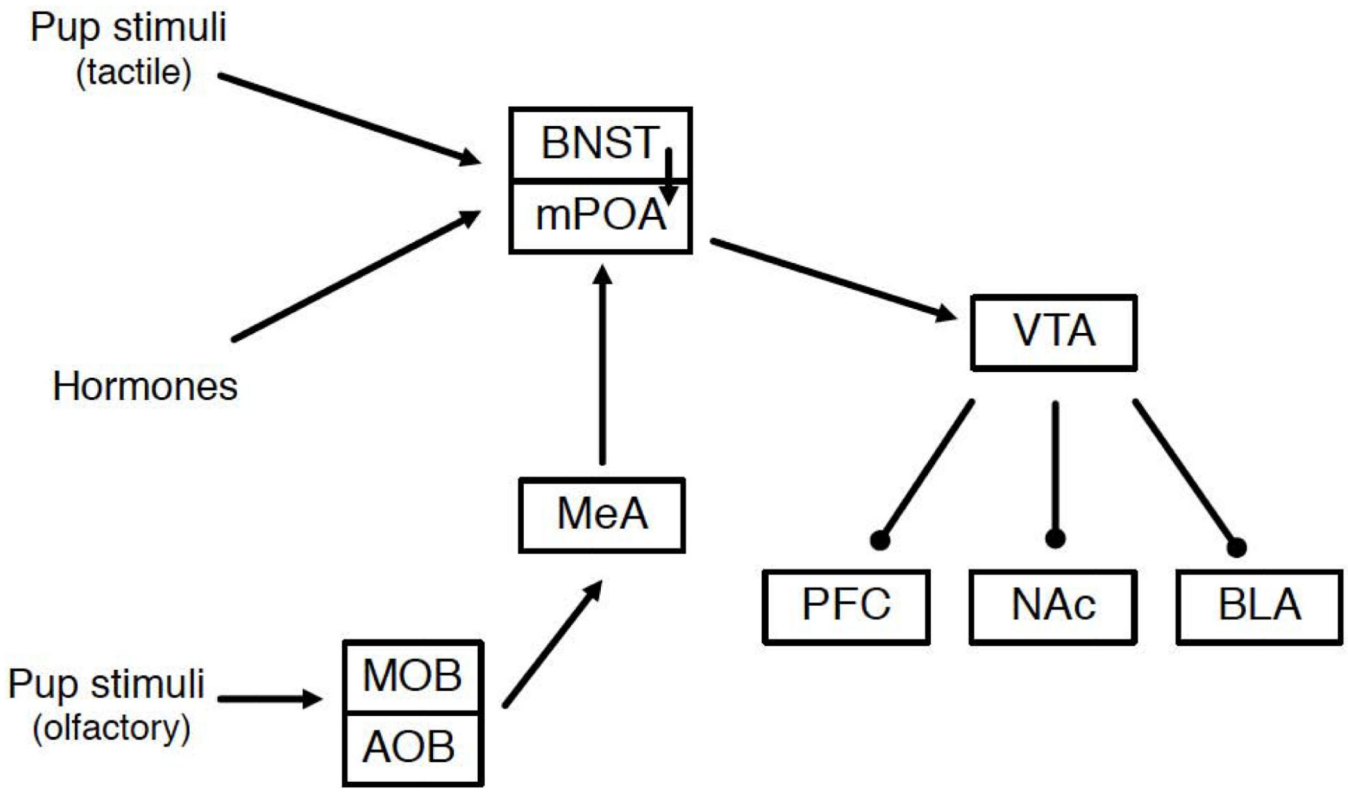

Figure 1. Simplified schematic detailing medial preoptic area (mPOA) afferent and efferent connectivity implicated in maternal motivation.

The mPOA receives inputs from the bed nucleus of the stria terminals (BNST), medial amygdala (MeA), as well as indirect inputs from main olfactory bulb (MOB) and accessory olfactory bulb (AOB). The mPOA sends output to the VTA. The action of hormones (e.g. prolactin, oxytocin, estradiol) at the end of pregnancy and the presence of pup-related sensory cues stimulate the mPOA projection to the VTA, which activates the mesolimbic dopamine (DA) system. The VTA sends discrete dopaminergic innervation to the prefrontal cortex (PFC), nucleus accumbens (NAc), and basolateral amygdala (BLA) and increases DA release. Thus, the mPOA connections to the mesolimbic DA system are crucial for the rewarding aspects of maternal behavior.