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Plasticity of the Maternal Brain Across the Lifespan

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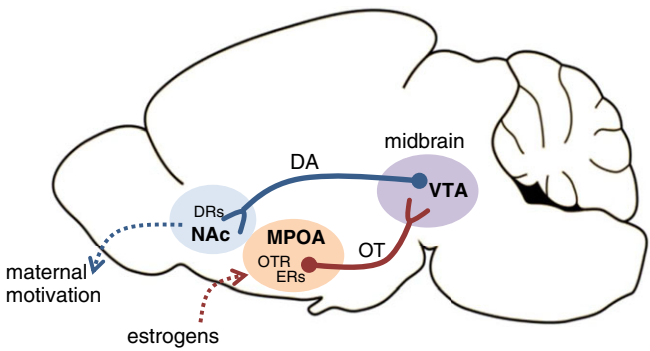
Abstract

Maternal behavior is dynamic and highly sensitive to experiential and contextual factors. In this review, this plasticity will be explored, with a focus on how experiences of females occurring from the time of fetal development through to adulthood impact maternal behavior and the maternal brain. Variation in postpartum maternal behavior is dependent on estrogen sensitivity within the medial preoptic area of the hypothalamus and activation within mesolimbic dopamine neurons. This review will discuss how experiences across the lifespan alter the function of these systems and the multigenerational consequences of these neuroendocrine and behavioral changes. These studies, based primarily on the examination of maternal behavior in laboratory rodents and nonhuman primates, provide mechanistic insights relevant to our understanding of human maternal behavior and to the mechanisms of lifelong plasticity. © *2016 Wiley Periodicals, Inc.*

Introduction

Maternal behavior is dynamic and highly sensitive to experiential and contextual factors. This plasticity allows mothers to adapt to the changing developmental needs of offspring and promotes reproductive success. Maternal behavioral complexity is mediated by multiple neural and endocrine systems that promote hormone sensitivity, responsivity to offspring cues, and motivation to engaging in parental care (Jensen & Champagne, 2012). In particular, mammalian maternal behavior is dependent on estrogen sensitivity within the medial preoptic area of the hypothalamus (MPOA) and activation within mesolimibic dopamine (DA) neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (see Figure 1.1; see Numan, 2007). These systems account for the behavioral changes observed in females as they transition from pregnancy to the postpartum period (Brunton & Russell, 2008) and for individual differences between mothers in the frequency and quality of maternal care (Jensen & Champagne, 2012). Plasticity within these systems is evident across the lifespan and likely accounts for the sensitivity of maternal behavior to the quality of the environment. Here, research will be highlighted linking the experiences of females from the time of fetal development through to adulthood on maternal behavior and to changes within the MPOA and mesolimbic DA circuits. These studies, based primarily on the examination of maternal behavior in laboratory rodents and nonhuman primates, provide mechanistic insights relevant to our understanding of human maternal behavior and to the mechanisms of lifelong plasticity. This research also

Figure 1.1. The maternal brain



In the rodent brain, maternal behavior is regulated by hormone sensitive hypothalamic regions (medial preoptic area—MPOA) projecting to dopaminergic systems involved in motivated behavior (see Numan, 2007): midbrain dopamine (DA) neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). DRs, dopamine receptors; ERs, estrogen receptors; OT, oxytocinergic neurons; OTR, oxytocin receptors.

highlights the multigenerational consequences of environmentally induced changes in maternal behavior and the maternal brain.

Prenatal Influence on the Maternal Brain

The prenatal period is a time of dynamic change within the brain of the fetus. Studies in female rodents suggest that expression of estrogen receptors within the MPOA emerge in mid to late gestation and reach adult-like levels at the time of birth (Vito & Fox, 1981). Midbrain DA neuron proliferation is also increasing during this stage of development and by the time of birth, the numbers of DA neurons projecting from the VTA in the female rodent brain is at the level observed in adulthood (Lieb et al., 1996). Thus, disruption to these systems prenatally (i.e., through exposure to stress or endocrine-disrupting chemicals), can result in long-term consequences for maternal behavior.

Prenatal Stress and the Developing Maternal Brain. Fetal exposure to stress in female rodents has consequences for motherhood, resulting in reductions in maternal behavior, reduced pup retrieval (Fride, Dan, Gavish, & Weinstock, 1985; Kinsley & Bridges, 1988), reduced nest-building (Kinsley & Svare, 1988), reduced contact and nursing of offspring (Bosch, Musch, Bredewold, Slattery, & Neumann, 2007), reduced pup licking/grooming (LG) (Champagne & Meaney, 2006), and increased infanticide (Perez-Laso et al., 2008). The mechanisms through which these behavioral outcomes are mediated are likely complex. Increased depression and anxiety-like behavior are also a consequence of prenatal stress and may inhibit the motivation to care for offspring or decrease sensitivity to offspring cues (Bosch et al., 2007; Coulon, Levy, Ravel, Nowak, & Boissy, 2014). Prenatal stress also impacts sexual dimorphism and the reduced maternal behavior exhibited by prenatally stressed female rodents may reflect a more masculinized pattern of parental behavior (Altman & Bayer, 1978; Kinsley & Svare, 1988). Though nonstressed female rodents typically provide more parental care toward offspring than nonstressed males, this sex difference is ablated following prenatal stress (Perez-Laso et al., 2008).

Stress-induced disruption to developing hypothalamic and DA circuits may be particularly relevant to our understanding of prenatal influence on the maternal brain. Levels of estrogen receptors within the MPOA are masculinized within the brain of prenatally stressed females (i.e., increased in stressed females) as are circulating levels of estrogen, which are decreased in prenatally stressed females (Del Cerro, Ortega, Gomez, Segovia, & Perez-Laso, 2015). Prenatal stress alters the activity of midbrain DA neurons (Hausknecht, Haj-Dahmane, & Shen, 2013; Kaiser, Kruijver, Swaab, & Sachser, 2003), increases levels of the DA transporter within striatal regions (Converse et al., 2013), and increases DA release in the nucleus accumbens (Alonso, Navarro, Santana, & Rodriguez, 1997). These outcomes

in adulthood may be a consequence of prenatal stress-induced alterations in the developmental expression of transcription factors involved in DA neuron differentiation and survival, namely *Nurr1* and *Pitx3* (Baier, Katunar, Adrover, Pallares, & Antonelli, 2012; Sousa et al., 2007; Volpicelli et al., 2007). Expression of *Nurr1* is increased in the VTA of prenatally stressed female rat offspring at postnatal day 7 and this effect persists through adolescence and into adulthood. *Pitx3* expression in the VTA is decreased transiently in adolescence and then increases in the adult brain of prenatally stressed female offspring (Katunar, Saez, Brusco, & Antonelli, 2010). Collectively, these neuroendocrine effects of prenatal stress may reduce the activation of hormone-dependent systems within the brain that increase maternal motivation. Increasing the levels of circulating estrogen in prenatally stressed females restores motivated behavior and functioning within DA circuits (Reynaert et al., in press)—a finding that also highlights the interplay between hypothalamic/endocrine systems and DA neurons.

Prenatal Endocrine Disruption of the Maternal Brain. The hormonal environment experienced by the fetus can shape developing neural circuits with consequence for sexually dimorphic behaviors and social development. For example, in humans, elevated *in utero* testosterone levels are predictive of social relationships and may serve as a risk factor for the development of autism (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010; Knickmeyer, Baron-Cohen, Raggatt, & Taylor, 2005). Studies of the impact of fetal exposure to endocrine-disrupting chemicals in rodents confirm the critical role of prenatal hormones in shaping social and reproductive behavior (Rosenfeld, 2015). In mice, gestational exposure to bisphenol A (BPA), an endocrine-disrupting chemical used in the manufacture of plastics, which likely acts as an antagonist/agonist at estrogen receptors (Wetherill et al., 2007), results in reduced contact with pups by adult female offspring (Palanza, Howdeshell, Parmigiani, & vom Saal, 2002). Similar to the case of prenatal stress, disruption to hypothalamic and DA circuits may mediate BPA-induced effects on maternal behavior. Midbrain DA projections are decreased in nonhuman primate offspring prenatally exposed to BPA (Elsworth, Jentsch, Vandervoort, Roth, & Leranth, 2013) and DA receptor binding within limbic regions of the mouse brain is decreased following prenatal exposure to BPA (Mizuo, Narita, Yoshida, Narita, & Suzuki, 2004). Expression of estrogen-receptor alpha (*Esr1*) and beta (*Esr2)* is altered in the neonatal hypothalamus in rats prenatally exposed to BPA (Cao et al., 2013) and nonlinear dose-dependent effects of prenatal BPA have been observed on both *Esr1* and *Esr2* mRNA levels within the hypothalamus of adult female mice (Kundakovic et al., 2013). These gene expression changes are associated with epigenetic variation—decreased DNA methylation—of the *Esr1* gene in the female hypothalamus (Kundakovic et al., 2013), which may account for the stable maintenance of these hypothalamic changes into adulthood.

Postnatal Sensitivity of the Maternal Brain. Hypothalamic and dopaminergic pathways involved in the regulation of maternal behavior continue to develop following birth, extending the sensitivity of the maternal brain and behavior to the postnatal period. In humans, the quality of attachment relationships and parental bonding established during this period is predictive of the quality of caregiving observed in adulthood (Benoit & Parker, 1994; Miller, Kramer, Warner, Wickramaratne, & Weissman, 1997). In rodents, the quality of mother–infant interactions occurring during the postnatal period has long-term effects on the hypothalamic-pituitary-adrenal response to stress, cognition, and social/reproductive behavior (Meaney, 2001). Female rats that receive elevated levels of LG during the first week postpartum engage in higher levels of LG toward their own offspring (Champagne, Francis, Mar, & Meaney, 2003). In rats, brief periods of maternal separation, which stimulates maternal care, leads to increased maternal LG in female offspring (Francis, Diorio, Plotsky, & Meaney, 2002). Female mice reared in a communal nest receive elevated levels of LG and in adulthood exhibit elevated LG and nursing (Curley, Davidson, Bateson, & Champagne, 2009). In contrast, disruptions to the quality of care received during infancy are predictive of reduced maternal care in female offspring. Female rats reared under conditions of complete maternal deprivation (artificially reared: AR), engage in reduced pup retrieval and decreased frequencies of LG and nursing compared to mother-reared females (Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001). These observed deficits in maternal behavior can be partially ameliorated if females are provided with licking-like tactile stimulation during the postnatal period. In rhesus monkeys, postnatal maternal deprivation leads to impaired maternal behavior of offspring, with deprived females exhibiting reduced overall contact with offspring and reduced maternal competency (Seay, Alexander, & Harlow, 1964).

Prolonged postnatal maternal separation in rodents reduces frequency of nursing and LG exhibited by female offspring. Among rodent females that experience both reduced nurturing maternal care (i.e., nursing and LG) and increased abusive care (i.e., stepping on and dragging), there is an increased frequency of abusive care observed in adulthood (Roth, Lubin, Funk, & Sweatt, 2009)—a phenomenon also observed in abused nonhuman primates (Maestripieri, 2005). The impact of mothering on the maternal behavior of offspring leads to the multigenerational transmission of maternal behavior that has been observed in humans (Benoit & Parker, 1994; Miller et al., 1997), nonhuman primates (Fairbanks, 1989; Maestripieri, 2005; Maestripieri, Wallen, & Carroll, 1997), and rodents (Champagne et al., 2003; Fleming et al., 2002).

The modulating effects of maternal care received during infancy on the brain may account for the multigenerational effects of postnatal maternal behavior. Female offspring that experience elevated levels of LG (high LG compared to low LG) have increased expression of *Esr1* in the MPOA

in adulthood and increased estrogen sensitivity within this brain region (Champagne, Diorio, Sharma, & Meaney, 2001; Pena, Neugut, & Champagne, 2013). These changes in the MPOA emerge during the first week postnatal and are likely maintained through changes in DNA methylation within the *Esr1* gene (Pena et al., 2013). Cross-fostering studies indicate that the expression of *Esr1* within the MPOA is determined by the level of LG experienced prior to postnatal day 10, suggesting a sensitive period within postnatal development (Pena et al., 2013). Artificial rearing likewise impacts the MPOA, resulting in reduced c-fos activation following exposure to pups and decreased hormone sensitivity in AR-reared female offspring (Gonzalez & Fleming, 2002; Novakov & Fleming, 2005). Within developing mesolimbic DA pathways, high levels of LG lead to increased DA neuron projections from the VTA and elevated expression of DA receptors within the nucleus accumbens (Pena, Neugut, Calarco, & Champagne, 2014). During the postnatal period, females that receive high levels of LG have elevated levels of expression of *Cdkn1c* and the transcription factor *Lmx1b* within the VTA (Pena et al., 2014). These two factors may shape the DA system through effects on cell proliferation, survival, and interactions with other factors, such as *Nurr1,* that exert a developmental influence on DA neurons (Joseph et al., 2003; Smidt et al., 2000). Postnatal maternal deprivation (AR vs. MR) is associated with elevated basal DA release and reduced pup-associated DA elevations within the nucleus accumbens (Afonso, King, Novakov, Burton, & Fleming, 2011). Similar to the case of prenatal stress effects on DA function, the long-term effects of maternal deprivation on the DA system can be ameliorated following hormonal treatments (Afonso et al., 2011). This interplay between DA function and hormones is also evident following targeted manipulation of the levels of *Esr1* within the MPOA. Increasing *Esr1* in the MPOA of female offspring during the first week postnatal results in increased maternal behavior and increased numbers of DA neurons projecting from the VTA (Pena & Champagne, 2014). Thus, rather than developing independently, these systems are interacting throughout the postnatal period, and this interplay likely accounts for the hormonal influence on maternal motivation.

Plasticity of the Juvenile Maternal Brain

Adolescence is a period of hormonal change characterized by continued refinement of the nervous system and emergence of adult-like patterns of behavior. Neural systems regulating self-control and reward salience within the adolescent brain have yet to reach maturity resulting in functional consequences that may impact risk-taking behavior and response to social stimuli (Casey, 2015). Though experiences during this period can impact brain function and reverse the effects of early-life maternal separation (Francis et al., 2002; Vivinetto, Suarez, & Rivarola, 2013), less is known regarding the specific impact of this period on maternal behavior and associated

neuroendocrine systems. Among female rats reared by low LG dams, the experience of social enrichment (social and environmental complexity) during the juvenile/post weaning period results in increased LG (Champagne & Meaney, 2007). In contrast, female rats that have experienced high levels of postnatal LG will engage in low levels of LG in adulthood following juvenile/post weaning social isolation. These juvenile experiences ameliorate postnatal rearing effects on later maternal behavior and lead to altered levels of oxytocin receptor (*Otr*) levels within the hypothalamus and amygdala (Champagne & Meaney, 2007). However, it is not known how these experiences shape dopaminergic function or hypothalamic expression of *Esr1*.

Experiences in Adulthood and the Quality of Mother–Infant Interactions

Despite an overall reduction in plasticity that is associated with progression into adulthood, the transition to motherhood is a time of heightened neuroendocrine and behavioral change. Childbirth and lactation involve restructuring of hypothalamic neurons and variation in circulating estrogens, progesterone, prolactin, and other hormones/neuropeptides that facilitate heightened sensitivity to infant cues (Brunton & Russell, 2008). This period of hormonal fluctuation can also lead to altered mood and an increased susceptibility to psychiatric disorder. Thus, mothers enter into a sensitive period during which time experiences may have both short- and long-term effects on maternal behavior and the brain. Similar to the prenatal period, stress and exposure to BPA during the prepartum period in adult mothers impacts the quality of mother–infant interactions. In rats, gestational stress results in reduced postpartum LG, particularly the frequency of LG directed at male offspring (Champagne & Meaney, 2006; Moore & Morelli, 1979). This influence of gestational stress on postpartum maternal behavior may account for many of the phenotypes observed in prenatally stressed offspring (Moore & Power, 1986). Moreover, female rats stressed during gestation continue to engage in reduced maternal care toward subsequent litters (i.e., following nonstressed pregnancies) (Champagne & Meaney, 2006). Exposure to elevated levels of BPA during gestation results in altered postpartum maternal behavior in adult female rats and mice, leading to reduced frequency of nursing and LG of offspring (Boudalia et al., 2014; Della Seta, Minder, Dessi-Fulgheri, & Farabollini, 2005; Palanza et al., 2002). Similar to the case of BPA-associated effects in prenatally exposed offspring, nonlinear dose-dependent effects of BPA have been observed in mothers on measures of postpartum nursing and LG, with lower BPA doses decreasing maternal behavior and higher doses increasing both nursing and LG (Kundakovic et al., 2013). A consideration in the effects of both gestational stress and BPA on maternal behavior is exposure-induced changes in the behavior of offspring. Altered sexual dimorphism and social development

in offspring may result in a decrease or augmentation of cues typically used by offspring to solicit maternal care (Nakagami et al., 2009).

The quality of the rearing environment—a factor that contributes significantly to offspring development—also results in changes to the behavior of mothers. Brief maternal separations stimulate increased LG behavior toward pups, particularly among low LG mothers (Francis, Diorio, Liu, & Meaney, 1999), whereas prolonged maternal separations between mother and pups leads to reduced LG (Boccia & Pedersen, 2001). These alterations in postpartum maternal behavior are associated with changes in hypothalamic levels of estrogen receptors and oxytocin receptors in the brain, with brief separations leading to increased *Esr1*, *Esr2*, and *Otr* in the MPOA (Stamatakis et al., 2015). In rats, removal of bedding material from the home-cage leads to a reduced frequency of nursing/contact, decreased LG, increased frequency of abusive caregiving, and more fragmented patterns of maternal behavior (i.e., frequent shifts between contact and noncontact behaviors). This experience leads to increased adrenal weights and basal plasma corticosterone levels—suggesting a state of chronic stress, which may inhibit females from engaging in maternal care (Ivy, Brunson, Sandman, & Baram, 2008). In contrast, lactating adult female mice that are placed together in a communal nest engage in elevated levels of nursing and LG. This increase in maternal behavior is particularly evident in mice strains that typically display reduced frequency of mother–infant interactions (Curley et al., 2009).

The experience of motherhood in adulthood results in a broad change in the biology of mothers which includes but is not limited to changes in the brain (see Bridges, 2016). Neural complexity is increased within both the nucleus accumbens and MPOA following maternal experience (Shams et al., 2012) and may contribute to the impact of motherhood on the quality of subsequent mother–infant interactions. In rhesus monkeys reared under conditions of maternal deprivation, impaired maternal behavior is observed in first-time mothers (primiparous). However, over subsequent births, maternal competency is increased and level of abusive behavior is decreased (Ruppenthal, Arling, Harlow, Sackett, & Suomi, 1976). In laboratory mice, it has been observed that, in contrast to primiparous mothers, multiparous females engage in reduced frequency of nursing with no alterations in frequency of LG. Though this finding is counterintuitive, given evidence that maternal experience leads to increased maternal motivation and reduced rejection of offspring (Dwyer & Smith, 2008; Ruppenthal et al., 1976), it is likely that increased efficiency of energy usage and lactation by multiparous females accounts for these effects (Kunkele & Kenagy, 1997). In multiparous females, there are significant brain changes that may account for the altered nurturance displayed by experienced mothers, including increased DA release in response to neonates (compared to inexperienced females) (Afonso, Grella, Chatterjee, & Fleming, 2008) and increased expression of *Esr1*, *Otr*, and opiate receptors in the MPOA (Akbari et al., 2013; Meurisse

et al., 2005; Munetomo, Ishii, Miyamoto, Sakuma, & Kondo, 2015). Moreover, the experience of elevated circulating estrogens occurring during pregnancy may alter the functioning of DA pathways resulting in amelioration of deficits in maternal care observed in inexperienced mothers. These effects may also account for the recovery of maternal behavior observed in maternally deprived nonhuman primates following repeated pregnancies (Ruppenthal et al., 1976).

Conclusions

Dynamic changes in mother–infant interactions coincide with plasticity within neuroendocrine circuits that regulate maternal behavior. Beyond the classic prenatal and postnatal sensitive periods for neural development, it is clear that the maternal brain can be modified by experiences during adolescence and adulthood with consequences for the quality of mother–infant interactions. Viewing motherhood as a sensitive period may promote the development of interventions that alter hypothalamic and DA circuits and increase maternal responsiveness. Targeting these systems may have lasting and multigenerational consequences for mothers and offspring. Though much of our understanding of these processes is derived from animal models, the perspective generated by these studies may guide hormonal and neuroimaging studies in humans aimed at determining the mechanisms of plasticity within the human maternal brain. These studies may provide critical insights into how both hormonal and nonhormonal (i.e., experience-associated and cognitive) processes interact to influence caregiving behavior.

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