

Annual Research Review: All mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences

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Quality of mothering relies on the integrity of multiple physiological and behavioral systems and on two maternal factors, one proximal and one distal, that have a great impact on how a mother mothers: postpartum depression and early experiences. To mother appropriately requires the action of systems that regulate sensation, perception, affect, reward, executive function, motor output and learning. When a mother is at risk to engage in less than optimal mothering, such as when she is depressed or has experienced adversity in childhood, the function of many or all of maternal and related systems may be affected. In this paper, we will review what is currently known about the biological basis of mothering, with attention to literature on hormones but with a particular focus on recent advances in the fields of functional neuroimaging. Instead of discussing strictly 'maternal' brain imaging studies, we instead use a systems approach to survey important findings relevant to brain systems integral to and/or strongly related to the mothering experience: (a) social behavior; (b) reward and affect; (c) executive function; and (d) maternal behavior. We find that there are many commonalities in terms of the brain regions identified across these systems and, as we would expect, all are sensitive to the influence of, or function differently in the context of, depression and adverse early experience. It is likely that the similarity and cross-talk between maternal, affect and stress systems, observed behaviorally, hormonally and in the context of brain function, allows for mood disturbance and early adverse experiences to have a significant impact on the quality of mothering and the motivation to mother. **Keywords:** Adversity, maternal depression, brain imaging, parenting, mothers.

The interaction between a mother and her infant can be like a dance. There are routines, standards and missteps, there is give and take, there is unparalleled intimacy, there are often vast differences in skill level and motivation, there is learning. A mother must learn to be an adept partner, being sensitive to the needs of her offspring while ultimately guiding the quality and nature of care to ensure normal growth and development. This dance can be beautiful, it can be tender, it can be awkward, it can be difficult. And sometimes it just does not occur!

Romanticism aside, the mother–offspring dance is influenced by and interacts with many factors, including mothers' physiology, cultural and family context, maternal cognitions, maternal affect and stress and the early environment, notably a mother's own early experiences in her family of origin. Biological influences certainly include how mothers' brains are organized and how genes and environment interact in brain development. It is believed that over the course of pregnancy and through the postpartum period, changes in the levels of certain hormones likely 'activate' or affect key brain regions to ensure that the mother is especially attracted to her baby, that she is attentive and sensitive to her

baby's needs, that she learns from her experiences and that she behaves appropriately.

In humans, across cultures there exist as many differences as similarities in the ways that mothers interact with their infants (Leiderman & Leiderman, 1977). In some cultures the infants are carried in cradleboards on the mothers' backs; in others they are carried in a pouch or sling on the mothers' ventrum; in many Western cultures, especially if the terrain is smooth, infants are transported in strollers or perambulators (Anisfeld, Casper, Nozyce, & Cunningham, 1990; Chisholm, 1978). Customs relating to sleeping also vary across cultures, from swaddling, sleeping in the mother's bed, to sleeping in a cot next to the mother, to sleeping away from the mother in another room (Van Sleuwen et al., 2007; Thoman, 2006). Mothers also exhibit a range of different kinds of communicative responses to their infants: some look at them directly while others gaze avert (Brazelton, 1977); some keep their babies unclothed and stroke their bodies; others swaddle them instead (see Corter & Fleming, 2002). Some talk or sing to their babies; others do not (Tronick, 1987). Soothing methods, for example pacifier use or use of specific herbs or teas, can greatly vary by culture (Abdulrazzaq, Kendi, & Nagelkerke, 2009). More subtly, within a culture mothers show large variations in the postpartum development of

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nurturant feelings, from minutes to months (Leifer, 1980; Moss & Jones, 1977; Robson, 1967; Robson & Kumar, 1980; Trevathan, 1983), and, once 'attached' or emotionally committed, in the intensity with which they exhibit different caregiving behaviors. Within all cultures most mothers are motivated to provide warmth, shelter, and food to the infant while in all cultures there are mothers who neglect or even abuse their infants (see Corter & Fleming, 2002; Hrdy, 2005, 2009).

Despite these differences, in most cultures mothers nurse their infants, although there are some mothers in each that may also bottle-feed (Kannan, Carruth, & Skinner, 2004; Pak-Gorstein, Hak, & Graham, 2009; Thulier, 2009). In many different cultures, mothers engage in a form of expression called 'motherese', where the mother talks to the infant in a high prolonged pitch and sings with a characteristic cadence and rhythm (Trehub, Unyk, & Trainor, 1993). In most cultures mothers provide kinesthetic stimulation by stroking and rocking the baby and respond contingently to infant cries and other indices of distress, often by vocalizing 'in response' (Ainsworth, Bell, & Stayton, 1974; Corter & Fleming, 2002; Pederson et al., 1990). Here we will not address the issue of cross-cultural differences, important though they are (Cote & Bornstein, 2009; Güngör & Bornstein, in press). Instead we focus on the cross-cultural similarities and focus most discussion on studies that describe mothers from Western and industrialized societies, where most of the psychobiological research has occurred (see the work of Marc Bornstein for a program of research well suited to a cross-cultural analysis).

For this paper our primary focus is reflected in the idea that mothering is not unitary, but is instead complex, and comprised of many behavioral propensities that are mediated, moderated, and regulated by multiple physiological and brain systems. To engage in mothering behavior, mothers have to be sensitive to infant cues and select those cues for processing, utilizing multiple sensory and perceptual modalities; the cues must be attractive and salient for the mother, recruiting reward and approach systems. Mothers must be emotionally prepared and positively motivated to engage socially with the infant, depending on systems regulating affect. They must selectively attend to the offspring in the context of competing stimuli, enacted through systems that regulate attention; and they must be restrained and consistent in their responsiveness, depending on systems that regulate impulsivity. Finally, mothers gain through experiences, acquired both early in life and with young as juveniles and in adulthood. These experiences are acquired, consolidated, and stored as motor or sensory memories and are based on extensive brain plasticity.

Thus, to mother appropriately requires the action of multiple systems in the domains of sensation, perception, affect, reward, executive function, motor

output and learning. When a mother is at risk to engage in less than optimal mothering, such as when she is depressed or has experienced adversity in childhood, the function of many or all of these systems may be affected. In this paper, we will use a systems approach to review and critique what is currently known about the biological basis of mothering, with a particular focus on recent advances in the field of functional neuroimaging. We will often combine information from the animal world with the human. We will briefly review what has informed knowledge of the neurobiology of mothering up until this point (hormones). Finally, whenever possible, we will try to put these basic mechanisms into the context of important individual differences related to maternal psychopathology (depression) and early adversity.

I. Maternal behavior is affected by mothers' cognitions, executive function, and theory of mind

Overview

How mothers relate to their infants is affected by multiple psychological propensities, including her cognitive style and her affective state. In this first section we discuss individual differences related to cognitive functions: functions that are thought to provide an important foundation for quality of mothering and maternal behavior and are also, in many cases, known to interact with affect/mood and early experiences. Processes such as cognitive flexibility, working memory and attentional control are fundamental components of mothering and key to maternal sensitivity. A mother must have the attentional command to focus on her infant which allows her to be sensitive to infant needs, that is, to respond contingently, appropriately and in a timely manner. She must also have the cognitive flexibility to switch her attention efficiently across many situational demands, in highly stimulating environments. She must also maintain and manipulate information in her working memory to plan and guide mother-infant interaction and infant care. In addition, the application of the concept of Theory of Mind (ToM) to mothering, where the strongly related concept of 'mind-mindedness' has also been examined (see Meins et al., 2003), is relatively new and exciting. Theory of Mind, which, among other things, is a theory relevant to social cognition and describes how we understand the intentions and emotions of others, has obvious implications for mothering, where correctly identifying and responding to infant signals or intentions is key.

Executive function

Work in the rat has demonstrated that the integrity of maternal behavior is linked to executive functions

such as attentional set-shifting and prepulse inhibition (e.g., Afonso, Sison, Lovic, & Fleming, 2007; Lovic & Fleming, 2004). In terms of human mothers, recent work in our lab by Andrea Gonzalez examined neuropsychological and physiological factors as intervening variables between maternal retrospective reports of early adversity (childhood maltreatment and consistency of care) and current parental ability (maternal sensitivity) in a sample of 90 mothers. In this work, Gonzalez proposed and tested a model linking maternal early adversity to maternal sensitivity through the hypothalamic-pituitary-adrenal (HPA) axis and executive functions (e.g., attention). It is of note that the latter was predicted to be important for maternal behavior and thought to be mediated by HPA axis function. A composite maternal sensitivity score was correlated with measures of attentional set-shifting, spatial working memory, and a sustained attention measure; results revealed that maternal sensitivity was significantly related to both set-shifting and spatial-working memory. Importantly, path analyses revealed that maternal early adversity was indirectly related to maternal sensitivity via two pathways: (1) early adversity-HPA function-maternal sensitivity; and (2) early adversity-HPA function-executive function-maternal sensitivity. In this population of mothers, the mothers' affective state did not enter into the model. Of interest to us is the possibility that in a population of mothers where postpartum depression is high, early experience effects may also affect cognition and maternal sensitivity by acting to alter mothers' affective state. However, the importance of HPA function in mothering will be described in detail, in the section to follow.

Atkinson and colleagues investigated mother-infant interaction, attachment and selective attention using the emotional Stroop task and found that mothers with a classification of disorganized attachment responded more slowly to negative attachment words and that the speed of response to such stimuli was correlated with the number of times the mother-infant dyad was labeled as disorganized (Atkinson et al., 2009). The authors interpret these findings in the context of parallel processing and distributed semantic (neural) networks, where attachment stimuli (i.e., infant) are connected to negative associations (e.g., threat, loss). Such mechanisms may contribute to ongoing cognitive (attentional) interference/difficulties during mother-infant interactions (Atkinson et al., 2009). The results of these studies underscore the complexity of the mechanisms underlying mothering and how a multi-system approach is important when trying to understand individual differences that may contribute to maladaptive mothering styles.

In terms of individual differences in mothering and executive functions, in rats maternal deprivation is related to deficits in executive function-processes such as prepulse inhibition (PPI) and set-shifting

(Burton, Lovic, & Fleming, 2006; Garner, Wood, Pantelis, & van den Buuse, 2007; Lovic & Fleming, 2004). Many studies of early adversity in children have found a relationship between abuse or neglect and executive function (Bos, Fox, Zeanah, & Nelson, 2009; De Bellis, 2005; Kreppner, O'Connor, & Rutter, 2001; Pears & Fisher, 2005). Bos and colleagues examined executive function (CANTAB) in children with a history of early deprivation as a result of institutionalization and found that early adversity is related to performance deficits on tasks involving planning and working memory (Bos et al., 2009). Early adversity as a result of familial violence has also been linked to deficits in a broad range of executive functions, including problem solving, working memory, inhibition and attentional control (Fishbein et al., 2009; Nolin & Ethier, 2007; Pears, Kim, & Fisher, 2008). Although we may expect that observed early adversity-related deficits in executive function may persist into adulthood, less is known about the general influence of early adversity on executive function in adults. In the context of mood, deficits in executive function have also been widely linked to major depression and other affective disorders (Fossati, Ergis, & Allilaire, 2001). Although results have been mixed (see Rogers et al., 2004), individuals with depression have been shown to have difficulties with executive functions such as working memory (Elliott et al., 1996; Kaneda, 2009; Sweeney, Kmiec, & Kupfer, 2000), set-shifting (Grant, Thase, & Sweeney, 2001; Moritz et al., 2002) and attentional control (Nakano et al., 2008).

Theory of Mind

Maternal mind-mindedness reflects the tendency to treat one's infant as an autonomous human being with complex desires and intentions and not just basic or reflexive organismic needs, as well as the ability to correctly interpret infants' implicit and explicit signals (Meins et al., 2003). Interestingly, this trait or tendency has been identified across the perinatal period, even before the infant is born, with mothers more likely to comment on the 'personality' of the fetus exhibiting more appropriate comments regarding the infant's internal state during mother-infant interaction at six months postpartum (Arnott & Meins, 2007). Individual differences in mind-mindedness have been associated with maternal sensitivity. The work of Meins and colleagues (1998, 2001) has demonstrated that more securely attached mothers are more likely than insecurely attached mothers to have high mind-mindedness and focus on their children's mental or cognitive attributes, rather than their physical appearance or behavioral tendencies. More recently, Laranjo, Bernier, and Meins (2008) examined the relationship between maternal sensitivity, maternal mind-mindedness and infant attachment: 50 mother-infant dyads were assessed at two time points (15 and 18 months).

Results revealed that sensitivity, attachment, and mind-mindedness were all positively interrelated. In addition, the relationship between mind-mindedness and attachment was partly mediated by maternal sensitivity, a finding that was thought to support the notion that mind-mindedness is a prerequisite for maternal sensitivity, and that the correct interpretation of infant cues is fundamental to the generation of an appropriate response to such cues (Laranjo et al., 2008).

Interestingly, one individual difference that has been associated with Theory of Mind abilities is non-postpartum depression. Theory of Mind deficits have been found in remitted depressed patients and been demonstrated to be risk factors for depression relapse (Inoue, Tonooka, Yamada, & Kanba, 2004; Inoue, Yamada, & Kanba, 2006). In the context of depression, Theory of Mind deficits have been associated with impaired social cognition and cognitive distortions regarding the state of mind of others. Such impairments in social functioning may contribute to or help perpetuate the biased, negative thinking and false beliefs that often characterize depressive episodes (Sheline et al., 2009). Relatedly, one may expect that infant-related social cognition deficits related to Theory of Mind may play a strong role in depression during the postpartum period, where depressed mothers may be more likely to incorrectly assess the intentions of their infants and be biased toward more negative assessment (e.g., my baby is crying because she hates me).

II. Maternal behavior is affected by concurrent mood or depression

Overview

One of the most profound experiences a woman can have is giving birth to a new baby. She experiences intense emotions involving both extreme elation and happy feelings mixed with mild distress, lability, and tearfulness. Rapid changes in affect and extremes in affect intensity are very common and may function to heighten mothers' earliest impressions and experiences of the baby. Likely hormonally mediated, the first postpartum week is for most women an exciting and positive experience and one that maps on to many changes in mothers' awareness of their new role and the experience of 'falling-in-love' with the baby, with all the anxiety and happiness that that experience normally entails. Fleming and colleagues describe the development of these strong positive feelings of nurturance – and the associated anxiety – as they occur across pregnancy and through the first postpartum year (Fleming et al., 1997a).

In contrast to these positive feelings are the more negative feelings experienced during the first postpartum months by a substantial number of women (Friedman & Resnick, 2009; Gale & Harlow, 2003; Marcus, 2009). Although this dysphoria or

depression usually remits by 6 months postpartum, it is a source of considerable distress for the mother and her family. A great challenge of any type of depression experienced in the postpartum period is that it is in direct conflict with societal and often self-expectations of what being a new mother should and will feel like. The truth is, the early postpartum period is a time of upheaval in the physiology and psychology of the mother, when in a short time she evolves from being a pregnant woman to the caregiver of a newborn, and this change comes with new and considerable responsibilities. Although the precise reasons for it are unclear, mood disturbances during this time are incredibly common and many new mothers feel depressed at some point after the birth of their infants (Friedman & Resnick, 2009; Marcus, 2009; Moses-Kolko & Roth, 2004). Mild depressed mood, often termed 'baby blues', is experienced by up to 85% of mothers and typically resolves without treatment by the end of the first postpartum month (Buist, 2006; O'Hara, Zekoski, Philipps, & Wright, 1990).

Postpartum depression

In some women, mood disturbance may persist beyond the initial postpartum period, leading to more serious postpartum depression. Epidemiologic studies have found that up to 20% of women exhibit symptoms of depression in the first weeks following delivery (Gavin et al., 2005; Marcus, 2009), that the rise in incidence is within 30 days post-partum but persists for up to two years, and that the great majority of these depressive episodes resolve spontaneously within six months to a year (Cooper & Murray, 1995; Cox, Murray, & Chapman, 1993). The symptom profile of postpartum depression, which includes sad mood, restlessness/agitation, and impaired concentration, resembles that of a major depressive episode experienced at other times in life, but it is unique in its timing and usually involves the mother–baby dyad and in most cases affects the entire family unit. Interestingly, there is also some suggestion that greater psychomotor disturbance may distinguish postpartum from non-postpartum depression (Bernstein et al., 2008). As with depression outside of the perinatal period, postpartum depression often co-occurs with other psychiatric disorders, the most common being generalized anxiety disorder, obsessive-compulsive disorder, social phobia and agoraphobia (Figueira, Fernandes Malloy-Diniz, Aurélio Romano-Silva, Silva Neves, & Corrêa, 2009). In some rare cases, postpartum depression has been linked to suicidality and filicide (Kauppi, Kumpulainen, Vanamo, Merikanto, & Karkola, 2008; Paris, Bolton, & Weinberg, 2009). Alarmingly, studies have also shown that as many as 50% of postpartum depression cases are undiagnosed (Chaudron et al., 2005; Murray, Woolgar, Murray, & Cooper, 2003), and reasons for this

statistic include lack of attention on the mental health of the mother by health care providers as well as under-reporting of symptoms by the mother herself. Many factors have been found to influence or mediate mothers' vulnerability to becoming depressed in the postpartum period, including: (1) factors related to childbirth and childcare such as sleep patterns, type of delivery and lack of social support; and (2) non-specific factors such as history of depression outside of the perinatal period, seasonal mood fluctuations, socioeconomic status, lack of social support, stressful recent life events and marital conflict (Boyce & Todd, 1992; Goyal, Gay, & Lee, 2009; Koo, Lynch, & Cooper, 2003; Panthangi, West, Savoy-Moore, Geeta, & Reickert, 2009; Vik et al., 2009; Xie, He, Koszycki, Walker, & Wen, 2009).

Mothering and maternal mood

Mothers with postpartum depression tend to be more intrusive and irritated, respond less sensitively, contingently and more negatively to their infants and demonstrate disrupted patterns of communication compared with mothers without postpartum depression (Beebe et al., 2008; Cohn, Campbell, Matias, & Hopkins, 1990; Field, Healy, Goldstein, & Guthertz 1990; Field et al., 1985; Fleming, Ruble, Flett, & Shaul, 1988; Paris et al., 2009; Righetti-Veltma, Conne-Perréard, Bousquet, & Manzano, 2002, for a review see Field, 2009). When observed later in the postpartum period, depressed dyads (i.e., mother-baby pairs) exhibit reduced mutual attentiveness, vocal and visual communications, touching interactions or smiling compared with non-postpartum depression dyads (Field et al., 1990; Fleming et al., 1988; Righetti-Veltma et al., 2002). For example, a recent study by Field and colleagues (2007) examined mother-infant interaction in depressed and non-depressed dyads using the still-face paradigm. Infants were approximately 4 months old at the time of testing. One of the authors' main findings, in terms of maternal responsiveness, was that the mothers with postpartum depression were less interactive with their infants at baseline (less smiling and moving of infant limbs) as well as in the still-face reunion period (less smiling, touching and moving of infant limbs). The latter finding is especially telling as a main feature of the reunion period of the still-face paradigm is to attempt to reinstate more positive interaction or regulate the emotion of the infant. It is of note that more practical, but equally important, maternal activities are also influenced by depression, including breastfeeding, bedtime routines, medical care and safety practices (reviewed in Field, 2009).

Postpartum depression also has deleterious implications for the cognitive, emotional, motor and even neural functioning of the infant (Tronick & Reck, 2009; also see Diego, Jones, & Field, 2010; Diego et al., 2004; Diego et al., 2006; Feldman et al., 2009;

Field, Diego, & Hernandez-Reif, 2009; Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2002; Field et al., 2007) and is associated with increased risk of developing psychopathology in adolescence or young adulthood (Brand & Brennan, 2009; Cicchetti, Rogosch, & Toth, 1998; Gump et al., 2009; Halligan, Murray, Martins, & Cooper, 2007).

III. Maternal behavior is affected by early experiences in family of origin

Overview

As we have seen, how mothers feel at the time they are mothers, whether depressed, anxious or stressed, has an impact on the quality and intensity of their maternal responsiveness. These affective characteristics that exert a proximal influence on mothering behavior have their own origins, often within the mothers' early experiences. In fact, among the most powerful influences on how mothers' mother their infants come from their own experiences growing up. Important aspects of mothering in the child's early life include the quality of the interaction, the warmth expressed by the mother, whether the mother-infant interaction involves predominantly physical contact and play, vocal exchanges, and/or visual mutuality. Also important for mothering is the extent to which mothers respond contingently to their infants, regardless of modality (Bornstein, Tamis-Lemonda, Hahn, & Haynes, 2008; Tamis-LeMonda, Bornstein, & Baumwell, 2001). Contingent responding encompasses the concept of mutuality and is one aspect of mothering that 'empowers' the developing infant by providing an experience of efficacy (for an example see Tamis-LeMonda & Bornstein, 1989). Hence, parents provide experiences through expression of acceptance, affection, liking and caring.

Parents also provide 'negative' and adverse experiences that impact infants and the way they come to parent their own infants when they grow up. Adverse early experiences or early adversity has been operationalized or quantified in a number of different ways, including socioeconomic factors related to housing and parental employment, illness affecting the child or close family members, family discord including parental separation and divorce, and finally, parenting practices and parenting styles (Bifulco et al., 2006; Carpenter et al., 2004; Karevold, Røysamb, Ystrom, & Mathiesen, 2009; Klein et al., 2009; Levitan, Rector, Sheldon, & Goering, 2003; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Rao, Hammen, Ortiz, Chen, & Poland, 2008; Repetti, Taylor, & Seeman, 2002; Rikhye et al., 2008). Here we will focus on early experience and early adversity as they relate to parenting practices and styles. These include physical, sexual and emotional abuse, parental neglect in terms of disinterest in material care and health, direct and indirect

control exerted over the child by the parent, and parental psychopathology such as depression and anxiety. Other known influences on mothers' ability to mother include the stability of their early family environment, the presence of both their primary caregivers as well as other immediate family members (e.g., siblings). In general, these early experiences that mothers have been exposed to affect the subsequent attachment status of the mother-child dyad, reflected in specific maternal behaviors and mothering styles.

Early experiences and intergenerational transfer of mothering styles

There is a growing literature both in humans and in other animals that shows that the quality of mothering received from one's own mother influences the quality of mothering the daughter expresses with her own offspring. For example, in rats, maternal traits such as licking and grooming have been shown to be transmitted across generations (reviewed in Champagne, Francis, Mar, & Meaney, 2003; Fleming et al., 2002; Numan, Fleming, & Levy, 2006). In human mothers, evidence exists for the intergenerational transmission of affective traits (Miller, Warner, Wickramaratne, & Weissman, 1999), parenting styles (Putallaz, Costanzo, Grimes, & Sherman, 1998; Serbin & Karp, 2004; van IJzendoorn, 1992), as well as maternal factors such as bonding and attachment (Benoit & Parker, 1994; Miller, Kramer, Warner, Wickramaratne, & Weissman, 1997; van IJzendoorn, 1992).

How parenting is transmitted across generations and the importance of early experience in the family of origin are just really beginning to be understood, mostly at the cognitive or behavioral level in human moms. There is, however, a large body of work on the behavioral and biological bases of the intergenerational transmission of maternal style in rat mothers and as this work is relevant to the present discussion we will now describe it in brief. Four major components of maternal behavior in rats are retrieval behavior, nest building, nursing behavior, and pup grooming, which includes licking (Numan & Insel, 2003). In rat studies of mothering, the best approximation of variation in maternal care is demonstrated by the elegant studies of Michael Meaney and his students in which they show that the licking exhibited by mother rats shows a very large variation, variation that influences the quality and intensity of the licking behavior of their female offspring that become the next generation of mothers (Champagne & Meaney, 2001). The observation from cross-fostering studies that the licking profile of offspring is determined by their preweaning experiences (hence, the pattern shown by the foster mothers) and not by their genetic origins suggests that the postnatal experiences of the young are crucial to their later behavior with their own off-

spring (Champagne & Meaney, 2001). Thus, as we would expect, maternal behavior deficits observed in adulthood are related to the degree of maternal deprivation received as a neonate (Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001; Lovic et al., 2001; Rees, Akbari, Steiner, & Fleming, 2008) and, importantly, observed behavioral differences are accompanied by structural brain changes (Burton et al., 2007; Chatterjee et al., 2007; Gonzalez & Fleming, 2002). Offspring of high licking moms become high licking moms (Champagne & Meaney, 2001). Rat pups reared in isolation from their mother and without such stimulation, however, show maternal behavior deficits in behaviors such as crouching and licking (Gonzalez et al., 2001; Melo et al., 2006), an effect that is retained even towards foster pups (Palombo, Nowoslawski, & Fleming, 2010). Furthermore, deficits are related to the degree of early maternal separation with more extreme separation paradigms associated with the most severe behavioral deficits (Lovic et al., 2001; Rees et al., 2008). Maternal separation and the associated reductions of stimulation in pups are further related to the progressive dysregulation of physiological processes in the offspring as well as behavioral deficits related to social learning, sustained attention, inhibition of acoustic startle, and perseveration. It is generally accepted that early experience, notably the quality and quantity of maternal care, influences the plasticity and function of set of brain structures that are genetically mandated to express maternal behavior; this circuit interfaces with brain structures that mediate emotion, sensation, perception, memory and cognitive functions.

In human mothers, research also suggests that early adversity as indexed by quality of care in the family of origin may also affect subsequent parenting (Belsky, 1984; Champagne & Meaney, 2001; Fleming et al., 2002; Maestripieri, 2005). The significance of this statement is underscored by the fact that maternal history of abuse has been proposed as a risk factor for child maltreatment. Approximately 30% of mothers who were abused as children go on to abuse their own children, compared to 5% in mothers not reporting abuse (Knutson, 1995). While the mechanisms underlying a posited 'cycle of abuse' are not well understood, as previously noted, there is support for the intergenerational transmission of parenting styles, which includes factors such as bonding, attachment and maternal rejection (Benoit & Parker, 1994; Miller et al., 1997; Serbin & Karp, 2004; van IJzendoorn, 1992). Moehler, Biringen, and Poustka (2007) analyzed whether emotional availability measured during mother-infant interaction is altered by experiences of physical or sexual abuse in the mother's family of origin. Results revealed that mothers with a history of physical or sexual abuse were significantly more intrusive toward their children than were control mothers. The relationship between maternal early experiences and perceived

parental stress has also been examined. In a study of 120 mothers, Willinger and co-authors (Willinger, Diendorfer-Radner, Willnauer, Jörgl, & Hager, 2005) measured recalled parental bonding and parenting stress and found that higher levels of parenting stress were experienced by mothers reporting less optimal parental bonding. Adverse early experiences are also risk factors for difficulties in mothering, albeit indirectly, through their relationship with maternal psychopathology.

Epidemiological studies indicate that children exposed to early adverse experiences, including those related to bonding and attachment, are at increased risk for the development of depression, anxiety and other stress-related disorders in adulthood (Enns, Cox, & Clara, 2002; Putnam, 2003) and during adolescence (Herrenkohl et al., 2010; Martin, Bergen, Roeger, & Allison, 2004; Rey, 1995). Spertus, Yehuda, Wong, Halligan, and Seremetis (2003) found that a history of emotional abuse and neglect was associated with increased anxiety, depression, posttraumatic stress and physical symptoms and that long-standing behavioral consequences may arise as a result of childhood emotional abuse and neglect, specifically, poorer emotional and physical functioning, factors that would certainly put these women at risk for difficulties in mothering. In addition, an intergenerational effect may account for cyclical occurrence of teenage motherhood (de Paúl & Domenech, 2000; Rebollo & Montero, 2000; Giardino, Gonzalez, Steiner, & Fleming, 2008), where teen mothers often raise poorly adjusted children who tend to become teen parents (Furstenberg, Brooks-Gunn, & Morgan, 1987).

Now a disclaimer! Despite these clear relations between early adversity (and/or retrospective perception of that adversity) and later emotional and parenting problems, the statistic in humans relating to the intergenerational transmission of abuse indicates that 70% of mothers who were abused will NOT abuse their own offspring, indicating that there exists a host of factors that protect prospective mothers from the riskiness of their early experiences. Included among the buffers that are in play are having social supports or a supportive adult somewhere in the environment of the developing child (Jaffee, Caspi, Moffitt, Polo-Tomás, & Taylor, 2007; Kaufman et al., 2004; Wind & Silvern, 1994) as well as forming a partner relationship with a supportive spouse in adulthood (Seeman, Singer, Ryff, Dienberg Love, & Levy-Storms, 2002). These buffers also speak to the issue of the plasticity of the mothering system. Early experiences can have profound influences on the development of all the constituents that must develop for appropriate mothering to be expressed in terms of affect, attention, learning and so on. And it may well be that the early periods are more susceptible to 'negative' experiences than are the later periods in development (Heim & Nemeroff, 1999; McEwen, 2003); however, experiences acquired later on are either able to reverse earlier

effects or cause development to follow a different path (McEwen, 2003). In support for this, recent work by Bergman, Sarkar, Glover, and O'Connor (in press) demonstrated that the (potentially) deleterious influence of maternal prenatal cortisol on infant development is mediated by mother–infant attachment in the second year of life, with more securely attached toddlers showing no effect of prenatal maternal cortisol on cognitive abilities and insecurely attached toddlers showing a significant, positive relationship.

IV. What has informed us up until this point: Hormones

Basic mechanisms

Hormones play a fundamental role in maternal behavior and have been a focus of much research in animal mothers and only more recently, in humans. Research in rats and other mammals has shown that the hormonal cocktail of pregnancy and parturition, which includes high levels of the peptide hormones, oxytocin and prolactin, against a background of changing levels of steroid hormones, estradiol and progesterone, is essential for the onset and maintenance of maternal behavior (Bridges, 1990; Bridges, 2008; Insel, 1990; Numan et al., 2006; Pryce, Martin, & Skuse, 1995; Rosenblatt, Olufowobi, & Siegel, 1998).

Although evidence for this is stronger in rat compared with human mothers, this hormonal profile is thought to increase mothers' attraction to infant cues, enhance the reinforcing value of pups, and influence affective state (Fleming, Ruble, Krieger, & Wong, 1997a; Numan et al., 2006; Numan & Insel, 2003). In pregnant women, feelings of attachment to the fetus appear to be unrelated to changing levels of pregnancy hormones. However, Fleming et al. (1997a) did find a relationship between hormones and attachment: high attachment to new babies postpartum was related to an increase from early to late pregnancy in estradiol/progesterone ratio and low attachment was related to a decrease in the estradiol/progesterone ratio.

Furthermore, mothers with a greater shift in the estradiol to progesterone ratio across pregnancy also experienced greater feelings of well-being in the postpartum period. Hormones and well-being together explained 40% to 50% of the variance in mothers' attachment (Fleming et al., 1997a). A role for oxytocin in humans is also suggested by recent work by Feldman, Weller, Zagoory-Sharon, and Levine (2007) in which they found that oxytocin levels both during early pregnancy and postpartum were associated with behaviors in mothers normally measured in mother–infant interactions, including gaze, vocalizations, positive affect, and affectionate touch; they also found oxytocin levels related to attachment-related thoughts. These results are

striking in their similarity to what has been described in other mammals and likely reflect an effect of oxytocin in a mother who has been previously primed by estrogen.

Similar to what has been shown in rat mothers (Rees, Panesar, Steiner, & Fleming, 2004, 2006), postpartum hormones from the hypothalamic-pituitary-adrenal (HPA) axis may also be important in mothers' response to their newborns. The HPA axis and HPA-reactivity have been widely studied in humans and animals in the context of emotion, stress and psychopathology (see Heim & Nemeroff, 1999; Heim, Plotsky, & Nemeroff, 2004; McEwen, 2003). We have (Fleming, Steiner, & Anderson, 1987; Corter & Fleming, 1990) examined cortisol in relation to maternal behavior in the early postpartum period when cortisol levels are relatively high and mothers' emotional status is labile. Higher cortisol levels on days 3 and 4 postpartum were significantly and strongly associated with maternal approach behaviors, positive maternal attitudes, or more vocally active infants. Generally, our work suggests that in the early postpartum period (i.e., first postpartum week) in first-time mothers, the HPA system may influence maternal responsiveness by enhancing the salience of infant stimuli and attention to it. Later in the postpartum period (i.e., five to six months postpartum) or in mothers who are stressed and/or 'at risk', however, the HPA axis may have a negative relation with mothering (Krupan, Coombs, Zinga, Steiner, & Fleming, 2005). In short, the precise relation between the HPA system and mothering is unclear and likely varies as a function of the age of the mother, the postpartum period being assessed, the source of the HPA activity (whether through stress or not) and the early experiences of the mother (Gonzalez et al., 2009; Krupan et al., 2005; Stallings, Fleming, Corter, Worthman, & Steiner, 2001).

Depression and HPA function

Activity in the HPA axis has been linked to postpartum depression, albeit inconsistently. Increased cortisol plasma levels have been associated with postpartum depression in some studies (Nierop, Bratsikas, Zimmermann, & Ehlert, 2006), but not in others (Groër & Morgan, 2007; Jolley, Elmore, Barnard, & Carr, 2007; Kammerer, Taylor, & Glover, 2006) and have even been associated with positive affect (e.g., Groër, 2005). As with studies of non-depressed mothers, work suggests that when examining the relationship between cortisol, maternal behavior and mood, factors such as the context for cortisol elevation (e.g., relationship between early life stress and cortisol), maternal age and postpartum stage must be considered. More clues as to the relationship between postpartum depression, cortisol and early experience may be found in the literature on HPA function and non-postpartum depression. Abnormal HPA-axis function has been

frequently observed in major depression. Depression is thought to be characterized by reduced sensitivity of stress-hormone-related negative feedback mechanisms which are associated with larger hormonal response to stressors, higher baseline levels of stress hormones and reduced suppression of the HPA axis in response to the dexamethasone test (Heim et al., 2004). Studies of corticotrophin releasing factor measured in human lumbar cerebrospinal fluid (CSF) have shown increased levels of this stress-related peptide in depressed patients compared to control participants (Banki, Bissette, Arato, O'Connor, & Nemeroff, 1987; Banki, Karmacs, Bissette, & Nemeroff, 1992; France et al., 1988; Nemeroff et al., 1984). When examined post-mortem, the brains of depressed patients have been found to have increased CRF mRNA and increased CRF concentrations in the hypothalamus. In addition, CRF levels in CSF have been found to normalize following successful antidepressant treatment (Nemeroff, Bissette, Akil, & Fink, 1991; Rudorfer, Risby, Osman, Gold, & Potter, 1991). It is important to note that, as with postpartum depression, results for HPA axis function in depression have been mixed; one intriguing explanation given for the disparate results is the notion that HPA function in depression may differ depending on depression subtype (e.g., melancholic, atypical) or on the history of early adversity (Gunnar & Fisher, 2006; Heim et al., 2004).

Early adversity and HPA function

There is little question that adverse early experiences (or early adversity) can lead to heightened stress reactivity that in many cases persists into adulthood. Evidence from animal work suggests that early life experiences related to maternal separation and quality of early maternal care modulate the development of a number of endocrine systems, including the stress system or HPA axis (Champagne & Meaney, 2001). Rat moms who were raised without their mothers or who were raised by mothers who expressed low levels of maternal licking show elevations in postpartum glucocorticoids (Burton et al., 2007; Francis, Diorio, Liu, & Meaney, 1999). Moreover, maternal separation is associated with increased CRF mRNA expression and sensitization of neurons in hypothalamic and limbic regions, decreased glucocorticoid receptor density in the hippocampus and prefrontal cortex, decreased neurogenesis in the hippocampus, as well as altered function of important neurotransmitters (reviewed in Heim et al., 2004). Work on early adversity in primates, where maternal separation or stress paradigms more closely resemble what happens between human moms and infants, has been a bit more complex, demonstrating both HPA axis hypoactivity (Coplan et al., 1996; Rosenblum et al., 2002) and hyperactivity (Fahlke et al., 2000; Higley, Suomi, & Linnoila, 1991, 1992). Results with human children

and adults map onto some animal HPA axis findings quite nicely. Attachment status has been found to influence the reactivity of cortisol secretion in infants (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Nachmias et al., 1996) and adverse early experience has been shown to relate to adrenal response to stress in adolescence (Rao et al., 2008). In adults, in a series of recent studies we found that mothers who were either at-risk teens (Krpan et al., 2005) or clinically depressed (Gonzalez, Steiner, & Fleming, in preparation) were more likely to show less affectionate and disrupted interactions with their infants and had elevated basal cortisol levels. Teen mothers with this endocrine and behavioral profile were also more likely to experience inconsistent care and to have experienced multiple and changing caregivers (Krpan et al., 2005). In addition, adult mothers who were exposed to early adversity (inconsistent care and/or maltreatment) had higher levels of diurnal cortisol (measured from an area under the curve over two consecutive days) and were less sensitive when interacting with their infants (Gonzalez, Steiner, & Fleming, in preparation). The question remains as to whether the elevated cortisol levels in high-risk mothers are especially related to the postpartum period or also present through childhood and adulthood. In fact, a number of retrospective studies have found that outside of the postpartum period, women abused as children do show elevated peak adrenocorticotrophic hormone (ACTH) responses to stress and more prolonged cortisol responses. This effect seems to be strongly related to the woman's current mood state, however, where abused women *without* current depression actually demonstrate decreased cortisol responsiveness and basal cortisol levels and abused women with depression demonstrate features more consistent with hyperactive HPA function (Heim et al., 2004).

Relation of early adversity to depression

It is difficult to talk about hormones, early adversity and depression without integrating the three. In fact, it is also challenging to find research papers where these topics are not interrelated in some manner. Many of the neurobiological effects of early adversity resemble those of depression and, not surprisingly, early adversity is thought to precipitate depression or contribute to a vulnerability to become depressed. One of the strongest risk factors for the development of depression in adulthood is a history of childhood adversity, including parenting factors such as abuse, insecure attachment, parental rejection and lack of warmth (reviewed in Heim, Plotsky, & Nemeroff, 2004; Karevold et al., 2009; Penza, Heim, & Nemeroff, 2003). In terms of depression, early adversity is associated with earlier onset, greater number of episodes, more chronic course of the illness and greater suicidality (Bernet & Stein, 1999; Bifulco, Moran, Baines, Bunn, & Stanford, 2002;

Brown & Moran, 1994; Brown, Cohen, Johnson, & Smailes, 1999; Harkness & Monroe, 2002; Lizardi et al., 1995; McCauley et al., 1997; Moskvina et al., 2007). Some factors thought to mediate the relationship between early adversity and depression are gender (women are more vulnerable), the timing of the early adversity (earlier childhood is a more vulnerable period), the experience of stress in later life and genes (Heim & Nemeroff, 1999; Heim et al., 2004).

Generally speaking, the effects of early adversity on physical and emotional health beginning in early childhood and continuing throughout development are believed to be related to plasticity of the central nervous system as a function of environment and experience. As already noted, stress or trauma experienced during development can permanently shape brain regions that mediate stress and emotion, including the prefrontal cortex and amygdala (Heim & Nemeroff, 1999; Roceri et al., 2004). At the pre-clinical level, much work in animals has also demonstrated that the repeated stress and associated physiology can lead to coordinated changes in numerous behavioral, autonomic and endocrine systems that share features with those observed in depression (for reviews see Heim & Nemeroff, 1999; Kaufman, Plotsky, Nemeroff, & Charney, 2000; McEwen, 2003). A prevailing theory about pathways from early adversity to depression involve the notion that repeated or severe stress early in life is associated with sustained cortisol responses, which is related to brain damage in stress/emotion circuits, which is related to further impairments in stress and emotion responses (Heim et al., 2004). Interestingly, it has also been proposed that not all depression is related to early adversity and that early-adversity precipitated depression may represent a distinct depression subtype (Heim et al., 2004). This suggestion may underscore the importance of examining early experiences in order to understand the nature and etiology of postpartum mood changes.

V. Functional neuroimaging of mothering

Identifying regions of interest

To this point we have described a complex set of psychological and endocrine factors that are known to affect maternal motivation, attitudes, and behavior. What we have not discussed and what follows is an analysis of the growing literature on the neuroanatomy of mothering, taken from both the animal literature and the recent functional magnetic resonance imaging (fMRI) literature. The approach we adopt to understanding that neuroanatomy is to consider functional neuroanatomy that underlies mothering itself as well as the psychological systems that affect mothering and that are discussed above. Included among these are systems related to maternal affect and depression, reward, cognition,

and early experience. How these functional and neural systems interface with the maternal circuitry is what we now explore.

The increasingly widespread use of magnetic resonance imaging (MRI) as a tool to non-invasively investigate the structure and function of the human brain has opened up the field of human neuroscience to a broad number of topics, including maternal behavior. Despite this, there are currently fewer than 20 published investigations of the neuroanatomy of mothering and very few reports of at-risk mom populations. While recent fMRI work (to be detailed later) has made a promising start, there is clearly much work to be done. Despite the relative paucity of human mother studies, when looking to understand the maternal brain in human mothers and when formulating our hypotheses/expectations, we are fortunate to be informed by a large body of work on the maternal brain in animal species.

Animal studies. The neuroanatomy of animal maternal behavior is based predominantly on work with rats, voles, sheep, and primates (summarized in Numan et al., 2006). Taken together, these cross-species studies indicate a striking similarity in the neuroanatomy that underlies mothering. Numan has provided us with an exquisite description and analysis of the functional neuroanatomy of maternal behavior in the rat (see Numan & Insel, 2003; Numan et al., 2006; Numan, 2007). The circuit involves both

excitatory and inhibitory systems. However, most work in the area has focused on the final common path for the expression of the behavior, the medial preoptic area of the hypothalamus (MPOA), and its downstream projections into the midbrain (ventral tegmental area, VTA), hindbrain (periaqueductal gray; PAG) and sensory, limbic, and cortical systems that project into the hypothalamus (see Figure 1). The MPOA region of the hypothalamus contains receptors for all the hormones involved in the activation of maternal behavior, including receptors for estradiol, progesterone, prolactin, oxytocin, vasopressin, and opioids (see Numan et al., 2006). Neurons projecting into the MPOA region of the hypothalamus are also involved in other behavioral changes, including changes in mothers' affect (amygdala, prefrontal cortex), stimulus salience (amygdala and striatum/nucleus accumbens), attention (nucleus accumbens and medial prefrontal cortex), and memory (nucleus accumbens, medial prefrontal cortex). Some of these sites also contain hormone receptors (amygdala, medial prefrontal cortex) and may be the sites where the periparturitional hormones likely act to change behavior at the time of parturition (Numan et al., 2006).

While the rat/animal models of maternal behavior are elegant and informative and have identified some key regions in a putative mothering circuit (e.g., hypothalamus, amygdala, prefrontal cortex, nucleus accumbens), we know that the brains and behaviors

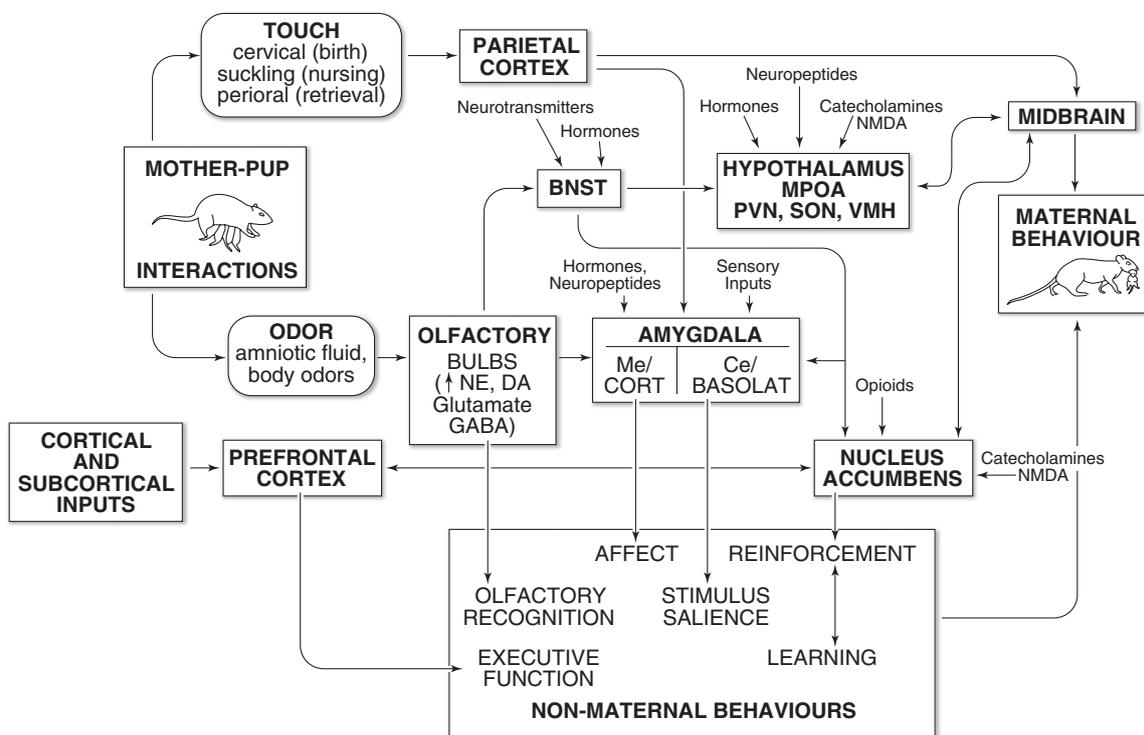


Figure 1 Functional neuroanatomy mediating maternal and related behaviors in mammals. Neuroanatomical structures include olfactory bulbs, amygdala, nucleus accumbens, bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), ventromedial hypothalamus (VMH), periventricular nucleus (PVN), supraoptic nucleus (SON), midbrain, and parietal cortex. Relevant neurochemistry includes the catecholamines norepinephrine (NE), and dopamine (DA), the neuropeptides, and the opioids

of human mothers and mother–infant interactions are far more complex than in lower mammals. Thus, while animal work provides one important framework, we must consider other brain systems as well. As already noted, to mother appropriately requires the action of multiple behavioral systems in the domains of sensation, perception, emotion and motivation, reward, executive function, motor output and learning. As a mother–infant dyad are interacting, the mother is receiving sensory input about how her child looks, sounds and smells, she has feelings that may change rapidly in the moment and also a baseline level of affect that may not be situation dependent, she is moving, touching, kissing, speaking, singing, rocking, reacting, she is attending and sometimes spreading her attention across a number of activities or stimuli, she is thinking about her child and perhaps other things and sometimes planning and controlling the nature of play. She is busy. Of course, as for essentially all experimentally manipulated or scientifically observable human behavior, every region of the brain and all major brain systems are active, in some manner. The brain does not have an off switch.

One strategy to reduce this complexity adopted by us (and others), however, is to focus on neural systems that are particularly relevant or compelling in the context of mothering: (a) social behavior; (b) reward and affect; (c) executive function; and, of course, (d) maternal behavior. Studies examining maternal behavior will be discussed last, not as a reflection of their (in)significance but rather to emphasize the broad overlap between work investigating maternal behavior proper and work investigating strongly related psychological constructs. After we have examined systems we feel contribute to and interact with systems mediating maternal behavior, we can more thoughtfully discuss imaging studies looking at maternal response to infant stimuli in the context of regions of interest (see Figure 2): Hypothalamus/MPOA (maternal behavior, drive states), nucleus accumbens (stimulus salience, affective valence), amygdala (emotion/affect response and regulation, affective valence), anterior cingulate cortex (affect response and regulation, affective valence, stimulus salience, executive function, social cognition), orbitofrontal cortex (stimulus salience, affective valence, executive function), dorsolateral prefrontal cortex (affect regulation, executive function). To aid the reader in this anatomical journey we include a schematic of the neural regions that will be discussed as well as a table listing the different neural structures, their known functions, and the relevant references (see Figures 2 and 3).

Social behavior, reward and affect

Social behavior. As mother–infant interaction is, broadly speaking, a social behavior, a focus on mothering within the context of social behavior is

appropriate. The study of social behavior and related constructs (e.g., social cognition, affiliation, love, attachment/bonding, empathy) is concerned with our perceptions of and interactions with familiar and unfamiliar others. The related fMRI studies have used a number of different paradigms using social stimuli, including reading empathy-eliciting scripts, exposure to stimuli of loved ones and exposure to emotional social stimuli (e.g., faces) with and without contextual factors. Brain regions that are commonly identified in these studies include the amygdala, anterior cingulate cortex (ACC) and dorsal and ventral striatum (e.g., Kim et al., 2009a; Kirsch et al., 2005; Platek & Kemp, 2009; Zahn, de Oliveira-Souza, Bramati, Garrido, & Moll, 2009); these brain regions are more generally implicated in emotion perception/regulation, action initiation and stimulus valence/salience and are also known to contain receptors for hormones thought to be important in social behavior (i.e., oxytocin, vasopressin; Debiec, 2005; Huber, Veinante, & Stoop, 2005; Keverne & Curley, 2004; Schorscher-Petcu, Dupré, & Tribollet, 2009; Smeltzer, Curtis, Aragona, & Wang, 2006). Studies of social cognition typically involve response to emotional and non-emotional human faces (e.g., Kirsch et al., 2005; Mitchell, Neil Macrae, & Banaji, 2005; Schulz et al., 2009). Kirsch and colleagues (2005) added the administration of the ‘affiliative’ peptide, oxytocin, to a social cognition paradigm which involved responding to an emotional (angry, afraid) face-matching task. Intriguingly, the authors found that the administration of oxytocin attenuated the expected amygdala response to the negative social stimuli (faces). Amygdala response to emotional or other self-referential faces is complex with increased activity in the amygdala associated with negative faces (e.g., fearful faces; Gamer & Büchel, 2009), positive faces (Derntl et al., 2009; Killgore & Yurgelun-Todd, 2004; Williams, McGlone, Abbott, & Mattingley, 2005) and familiar faces (Platek & Kemp, 2009). In contrast, some studies also report a decrease in amygdala activity in response to familiar faces (e.g., Bartels & Zeki, 2004). These discrepant findings could reflect the multifaceted role of the amygdala in the processing of emotional and/or social stimuli: the amygdala is involved in basic stimulus perception, the integration of stimuli with an affective ‘value’ and organizing output to guide affective, autonomic and behavioral responses (reviewed in Gobbini & Haxby, 2007). The amygdala’s function in integrating multiple brain systems in order to guide behavior is also sensitive to contextual demands (e.g., task requirements, environment), stimulus valence as well as, perhaps, the mood and affect of the individual. Thus, as with animal models, a positive relationship between activity in the amygdala and positive mothering behavior cannot be assumed and numerous factors should be considered when evaluating the role of the amygdala in maternal behavior.

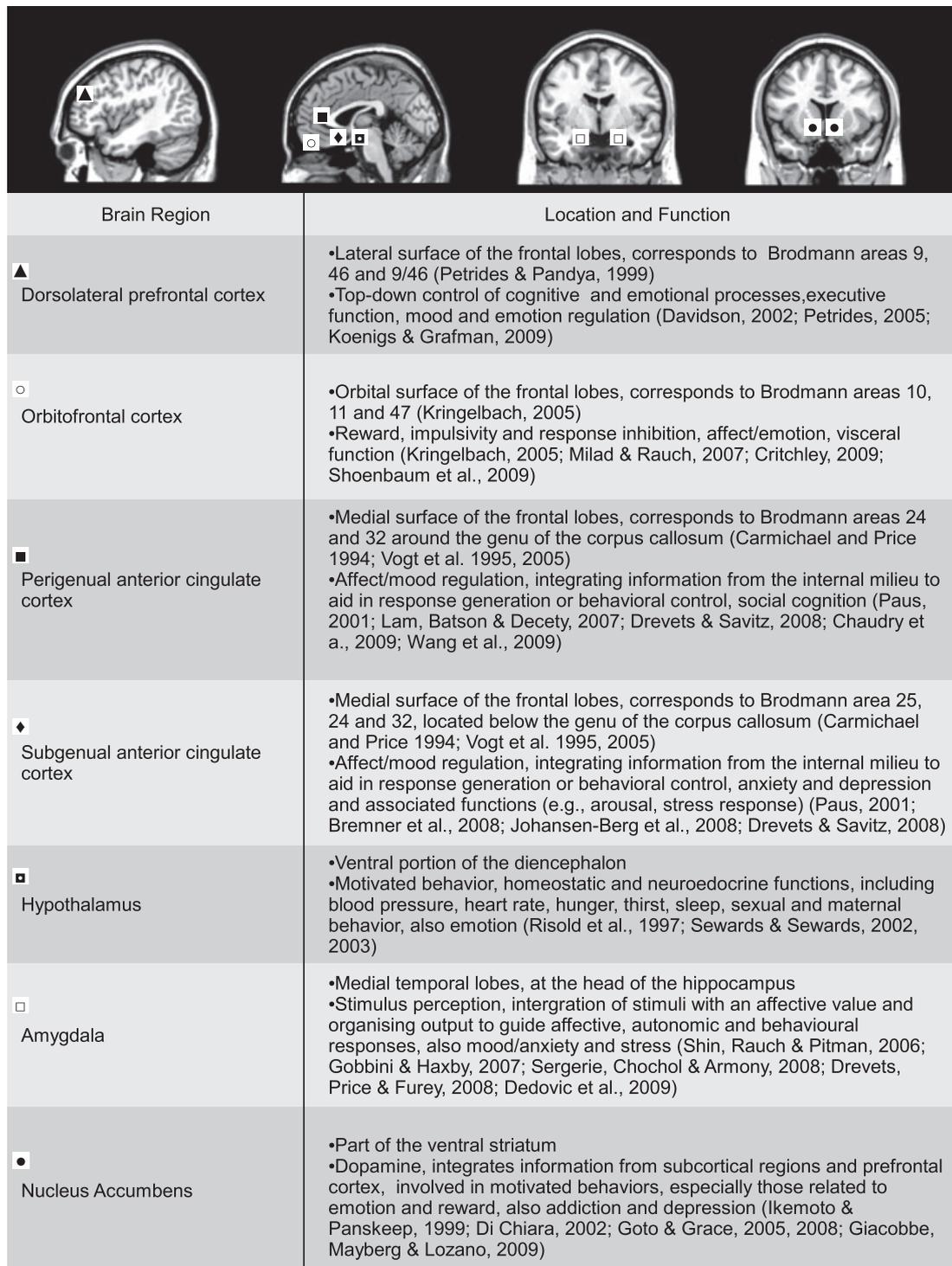


Figure 2 Brain structures thought to be important in human maternal behaviour. Note that these structures are comprised of classic maternal regions such as the hypothalamus, as well as regions with primary functions important to maternal behaviour. The top panel illustrates the approximate anatomical location of each region; the bottom table contains a coded legend describing each region in terms of location and function

Investigating more abstract concepts related to social behavior, a recent study by Kim and colleagues (2009a) examined the neural correlates related to compassionate concerns which was defined as ‘related to the motivation to approach, help, comfort or otherwise alleviate suffering’ (Kim et al., 2009a). During fMRI, male and female participants completed a task that involved a passive

condition of simply viewing a set of sad faces and an active condition where participants were instructed to view the face while attempting to feel/share/understand the person’s suffering. Viewing neutral and sad faces with a ‘compassionate attitude’, compared with passive viewing, was related to increased activity in the medial prefrontal cortex (including subgenual ACC), dorsal and ventral striatum as well

as the insula, thalamus and periaqueductal grey. The authors interpreted their results in the context of Theory of Mind, which has been associated, among other areas, with activity in the medial prefrontal cortex (Saxe, Moran, Scholz, & Gabrieli, 2006; Schulte-Rüther, Markowitsch, Fink, & Piefke, 2007; Spreng & Grady, 2009). As previously noted, Theory of Mind, a theory about how we understand the intentions and emotions of others, has obvious implications for individual differences in mothering, where correctly identifying and responding to infant signals is key. One aspect of Theory of Mind reasoning is that we understand the internal states of others (and hence experience empathy) by simulating their experience at the neural level (Blakemore & Decety, 2001; Rizzolatti & Fabbri-Destro, 2008; Schulte-Rüther et al., 2007). An extension of this notion is that our ability to understand the mental world of another is tied to mirror neuron activity, that is, brain response that is related to observation of another that mimics the brain response associated with the (other) occurring thought/emotion. This idea was first described as a motor phenomenon (see the excellent work of G. Rizzolatti; for a review see Rizzolatti & Craighero, 2004), but it has recently been applied to social cognition (e.g., Rizzolatti & Fabbri-Destro, 2008; Schulte-Rüther et al., 2007). Recent work has also linked Theory of Mind to the Default Mode Network, a core set of brain regions involved in reflecting on the past, present and future and on the minds of others that also includes the medial prefrontal cortex as a main player (Spreng & Grady, 2009).

Relatedly, Zahn and colleagues (2009) were also interested in the role of the subgenual ACC in empathic concern and noted that this region may be particularly important when stimuli are self-relevant and/or reflect individual differences in empathic behavioral response. In this study, a behavioral index of empathic concern was obtained from male and female participants and was later correlated with subgenual ACC response to reading scripts designed to elicit feelings of guilt compared with a control condition. The authors reported that subgenual ACC activity while reading the guilt-eliciting scripts was positively associated with an individual's level of empathic concern, with higher levels of empathic concern related to greater activity in the subgenual ACC. The ACC is an especially interesting region as its patterns of connections make it an ideal structure to integrate information about the internal milieu to guide action, subjective feeling or thought. The subgenual ACC in particular, with its strong connections with the amygdala and nucleus accumbens, is also believed to play a more general role in affect regulation and motivation.

Finally, much research in the area of social behavior has sought to investigate the neural correlates that underlie feelings of love for romantic

partners as well as for offspring. In an influential study, Bartels and Zeki (2000) found that viewing pictures of romantic partners compared with friends was related to increases in activity in the striatum, ACC, periaqueductal grey, insula and hippocampus and, interestingly, decreases in activity in regions of the prefrontal cortex (Bartels & Zeki, 2000). It is of note that this pattern of activity was also observed, in a separate study, for own children compared with familiar children (Bartels & Zeki, 2004). The authors conclude that love relationships are (should be) inherently rewarding and must be to ensure the perpetuation of the species. Thus, human attachment may be associated with increased activity in reward-related brain regions and, perhaps, decreased activity in brain regions involved in negative affect and/or negative social evaluation. Indeed, in humans as in animals, there has been much support for the involvement of dopamine-rich regions of the striatum in feelings of love and attachment (Fisher, Aron, & Brown, 2005; Aron et al., 2005).

Reward and affect. Mothering and nurturance are also often grouped within basic drive states of sexual desire, hunger/thirst, fear, power-dominance, etc. (Sewards & Sewards, 2003). As already mentioned, as infant (and species) survival depends on it, we expect that most mothers will be *motivated* to display maternal care to some extent and given the right circumstances and history, will find themselves more attracted to their babies than repulsed by them. That is, with birth, the balance of approach to avoidance will tip in favor of approach and increasingly so with additional positive experience. In animal models, maternal behavior has been framed in the context of approach-avoidance tendencies, where the onset of maternal behavior occurs when the tendency to avoid pups, find them aversive and/or view them with indifference is suppressed and the tendency to approach pups and find them rewarding and/or pleasant is enhanced (Fleming & Rosenblatt, 1974a, 1974b; Numan, 2007; Rosenblatt, 1969, 1975a). In the animal model, brain systems that initially mediate fear and avoidance include the olfactory bulbs and tracts, the medial amygdala, the bed nucleus of the stria terminalis, and the ventromedial hypothalamus (VMH); prior to late gestation, these systems inhibit the MPOA. However, with hormonal priming during late pregnancy and with parturition, these systems come under inhibition and pup odors which prior to birth were initially avoided take on a positive valence when the pups are born. It is of note that this priming can also occur in virgin females, to some extent, by prolonged experience with or exposure to pups. Thus, the inhibition that the MPOA is under in the virgin animal is removed when gestational/parturitional hormones are present or when a virgin experiences sensitization. One can think of this as disinhibiting the

inhibition that the MPOA is under from the amygdala, through the VMH. This motivational model of mothering involves brain systems important in stimulus salience and valence, for example, how positive pups are and how rewarding they become with experience, or how anxiety-inducing pups are.

There is certainly evidence at the behavioral level for changes in infant-related stimulus salience and emotion in mothering in human moms. Compared to mothers, non-mothers find infant odors less pleasing and show a different autonomic and emotional (i.e., emotion ratings) response to infant cries (Fleming, Steiner, & Corter, 1997b; Giardino et al., 2008; Stallings et al., 2001). In addition, a mother's own feelings of attachment to her baby increase over the course of her pregnancy, a phenomenon that may also reflect an increase in or readiness for 'approach' behaviors. However, as we are talking about motivation, affect and reward, terms which have been used interchangeably in some studies, we must emphasize that, in our conceptualization, mothering represents a motivated behavior that has an impact on and interacts with reward and affect systems.

Not surprisingly, in humans, the findings of neuroimaging studies focusing on reward and affect show considerable overlap with brain regions that are activated in mothers by infant cues; these include the prefrontal cortex (ACC, orbitofrontal cortex (OFC)), striatum (nucleus accumbens), amygdala and hypothalamus. In a striking example of the overlap between mothering neural circuits and those involved in affect (mood), Johansen-Berg and colleagues (2008) examined the connectivity of the ventral ACC, the anatomical target of deep brain stimulation that has alleviated depression in some patients (Mayberg et al., 2005). The anterior cingulate cortex has been widely implicated in the regulation of mood, including major depression, as well as anxiety (Drevets, Savitz, & Trimble, 2008). Using tractography of diffusion imaging data, which allows for the in-vivo mapping of white-matter tracts, the authors confirmed in humans what has been established in animals: the anatomical connections between the ACC and the hypothalamus, nucleus accumbens, amygdala, OFC, dorsomedial frontal cortex and frontal pole (Johansen-Berg et al., 2008). Depression is characterized by impairments in (or *depression of*) other drive states that operate on the same neuroendocrinological systems as maternal behavior (e.g., sexual desire, hunger/thirst, sleep) and is also characterized by impairment in reward processing (e.g., pleasure of interest in people and activities) which is known to be critical in the activation of maternal behavior. Thus, it is not surprisingly that mothering and depression share so much overlap in terms of brain systems, nor is it surprising that depression has such a powerful impact on the capacity for, or motivation to, mother.

Anxiety is also an important affective state that is relevant to animal models of mothering and is also strongly comorbid with depression. In fact, for the most part key cortical and subcortical structures implicated in the stress response (and also, the deleterious influence of early adversity) also completely overlap with those involved in mothering (e.g., the prefrontal cortex and amygdala; see Kaufman et al., 2000). Much research examining stress and fear-related processes, including anticipatory anxiety, have demonstrated a role for the ACC and the amygdala (e.g., Barrett & Armony, 2009; Nitschke et al., 2009; Sarinopoulos et al., 2009). One model of fear/anxiety learning and extinction posits that inhibition of the amygdala by the ACC is important in learning when a fear or stress response is appropriate and when it is not. Some work has also linked deficits in this system to mechanisms underlying the development of maladaptive fear responses as in post-traumatic stress disorder (reviewed in Rauch, Shin, & Phelps, 2006), the pathology of which is thought to share similar mechanisms with early adversity.

Given the motivational model of mothering in the rat, it will be interesting to examine further whether or not there exists an infant-related avoidance tendency in human women and if a similar ACC-inhibition of the amygdala may be related to a shift from avoidance to approach tendencies. An obvious problem with this suggestion is that human women rarely show overt avoidance of infants and in fact the opposite is often true for both nulliparous and multiparous mothers (see Glocker et al., 2009). However, differences do exist in terms of emotional and autonomic response to infants in nulliparous and multiparous mothers and there are often vast differences in the nature of responsivity to infants across mothers. It is also important to note that imaging studies have suggested that human attachment may be associated with increased activity in reward-related brain regions and, perhaps, decreased activity in brain regions involved in negative affect and/or negative social evaluation (Bartels & Zeki, 2004). It is possible, then, that a similar motivational push-pull exists in human mothers, albeit to a more subtle extent. In other words, in a human model the 'push' side of things may not be characterized by the unmistakable hostility or avoidance that has been observed in inexperienced or virgin rats, but by negative affect and anxiety or more subtle signs of rejection (e.g., looking away from the infant, negative comments about the infant). It is also possible that functional differences in important regions in such a push-pull circuit, for example hyperactivity of the amygdala and/or lack of inhibition by the ACC, in response to the infant, may explain variability in quality of mothering behaviors.

In terms of what is known about the neurocircuitry of reward, a great deal of focus has been on the dopamine system and neural structures rich in

dopamine receptors or key structures in dopamine-related brain circuits. Based on animal work, these regions include dopamine centers in the midbrain and the striatum (e.g., nucleus accumbens) and connected cortical regions (medial prefrontal cortex, OFC; Hollerman, Tremblay, & Schultz, 2000; Wise, 2000). There is now a substantial animal literature showing that the nucleus accumbens is important for maternal behavior and that dopamine is released in this site in response to pups or pup cues in new mother rats, experienced mother rats and virgins induced to be maternal through simple exposure (i.e., sensitized virgins) (Afonso, Grella, Chatterjee, & Fleming, 2008; Afonso, King, Chatterjee, & Fleming, 2009; Champagne et al., 2004; Mattson & Morrell, 2005; Olazábal, Abercrombie, Rosenblatt, & Morrell, 2004). Moreover, there is substantial evidence that the dopamine release profile to pups in mothers depends on the action of the parturitional hormones and is different from the profile of dopamine release to food in these mothers (Afonso et al., 2009). It is different as well from the profile shown by sensitized virgins, but not the profile shown by hormonally primed virgins (Afonso et al., 2008, 2009).

Human work has for the most part confirmed the (non-maternal) animal findings in imaging studies examining the rewarding nature of food (Goldstone et al., 2009; Grabenhorst, Rolls, Parris, & d'Souza, 2009), social acceptance (Davey, Allen, Harrison, Dwyer, & Yücel, 2009), money (Fujiwara, Tobler, Taira, Iijima, & Tsutsui, 2009; Simon et al., 2010) and, appropriately, infantile physical features (Glocker et al., 2009). While this recent work has confirmed posited reward structures and circuits, it has also revealed more subtle features and functionality of specific regions in this circuit. For example, Carter, Macinnes, Huettel, and Adcock (2009) examined the degree to which the striatum encodes both the motivational and affective relevance of anticipated outcomes. To do this, men and women completed a reward anticipation task during fMRI where monetary gains and loss outcomes could be either self- or charity-directed. They found that activity in the nucleus accumbens and ventral tegmental area was increased in anticipation of both gain and loss trials, supporting the notion that these regions are sensitive to the motivational relevance (salience), not the valence, of an event. Evidence regarding the specificity of response in the nucleus accumbens to stimulus salience versus valence is unclear, however, as it has also been demonstrated that accumbens activity correlates with *both* gains and losses only in conditions of uncertainty (Cooper & Knutson, 2008). An attempt has been made to reconcile these findings by noting that while the nucleus accumbens may be primarily sensitive to stimulus salience (e.g., reward-based or not reward-based), its response may be influenced by affective valence (e.g., gain or loss), especially in

individuals who are reward sensitive (Carter et al., 2009).

It is of note that an equally complicated formulation has also been proposed for the OFC and reward (see Kringsbach, 2005), which, depending on the subregion, is implicated in response to rewards of varying complexity (e.g., gain/loss versus taste) as well as positively versus negatively valenced reward stimuli. In addition, subregions of the ACC have also been associated with gain-specific (perigenual ACC), and gain- and loss-specific (supragenual ACC) change in activity in a manner consistent to what has been observed for positive and negative emotions (Fujiwara et al., 2009). Generally speaking, such distinctions may be important in studies of maternal response using positive and negative infant faces or in mothers with varying sensitivity to reward and affect stimuli (related to affective state, stress, early experience, etc.). Related to this, recent fMRI work has demonstrated that childhood adversity influences the neural (basal ganglia) and behavioral (emotion rating) response to monetary reward in adults, where individuals exposed to childhood adversity demonstrated attenuated brain response to reward cues in the globus pallidus and rated reward cues less positively (Dillon et al., 2009). This work nicely complements animal studies that have demonstrated a relationship between adverse rearing experiences related to maternal separation and altered responses to both rewarding and aversive stimuli (Nelson et al., 2009; Pryce, Dettling, Spengler, Spaete, & Feldon, 2004).

Not surprising, numerous fMRI studies have also demonstrated depression-related alterations in neural and behavioral response to emotional and/or rewarding stimuli (Dannowski et al., 2007, 2008; Dichter, Felder, & Smoski, 2009; Fu et al., 2008; Gray et al., 2006; Raes, Hermans, & Williams, 2006; Smoski et al., 2009). People with depression exhibit negative biases in processing facial expressions, altered activity in emotion-related brain regions in response to emotion faces (e.g., greater amygdala response to emotional faces) as well as blunted response to positive or rewarding stimuli (Dannowski et al., 2007, 2008; Dichter et al., 2009; Fu et al., 2008; Gray et al., 2006; Raes et al., 2006; Smoski et al., 2009). In a recent study investigating the reward system, Pizzagalli and co-authors (2009) examined activity in the striatum in patients with depression while they completed a monetary reward task. As expected, compared to control participants, participants with depression showed blunted response to monetary gain in the nucleus accumbens. Interestingly, depression severity was also associated with reduced volume in the caudate nucleus.

Executive function

We know that optimal mothering requires that the mother pays attention to her infant, that

she responds appropriately to her infant and that she responds contingently to the infant's cries and behavior. As indicated earlier, she must be flexible and be able to focus when appropriate and switch attention when the situation changes. And finally, she must retain information about the infant and adequately manipulate the environment to optimize it for the infant. In light of these cognitive demands, the activity of brain regions mediating planning, attention, flexibility and working memory are essential for adequate mothering and thus constitute the focus of a number of maternal studies.

Given its role in attention, cognitive flexibility and working memory, the dorsolateral prefrontal cortex (DLPFC) appears an ideal structure to help identify and attend to infant cues in a complex environment, efficiently switch-tasks and attention and maintain/manipulate information for on-line decision-making and action planning. Over the past decade or so, there has been much debate regarding the function of the DLPFC and whether this region is organized in a 'domain-specific' (i.e., visuo-spatial versus verbal) or 'process-specific' (i.e., monitoring versus retrieval) manner. Supporting the latter, the detailed work of Michael Petrides has contributed much to our understanding of the function of the DLPFC (specifically, the mid-dorsolateral prefrontal cortex, corresponding to areas 46 and 9/46), which he sees as:

a system for the conscious active control of planned behavior and cognition. Such a system must have the capacity to hold abstract coded representations of events that are expected to occur, so as to mark their occurrence or non-occurrence (i.e. monitor their relative status in relation to each other and the intended plan). Furthermore, such a system would be involved in the manipulation of these cognitive representations (i.e. planning) since such manipulation would require constant monitoring of the relative status of intended acts or events (Petrides, 2005).

Although executive functions rely on interactions between many brain regions (for reviews see Duncan & Owen, 2000; Leh, Petrides, & Strafella, 2009), numerous neuroimaging studies in humans have highlighted an important role for the DLPFC in tasks that involve task- or set-shifting (e.g., Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Nagahama et al., 2001; Ravizza & Carter, 2008), auditory and spatial attention (Krumbholz, Nobis, Weatheritt, & Fink, 2009), attention related to perceptual selection (Nee & Jonides, 2009), working memory involved in the Iowa Gambling Task (Li, Lu, D'Argembeau, Ng, & Bechara, 2009), solving anagrams with varying degrees of abstraction (Christoff, Keramiatian, Gordon, Smith, & Mädlar, 2009), memorial selection (Nee & Jonides, 2009) and active maintenance of information for ongoing task performance (Cole & Schneider, 2007).

Other regions of the frontal lobes that are relevant to maternal behavior also have prominent roles in executive functions: the ACC and OFC. The dorsal

anterior cingulate cortex has been widely linked to tasks involving attention and action monitoring, especially in the context of error or conflict (Barch, Braver, Sabb, & Noll, 2000; Brown & Braver, 2005, 2008; Modirrousta & Fellows, 2008; van Veen & Carter, 2002; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005) and the orbitofrontal cortex has been linked to impulse control (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Matsuo et al., 2009; reviewed in Fineberg et al., 2010; Winstanley, Theobald, Cardinal, & Robbins, 2004). While the relationship between prefrontal cortex function and maternal behavior has not been widely investigated, there is considerable evidence that both early adversity and non-postpartum depression have an impact on the structure and/or function of the prefrontal cortex (animal studies: Banasr et al., 2007; Roceri et al., 2004; Roth, Lubin, Funk, & Sweatt, 2009; human studies: Clark, Chamberlain, & Sahakian, 2009; Hercher, Turecki, & Mechawar, 2009; Koenigs & Grafman, 2009; Rogers et al., 2004; Savitz & Drevets, 2009; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007) and in some cases structure and function have been linked. For example, in rats, early experience-mediated deficits in executive function-processes such as prepulse inhibition (PPI) and set-shifting (Burton et al., 2006; Garner et al., 2007; Lovic & Fleming, 2004) are accompanied by structural changes in the pre-frontal cortex (PFC) (Burton et al., 2007; Chatterjee et al., 2007). Further work is needed, however, to confirm the predicted importance of prefrontal function in maternal behavior both outside of and in the context of important individual differences such as early experience and mood.

Maternal behavior

Work on the neural bases of maternal behavior in humans is derived primarily from fewer than 20 fMRI studies where mothers, non-mothers, and sometimes fathers are presented with either pictures of infants (Barrett et al., 2009; Bartels & Zeki, 2004; Leibenluft, Gobbini, Harrison, & Haxby, 2004; Nitschke et al., 2004; Strathearn, Fonagy, Amico, & Montague, 2009; Strathearn, Li, Fonagy, & Montague, 2008), recorded infant cries (Lorberbaum et al., 2002; Seifriz, 2003; Swain et al., 2008), or videotapes of infants (Noriuchi, Kikuchi, & Senoo, 2008; Ranote et al., 2004). For thorough and insightful reviews of the literature see recent papers by James E. Swain and colleagues (e.g., Swain, 2008; Swain, Lorberbaum, Kose, & Strathearn, 2007). By examining these studies (many are reviewed in Swain & Lorberbaum, 2008 and Swain et al., 2007), we can get an idea about the specificity of our posited maternal systems of interest to infant type (own, other), stimulus type (infant vs. non-infant) as well as stimulus familiarity, modality (auditory, visual, both) and even subject (mother, non-mother). For the

most part, the findings of fMRI work on the maternal brain demonstrate that irrespective of stimulus modality (e.g., visual or auditory) or stimulus familiarity (see Leibenluft et al., 2004), many of our maternal regions of interest (e.g., hypothalamus, nucleus accumbens, amygdala, anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex) are implicated in response to a mother's own infant compared to another infant or non-infant control. In studies comparing parents to non-parents, neural response to infants in maternal regions have also been found to be specific to parental status (e.g., Seifritz et al. 2003, but see Glocker et al., 2009 for a demonstration of how infant schema are rewarding for nulliparous women). That is, as we would expect, one's own infant is a special stimulus that engages brain regions that we know are important in maternal behavior and related systems (e.g., executive function, reward, affect). As the role of these systems in maternal behavior has not yet been addressed in a detailed manner, we cannot yet determine the functional significance of identified maternal regions in the context of the many domains involved in mothering. Indeed, the current state of literature on the human maternal brain holds many more questions than answers and we find that there are large differences across studies in what and how 'maternal' regions are implicated. In what follows we briefly discuss a few key areas that could influence brain imaging results. Also, we talk about how identifying and understanding important individual differences may help move this area of research forward.

Although no imaging paradigm will give us a spotlight on a maternal circuit, different patterns of results observed across maternal imaging studies can be attributed to factors such as the age of children studied (newborn to early childhood) and the comparison used to best capture the maternal brain (own baby compared to control stimuli, familiar infant or unfamiliar infant). In regard to the former, the early postpartum period is a unique time, both hormonally and behaviorally; the mother is learning much about her infant at this time, attachment patterns are forming, the maternal system may be especially primed for action and one would predict that this would be a time of great activity for brain systems important in maternal behavior. In fact, a main function of the maternal system in the early postpartum period is ensuring that the mother will respond to her infant, will find her infant pleasing and is attracted to her infant, is attentive, sensitive, etc. There are great differences, of course, across mothers in terms of the quality and quantity of these maternal behaviors and we predict that these differences are related to differences in the function of the maternal system. One may further predict that later on and in the postpartum period and throughout the life of the child, once the nature of mother-child relationship is more habitual and consolidated

and the hormones of parturition are not as influential on the brain and behavior, the function and/or response of maternal neural systems may be quite different. Given this possibility, examining maternal response to children with a broad range of ages may further add to unwanted 'noise' in the observed maternal system.

Discrepant findings across studies may also be attributed to differences in the experimental paradigm, or specifically, in the comparison used to best capture maternal response. Work on the human maternal brain rests on the acceptance of the notion that we are able to elicit a response in the fMRI scanner that is relevant to and reflective of something as complex as mothering. Capturing maternal behavior or maternal responsiveness in an fMRI scanner is a considerable challenge, however, and as previously noted, choice of a particular paradigm has many implications for how we interpret the results and the likelihood that a particular system or structure will be engaged. The choice of approach is at the discretion of the investigators and thus they tend to vary considerably. For example, some studies have used an unfamiliar infant compared to a control stimulus (e.g., computer-generated noise, house) to capture maternal response; most studies use mothers' own children and contrast responses to them with that of unfamiliar or familiar children. These approaches all have different strengths and weaknesses in regard to ecological validity as well as what can be inferred from the imaging results. One may argue that using a standard infant stimulus (not mother's own infant) in order to capture maternal response may not be as effective in engaging the maternal circuit, the function of which we assume is at least in part specialized for or uniquely connected to the mother's own offspring. That being said, we must concede that it is also possible (and likely) that certain regions within a maternal circuit will respond to any infant stimuli, and perhaps even find such stimuli rewarding compared to a non-infant stimulus, especially for a mother in comparison to a non-mother (see Glocker et al., 2009). Another major question in terms of studying the maternal circuit is in regard to the most optimal comparison stimulus for a mother's own infant. That is, to isolate brain activity associated with a maternal response to one's own infant while controlling for confounding factors or factors of no interest (i.e., the 'infantness' of the face, familiarity of the stimulus, emotionality of the stimulus). Strategies that have been used include a non-infant stimulus (e.g., an object, artificially created sound), an unfamiliar baby or a familiar baby. Using an unfamiliar infant as a control stimulus takes care of many confounds, with the exception of familiarity (of own baby) and novelty (of unfamiliar baby) which could bias results in manner that is not necessarily reflective of maternal response (e.g., Leibenluft et al., 2004). Furthermore, when comparing brain response to own and *familiar* infants to

which there are likely varying degrees of emotion and maternal feelings, there is also the risk that differences in brain regions of interest (especially small subcortical regions) will be too subtle to be detected. Thus, the main message we wish to convey is that the 'perfect' paradigm to identify a maternal circuit does not exist and that we have at our disposal a number of options with strengths and weaknesses that will influence the relevance (in terms of regions of interest) of brain imaging findings to something as complex as mothering.

Another factor that may impact the nature of maternal responsivity in brain imaging studies is maternal experience and parity. Patterns of brain response as a function of mothers' parity or maternal experience have not yet been adequately investigated in humans. However, based on the animal work we can make a number of predictions. In the rat work we know that certain brain regions are more active (established through expression of the *c-fos* gene) in experienced than inexperienced animals when presented with pup stimulation. These areas include sensory areas important for mothering in the rat and here the parietal cortex which mediates touch stimulation is implicated. Other areas that show greater activation in multiparous or experienced animals over primiparous animals include the MPOA (the so-called final common pathway) and the anterior cingulate region (Fleming & Korsmit, 1996).

Recent animal work also shows that the parity differences that are seen in brain activation patterns relate more to the presence and absence of mothering experience than to variations in mothers' hormonal profile, although hormones may well enhance or intensify brain responses to pups in maternal animals. For instance, virgin rats who become maternal through sensitization to pup stimulation, through simple exposure, show the same pattern of brain activation as do primiparous mothers who become maternal through hormonal mechanisms. The pattern of effects is the same in the two cases, although the hormonally primed primiparous animal shows a more 'robust' activation pattern than does the sensitized virgin animal when presented with pups, suggesting a role for the hormonal activation of behavior (Numan et al., 2006). And what of the human analogy of mothers who are adopting infants? Although, among humans, comparisons in brain response patterns between adoptive and non-adoptive parents to infant cues have not been explored, based on the animal work one might predict a pattern of activation in adoptive mothers that is similar to the pattern seen in new mothers. Anecdotal evidence suggests that adoptive parents and are certainly as motivated as biological parents and experience strong positive affect and feelings of attachment. This is certainly true of alloparents (see Hrdy, 2009).

The above discussions are for the most part speculative as there are at this time no discernible

patterns in the imaging literature related to methodology or maternal experience that predict a role for some maternal regions and not others. In mothers, factors have been found to mediate maternal response to infant stimuli, however, including type of delivery (Swain et al., 2008) and adult attachment status (Strathearn et al., 2009). Swain and co-authors (2008) examined the effect of type of delivery on the maternal response to own infant cries compared to an unfamiliar infant cry and temporally matched white-noise. A main rationale behind examining type of delivery was that the experience of childbirth by vaginal delivery (VD) compared with cesarean section delivery (CSD) uniquely involves the release of oxytocin (Swain et al., 2008). Using a similar design to that of Lorberbaum et al. (2002), six CSD and six VD mothers completed a block-design fMRI task 2–4 weeks postpartum. A region-of-interest analysis revealed that in response to their own infant cry compared to an unfamiliar infant cry, VD mothers showed a greater response in a number of regions including the hypothalamus, striatum and amygdala. It was noted that the results for the hypothalamus in particular may highlight its role in mothering and mothering behaviors such as breastfeeding as well as attachment (Swain et al., 2008). In a recent study, Strathearn and colleagues (2009) examined brain response to happy, sad and neutral own and unfamiliar infant faces in mothers whose attachment status was defined as secure or insecure/dismissing. A number of different measures, including questionnaire data, videotaped mother–infant interaction and blood collection for oxytocin sampling, were collected over an approximately one-and-a-half year period. The fMRI session was conducted at seven months postpartum. Their main findings were that compared to insecure/dismissing mothers, securely attached mothers demonstrated significantly more activity in the lateral prefrontal cortex, medial prefrontal cortex and the hypothalamus/pituitary region in response to their own infant faces and greater response in the ventral striatum, orbitofrontal cortex and medial prefrontal cortex in response to own happy infant faces. Interestingly, the authors also found that insecurely/dismissing mothers had greater activity in brain regions associated with negative affect (e.g., the insula) in response to their own infant's sad faces.

These two studies have nicely demonstrated how engagement of a maternal system by infant stimuli is not universal and is in fact influenced by maternal factors and individual differences relevant to mothering. Furthermore, it is likely that individual differences that are related to circuits that overlap with or interact with maternal circuits, such as depression and early experience, may be particularly influential in how a mother's brain responds to her infant.

Although published reports are few at this time, important individual differences in maternal brain

structure and function related to early experience and mood/affect are currently being investigated (e.g., Barrett et al., 2009; Kim et al., 2009b). A recent study by Kim and colleagues examined the relationship between retrospective reports of early maternal care and (1) mother's brain structure (gray matter volume) and (2) maternal brain response to infant cries. In the group of mothers, perceived higher maternal care in childhood was associated with higher gray matter volume in frontal, orbital and temporal cortices (Brodmann areas 10, 47 and 22/20, respectively) as well as greater brain response to infant cries in regions including the DLPFC and temporal cortex. Reports of low maternal care were also related to increased brain response in the hippocampus. The authors suggest that their findings reflect early experience-mediated differences in the ability to understand the infants' mental and physical states (key to sensitive mothering) as well as affective reactivity to cry stimuli.

In our own imaging work, we are examining mothers early in the postpartum period (three months postpartum) and collecting indices of behavioral (coded videotaped mother-infant interaction), affective (depression and anxiety scales, ratings of affective response to infant faces), attitudinal (infant-related), hormonal (cortisol) and neural (BOLD response to positive and negative own and unfamiliar infant faces) responsiveness as well as retrospective accounts of early experience in family of origin (parental bonding, childhood abuse).

Although our work is ongoing, one of our analysis strategies has been to extract brain data (i.e., beta weights derived by the general linear model) from a region of interest (the anterior cingulate cortex) and relate activity in this region to a maternal factor (retrospective reports of early experiences in family of origin, see Barrett et al., 2009). By linking brain structures or circuits to specific maternal factors and examining individual differences, we feel this approach will be helpful in understanding the neurobiology underlying the many components that comprise and influence how mothers mother. To this aim, our preliminary work in 12 mothers suggested that maternal retrospective reports of quality of early experiences related to parental bonding and abuse are significantly related to maternal anterior cingulate cortex response to own baby (compared to unfamiliar baby), where greater magnitude of anterior cingulate cortex response to one's own baby is related to reports of poorer parental bonding (maternal and paternal care) and more emotional abuse (Barrett et al., 2009). It is difficult at this time to know what increased ACC response to one's own infant *means* about the mother and her responsivity or maternal behavior in the context of quality of early experience. In addition, while we may infer that increases in BOLD signal reflect increases in population activity in a given brain region, we are not sure if the activity represents the

inhibition or facilitation of brain process or function. Based on what is known about the function of the ACC, we may speculate that increased response in this region is associated with self- or other-referential thoughts or evaluation, with the simulation of experience, with affective response and/or arousal. Note that all of these processes or states may vary along an affect dimension, having positive, neutral or negative valence. While we may predict that poorer quality of early parental care would be related to the negatively valenced side of things in terms of maternal responsiveness, this suggestion warrants further investigation.

VI. Final integration

The nature of the mother-infant dance is complex and relies on the integrity and function of numerous physiological and behavioral systems in the domains of sensation, perception, affect, reward, executive function, motor output and learning. To engage in mothering behavior, mothers have to be sensitive to infant cues, select those cues for processing and thus such cues must be attractive and salient for the mother. Furthermore, mothers must be emotionally prepared and positively motivated to engage socially with the infant, they must selectively attend to the infant in the context of competing stimuli, and finally, they must be restrained and consistent in their responsiveness. The nature of the mother-infant dance relies on the integrity of multiple physiological and behavioral systems and also on two maternal experiential factors, one proximal and one distal, that have a great impact on how a mother mothers: postpartum depression and early experiences. When a mother is at risk to engage in less than optimal mothering, such as when she is depressed or has experienced adversity in childhood, the function of many or all of maternal and related systems may be affected. In this chapter, we have detailed how mothering is intimately intertwined with affect and the deleterious effects of early experience (e.g., stress systems). The interrelation between maternal, affect and stress systems manifests in many ways. At the behavioral level, maternal affect and quality of early experiences are related to less than optimal attachment relationships, maternal attitudes and mother-infant communication. At the hormonal level, the neurobiology of these systems is strikingly similar. Furthermore, it is likely that the similarity and cross-talk between maternal affect and stress systems also allows for mood disturbance and early adverse experiences to have a significant impact on the quality of mothering and the motivation to mother.

The main purpose of this discussion was to extend what is known about the neurobiology of mothering to functional neuroimaging. Instead of focusing on strictly 'maternal' studies, we instead

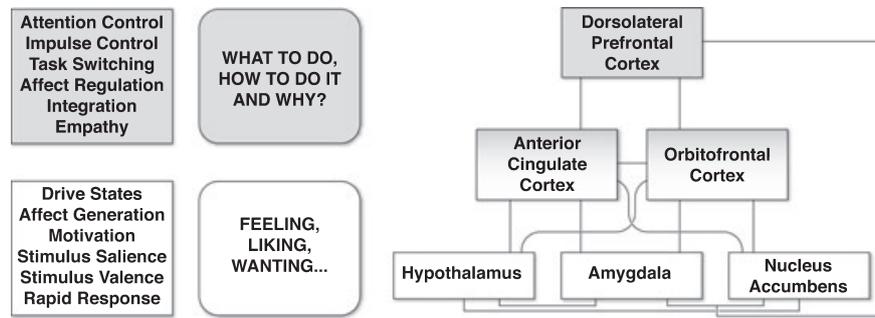


Figure 3 Schematic of a putative human maternal circuit. Brain regions known or believed to be important in human maternal behavior serve a number of important functions. There are (relatively) gross subcortical functions related to reward, affect and motivation that serve to ensure that the baby is a strongly positively reinforcing stimulus that the mother is driven to care for, to be responsive to and show affection to. There are also higher-order cortical functions that regulate maternal behavior in the context of the (internal and external) environment and in light of over-arching goals, standards, mores and intentions. Note that some regions, namely the anterior cingulate cortex and orbitofrontal cortex, operate at the interface of the two main systems

used a systems approach to survey important findings relevant to brain systems integral to and/or strongly related to the mothering experience: (a) social behavior; (b) reward and affect; (c) executive function; and (d) maternal behavior. In human neuroscience, without ablation techniques, microdialysis or electrical stimulation, direct brain-behavior relationships are difficult to nail down and we must often extrapolate and speculate. We have seen that this is especially challenging when examining something as complex as human maternal behavior. However, by examining each of our systems of interest in the context of maternal behavior, it becomes easier to envision the function of each region in our putative maternal circuit (see Figure 3). Furthermore, we find that there are many commonalities in terms of the brain regions identified across these systems and, as we would expect, all are sensitive to the influence of, or function differently in the context of, depression and adverse early experience. So, in addition to the behavioral and hormonal findings, we have identified another mechanism by which individual differences can impact the quality of mothering. Key to progress in mapping the maternal brain will be discovering and accounting for important individual differences that influence brain regions important in mothering and determining whether or not some circuits/regions are influenced more than others and how, in other words, to identify specific structure-function relationships in the context of maternal behavior. As often observed in studies of behavior and hormones, all mothers are not created equal and brain differences should, in part, reflect this.

To conclude then, although we have learned a great deal about the psychobiology of mothering over the past 20 years, there is still much to learn and much to revisit, given new knowledge. No discussion on individual differences is complete

without reference to genetics and their impact on the variety of ways the environment is expressed in mothers' behavior (Bakermans-Kranenburg & Van IJzendoorn, 2008). Some mothers are attentive, others not; some mothers are affectively attached, others not. Some mothers are predominantly talkers; others are quieter but interact through stroking and touching; others avoid or evade. And mothers differ enormously from one another in their temperaments, their hormones, and their brains. These individual differences cannot be entirely explained by knowing the early environment in which mothers were reared, or by knowing the present social context or affective state in which the mother finds herself.

The notions of psychological resilience in face of adversity and of susceptibility to positive effects of 'good' early experience bring with them questions about the mother's genotype and how polymorphisms in specific genes and gene sets interact with early and present experience to help create the vast differences in temperament, affect, reward susceptibility, sensitivity and executive function capabilities necessary for mothers to mother effectively. This next decade, when we use what we have learned about the genome to better understand behavior and brain, should be a very exciting time for the study of the psychobiology of mothering.

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Key points

- Mothering behavior and feelings are a product of a wide variety of behavioral and physiological propensities and underlying systems.
- Quality of mothering relies on maternal factors, one proximal and one distal, that have an impact on how a mother mothers: postpartum depression and adverse (stressful) early experiences.
- The brain mechanisms that regulate mothering include modules or systems within the hypothalamus, the limbic system and the cortex; these systems are interrelated and are sensitive to the influence of, or function differently in the context of, variations in maternal mood and early experiences in family of origin.
- In future work, the study of functional, molecular and gene expression changes in the brain that occur under different environmental contexts and/or that vary with genotype may help us to understand why mothers differ from one another in the extent to which their mothering and postpartum mood state is affected by adverse early experiences and stresses in their lives.

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