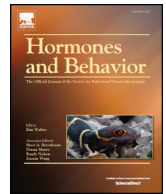




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The maternal brain and its plasticity in humans

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ABSTRACT

Early mother–infant relationships play important roles in infants' optimal development. New mothers undergo neurobiological changes that support developing mother–infant relationships regardless of great individual differences in those relationships. In this article, we review the neural plasticity in human mothers' brains based on functional magnetic resonance imaging (fMRI) studies. First, we review the neural circuits that are involved in establishing and maintaining mother–infant relationships. Second, we discuss early postpartum factors (e.g., birth and feeding methods, hormones, and parental sensitivity) that are associated with individual differences in maternal brain neuroplasticity. Third, we discuss abnormal changes in the maternal brain related to psychopathology (i.e., postpartum depression, posttraumatic stress disorder, substance abuse) and potential brain remodeling associated with interventions. Last, we highlight potentially important future research directions to better understand normative changes in the maternal brain and risks for abnormal changes that may disrupt early mother–infant relationships.

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Introduction

Maternal caregiving plays a critical role for infant survival and optimal development. After birth, the brain and body of mothers undergo dynamic changes to support the establishment and maintenance of maternal caregiving behaviors. In this review, we focus on neuroimaging studies that revealed neural plasticity among human parents using functional magnetic resonance imaging (fMRI). While animal literature elegantly demonstrate neural plasticity due to pregnancy, parturition, and caregiving (Cohen and Mizrahi, 2015; Fleming et al., 2002; Leuner et al., 2010), our review will be mostly limited to neural plasticity across the postpartum period beyond birth based on available literature in human parents. This review aims to contribute to the current literature by providing an overview of individual differences in brain plasticity and multi-dimensional factors that are associated with such individual differences. We will first review several important sets of maternal brain networks that support sensitive responses to infants. Auditory and visual signals from infants, such as infant cry sounds and infant

images, activate brain regions from emotion response and regulation circuits to executive function and attention cortical circuits that function in parental thoughts, empathy and sensitive behavior. Second, we will review environmental, behavioral and hormonal factors that may relate to variations in maternal brain responses to infants. We will also discuss psychopathology in mothers – that may be considered as maladaptive plasticity, including postpartum depression (PPD), posttraumatic stress disorder (PTSD) and substance abuse. Identifying problems with maternal brain plasticity may ultimately offer hope for effective treatments for concerned parents with the development of brain-based targeting of interventions.

Neurocognitive mechanisms underlying parental sensitivity

Sensitive caregiver responses to infant's cues involve an array of complex thoughts and behaviors contingent on infant cues, including recognition and acknowledgment of the child's signals, attribution of salience to the child's cues, maintenance of visual contact, expression of positive affect, appropriate empathy mirroring and vocal quality, resourcefulness in handling the child's distress or expanding the interaction, consistency of style, and display of an affective range that matches the infant's readiness to interact. Such behaviors are likely the result of complex and highly plastic neural networks involved in

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generating and organizing emotional responses (Kober et al., 2008), as well as dissociable and volitional attention and executive function, reward and motivation, and sensorimotor circuits (Buckner et al., 2008; Seeley et al., 2007; Sripada et al., 2014). At this point, we propose a model for maternal brain function based on task-based imaging studies (Swain et al., 2014b; Swain and Lorberbaum, 2008) (Fig. 1) and highlight brain processes that are mechanistically related to certain cortico-limbic circuits and are relevant for healthy parental sensitivity. The studies we reviewed largely use block design of infant stimuli and include analyses focusing on specific regions rather than connectivity. Thus, we would like to acknowledge that our model is necessarily over-simplistic and will require much more work to describe the physiology of key circuit elements, plus the connectivity between them which may itself also be plastic or flexible according to the demands of different stages of parenting and circumstances of psychopathology.

Reward/motivation

Both animal and human research (Numan and Woodside, 2010; Strathearn et al., 2009a) suggests that responses to infants form a model motivational system using dopamine (DA) and oxytocin (OT)-rich pathways. DA contributes importantly to reward-motivated behaviors, reinforcement learning, and drug addiction. Dopaminergic neurons, which originate in the brainstem's ventral tegmental area and substantia nigra, project to the ventral and dorsal portions of the striatum, as well as to the medial prefrontal cortex (PFC), via mesocorticolimbic and nigrostriatal pathways. Natural reward-related stimuli, including food, sex, and faces of one's sexual partner or child, activate the brain's "reward" system (Aharon et al., 2001; Delgado et al., 2000; Melis and Argiolas, 1995; Stoeckel et al., 2008; Strathearn et al., 2008). In mothers, the initial experiences of pleasure and activity in these brain circuits when exposed to their own infants' cues may increase the salience of their infants' stimuli and promote greater attention and bond-formation to ensure continuous engagement in sensitive caregiving (Strathearn et al., 2008, 2009a). Such reward pathways may be relevant very early in the postpartum period, as a mother's positive feelings toward her unborn fetus, as well as her perception of her fetus, have been associated with greater maternal sensitivity to the infant's signals and more affectionate vocalizations and touch (Keller et al., 2003; Keren et al., 2003).

The amygdala also interacts with the reward circuit to motivate maternal behaviors. OT receptors are also abundantly present in the amygdala (Viviani et al., 2011). In rodents, during the postpartum period, the increased basolateral amygdala activation provides sensory inputs to the reward circuit including the nucleus accumbens (NAcc) and ventral pallidum (Numan, 2014; Numan and Woodside, 2010). In response to infant stimuli, infant cry and smiles activate the amygdala (Barrett et al., 2012; Seifritz et al., 2003; Swain et al., 2008), which has often been interpreted as a sign of emotional salience (Seifritz et al., 2003; Strathearn and Kim, 2013) or positive emotion associated with attachment (Leibenluft et al., 2004). On the other hand, in virgin rats, activation in the medial nucleus of the amygdala was associated with reduced maternal behaviors (Morgan et al., 1999; Oxley and Fleming, 2000). Thus, while increased activation of the amygdala to infant stimuli is interpreted as a more negative response to infants among typical adults (Riem et al., 2011), in mothers, it can be associated with more positive responses to one's own infant (Barrett et al., 2012).

Another perspective on maternal motivations and rewards involve preoccupations that may be part of healthy maternal responses to their infants that draw them close in order to meet the infant's physical and psychological needs (Bowlby, 1969; Winnicott, 1956). This suggests the importance of "checking and worrying" brain circuits overlapping with those hyperactive in obsessional anxiety (Leckman et al., 2004). Indeed, parental anxiety peaks immediately after childbirth and then begins to diminish during the first three to four months postpartum (Feldman et al., 1999; Kim et al., 2013; Leckman and Mayes, 1999). This matches apparent increased responses to baby cry in postpartum anxiety circuits including the basal ganglia and orbitofrontal cortex that diminish over the first 4 months postpartum (Swain et al., 2014b, under review). This plasticity in anxiety circuits may be part of a healthy range of threat detection and harm avoidance (Feygin et al., 2006), yet also perhaps an opportunity for problems to occur with such adaptations – in which abnormally reduced or excessive worry may be part of postpartum psychopathology.

Emotion regulation

During interactions with an infant, particularly a distressed infant, it is critical for mothers to perceive the distressed cues of infants appropriately, and manage their own distress in response to their infants'

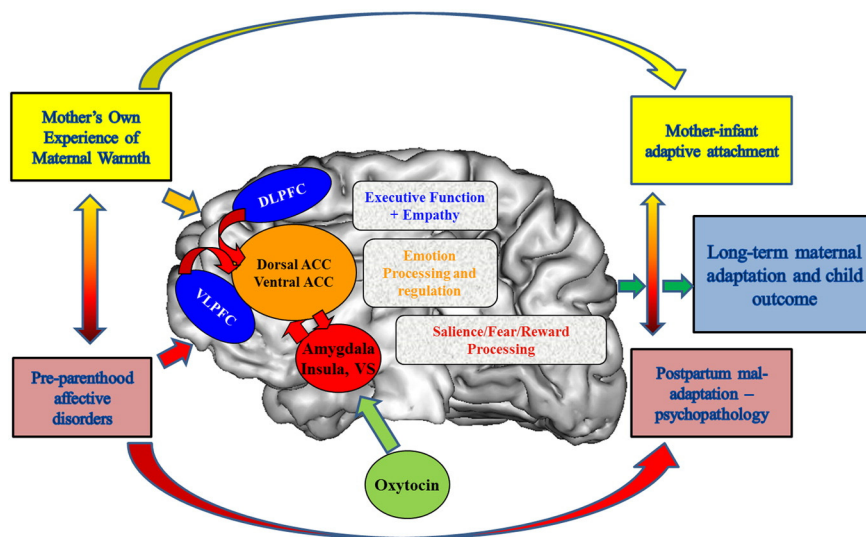


Fig. 1. Plasticity in the maternal brain—early life factors, such as experience of parental warmth and previous mental health affect plastic brain circuits that ultimately regulate maternal affective regulation capacity and caregiving outcomes. Plastic or adaptable circuits, some of which are overlapping, include those for Emotion Response and Processing [Amygdala, Dorsal Anterior Cingulate Cortex (ACC), Ventral ACC] and Salience/Fear/Motivation Processing [Amygdala, Insula, Ventral Striatum (VS)] working with cortical executive function [Ventrolateral Prefrontal Cortex (VLPFC), Dorsolateral Prefrontal Cortex (DLPFC)] and empathy [Medial Prefrontal Cortex (MPFC), Precuneus, Superior Temporal Sulcus] circuits. Adapted from Moses-Kolko et al. (2014).

negative emotions. A mother's sensitivity to distress has been a better predictor of the child's outcome than her sensitivity to non-distress cues (Joosen et al., 2012; Leerkes, 2011; Leerkes et al., 2009; McElwain and Booth-Laforce, 2006).

The medial and lateral PFC and anterior cingulate cortex (ACC) are involved in emotion regulation including suppression of the amygdalar responses to negative emotional information (Ochsner et al., 2012). Activation of the medial and lateral PFC and ACC are consistently observed among new mothers in response to an infant's cry (Laurent and Ablow, 2012; Lorberbaum et al., 2002), to videos of a distressed infant (Noriuchi et al., 2008), and to one's own child greater than to familiar/unknown faces (Leibenluft et al., 2004) were observed among new mothers.

Parental empathy

Parental empathy (the appropriate perception, experience, and response to another's emotion) may be especially relevant for pre-verbal infants. Experiencing pain of a loved one activates relatively focused anterior area of the dorsal ACC – perhaps a subset of a broader circuit for experiencing personal pain that also includes brainstem, cerebellum, and sensorimotor cortex. Such partial overlap of representations of empathy for others with self-related processing in cortical structures such as in the anterior insula are postulated as necessary for a theory of mind (Saxe, 2006), namely our ability to understand the thoughts, beliefs, and intentions of others in relation to ourselves (Frith and Frith, 2003; Hein and Singer, 2008). Humans may utilize separate circuitry to 'decouple' representations of external vs. internal information in order to understand many social exchanges. Indeed, considerable brain imaging research on empathy, largely related to the imitation of others' emotions using stimuli such as emotional faces, images of others in pain or crying sounds (Fan et al., 2011), has highlighted the functional importance of medial PFC, precuneus/posterior cingulate cortex, temporoparietal junction, and posterior superior temporal sulcus (Frith and Frith, 2006; Mitchell, 2009). Additional regions including the anterior insula, orbitofrontal cortex and amygdala may be important for emotion information processing but also for both sharing and explicitly considering affectively charged states (Decety, 2015; Zaki and Ochsner, 2012).

Such ability to share and understand others' emotional state is of importance for parental caring responses to own baby-cry (Swain et al., 2004) and other stimuli. For example, a complex set of brain responses was reported in a recent study of mothers responding to child visual feedback after a caring decision (Ho et al., 2014). Responses that correlated with dimensions of empathy included the aforementioned amygdala and ventrolateral PFC. Experiments using a parenting-empathy task will shed light on maternal brain function when actually asked to empathize with their infant. In sum, preliminary brain-based experiments suggest that parenting may be one instance of altruistic functions that apply to different social situations (Preston, 2013; Swain et al., 2012).

Executive function

Executive functions, including attention and inhibitory control, working memory, and flexible task-switching, are likely to be important to parents' sensitivity (Lovic and Fleming, *in press*). The dorsolateral and ventrolateral PFC are involved in cognitive flexibility (Mitchell et al., 2008), and the striatum is involved in inhibition control (Vink et al., 2005). Deficits in cognitive flexibility and spatial working memory have been linked with poor maternal sensitivity to non-distress infants' cues (Gonzalez et al., 2012). Mothers with a classification of disorganized attachment responded more slowly to negative attachment words (e.g. abandon, reject) during the stroop task; these findings suggest that negative associations with attachment stimuli may contribute to ongoing cognitive difficulties during mother–infant interactions (Atkinson et al., 2009). Increased attention bias to infants' distress

cues in late pregnancy also has been associated with higher scores on a questionnaire about parental bonding (Pearson et al., 2010) and on a continuum with healthy postpartum preoccupations. Attention bias to infants' distress has also been compared between breastfeeding and formula-feeding mothers of infants three to six months old and observed to be greater in breastfeeding mothers (Pearson et al., 2011).

Summary

Maternal adaptation to the role of motherhood and performance of associated behaviors for sensitive moment-to-moment responses to infant cues can be expected to depend on certain brain systems that need to be plastic to specific circumstances, and adapt to environmental cues. These included circuits that respond to and interpret emotional stimuli, provide reward and motivation for behavior, connect with more sophisticated executive function to process thoughts and attention and allow a mother to experience empathy and sensitively care for their child.

Postpartum factors of maternal brain plasticity

Anatomical changes in maternal brain

Drastic changes in hormones, neurochemistry, and experience can lead to neural plasticity in the maternal brain. In rodents, changes in the neural structure and function during the early postpartum period have been observed consistently to support maternal motivation and to enhance processing of sensory information that is specialized to detect and respond to infants' calls (Fleming et al., 2002; Numan, 2007). Similar changes have been found in human mothers. Structural images of mothers' brains from the first and third to fourth months postpartum were examined for longitudinal anatomical changes (Kim et al., 2010a). Several brain regions involved in maternal motivation and reward processing, including the striatum, amygdala, hypothalamus, and the substantia nigra, exhibited structural growth from the first time point to the next. Structural growth was also observed in areas involved in processing sensory information and empathy, including the superior temporal gyrus, thalamus, insula, and pre- and post-central gyri. Finally, regions associated with regulating emotions, such as the inferior and medial frontal gyri and the ACC, also showed structural increases. Interestingly, no neural regions showed reduction in gray matter during this time period. The evidence suggests that neural plasticity, particularly growth, occurs in a wide range of brain regions, each serving important aspects of child caregiving in human mothers during the first few months postpartum. Furthermore, the greater the observed structural growth in the midbrain region (involved in reward and motivation), the stronger the positive emotions a mother reported having about her baby in the third and fourth months postpartum. This finding further supports a bidirectional association between parenting experience and neural plasticity during the first few months postpartum.

Birth and feeding methods

To explain individual differences in the human maternal brain, studies have examined the maternal brain according to birth and feeding methods. Vaginal delivery provides critical sensory stimulation that increases release of OT and helps to establish maternal behaviors (Morgan et al., 1992). Such sensory stimulation is absent in cesarean section delivery. Although the sample size was relatively small, a fMRI study revealed significant associations between birth method and neural responses to cry sounds from their own babies (Swain et al., 2008). During the first month postpartum, mothers from the vaginal delivery group exhibited greater neural responses to their own babies' cries (vs. control babies' cries) compared to mothers who delivered via cesarean section. The vaginal delivery was associated with greater responses in areas important for the motivation region (striatum, hypothalamus, amygdala), sensory information processing (the superior and middle

temporal gyri, fusiform gyrus, and thalamus), and cognitive and emotional control regions (superior frontal gyrus), compared to the cesarean section. Interestingly, further plasticity among healthy mothers is exhibited by the disappearance of significant functional difference between vaginal and cesarean delivering mothers brains in response to baby-cry by three to four months postpartum (Swain, 2011).

During the first month postpartum, feeding methods may also be significantly associated with maternal neural responses to cries of one's own baby. Breastfeeding can increase the release of OT and in some studies is associated with higher maternal sensitivity and reduced levels of child neglect (Britton et al., 2006; Strathearn et al., 2009b). In an fMRI study, exclusive breastfeeding was associated with greater neural responses to cries of one's own baby (vs. unrelated baby's cry sounds), compared to exclusive formula-feeding (Kim et al., 2011). Interestingly, brain regions associated with breastfeeding vs. formula feeding largely overlapped those associated with vaginal vs. cesarean delivery. The neural regions showing greater activation among breastfeeding mothers included those related to maternal motivation (striatum, amygdala), sensory information processing (superior and middle temporal gyri), and cognitive and emotional control (superior frontal gyrus). Furthermore, greater neural responses in the striatum/amygdala and superior frontal gyrus to one's own infant's cries at the first month postpartum were positively associated with maternal sensitivity, observed during mother–infant interactions at three to four months postpartum. Thus, both delivery and feeding methods, which are potentially associated with maternal hormones such as OT, may enhance neural sensitivity to cries of one's own baby's in brain regions involved in maternal motivation, sensory information processing, and emotion regulation.

Hormones

Exciting recent discoveries about the impact of OT on neural responses to infant stimuli have been made using administration of OT. Among non-parent women, administration of OT was associated with reduced responses in the amygdala to negative emotional images that were stressful (Rupp et al., 2014), as well as stimuli that depict infants either crying (Riem et al., 2011) or laughing (Riem et al., 2013). In fact, in these studies, administration of OT was associated with increased activations in areas related to regulation of emotion and empathy, including the ACC, the OFC, and insula (Riem et al., 2011, 2013). Increased insula responses to infants' cries were found among non-parent women when testosterone was administered (Bos et al., 2010). This finding is not surprising given that testosterone is metabolized into estradiol, which can subsequently increase OT levels.

In addition to direct administration of hormones, genetic variations in hormonal receptor expressions have been associated with neural responses to child-related stimuli among mothers. In one study (Michalska et al., 2014), mothers' parenting quality was assessed based on observations of mother–child interactions when children were aged 4 to 6 years. Years later, genetic samples were collected from mothers to allow the examination of single nucleotide polymorphisms in the gene encoding the OT receptor. They also viewed images of their own children aged 4 to 6 years, as well as unrelated children, during a neuroimaging session. Supporting the importance of OT in the central brain for parenting, mothers with the AA genotype, which has been associated with greater receptor expressions, showed significantly higher levels of positive parenting as well as greater neural responses to images of their own children compared to mothers with the GA and GG genotypes (Michalska et al., 2014). The OT gene polymorphism was also associated with increased activations in the OFC, ACC and hippocampus, particularly those regions related to emotion and stress regulation.

Another study of a similar sample of mothers examined genetic variations in the estrogen receptor gene (Lahey et al., 2012). Estrogen is important in priming maternal motivation regions of the brain: in animals,

mothers with higher levels of estrogen show less hostile responses and increased caring behaviors toward their own pups. In this study of a human sample, a genetic variation associated with lower expressions of the estrogen receptor gene was related to harsh parenting practices. The associations were mediated by neural responses in the inferior frontal gyrus in response to one's own child versus an unrelated child. Taken together, these studies suggest that individual differences in hormonal levels, including testosterone, estrogen, and OT, may influence maternal neural responses to infants and, in turn, behavioral sensitivity to infants.

Exposure to stress and childhood adversity

Whereas OT has been shown to increase neural and behavioral sensitivity to infants, stress has been shown to diminish it. For example, current levels of parenting-related stress in human mothers were associated with individual differences in neural responses to infants (Barrett et al., 2012). Mothers at three months postpartum viewed images of their own versus an unrelated infant. Lower levels of parental distress and more positive attachment-related feelings about their own infants were associated with increased responses in the amygdala to their own infants' versus unrelated infants' positive images (e.g. smiling).

Early life stress also shapes later brain function (McGowan et al., 2009). Exposure to stress activates the hypothalamic–pituitary–adrenal (HPA) axis and increases cortisol levels, which may reduce neural responses of mothers to an infant's cry, in part due to difficulties in regulation of emotions. Mothers with infants aged 18 months old had their cortisol levels measured following a strange situation, a task that can elicit stress reactivity in the HPA axis to mother–child separation (Laurent et al., 2011). Mothers then participated in a neuroimaging session while listening to their own infant's cry versus an unrelated infant's cry sounds. Reduced reactivity to stress in the HPA axis was associated with greater activation in the midbrain and striatum, areas involved in maternal motivation; the insula and OFC, areas involved in negative-emotion processing; and the dorsolateral PFC and ACC, areas involved in emotion regulation. Thus, poor physiological stress regulation can contribute to diminished neural responses to infants' cry sounds among mothers.

In addition to current stress levels, early adversity may have long-term effects on stress regulation and maternal motivation (Champagne et al., 2003; Fleming et al., 2002). Mothers with infants aged one month old were divided into two groups based on retrospective self-reported quality of maternal care received during childhood (Kim et al., 2010b). Mothers with high vs. low scores on maternal care were compared on neural structure and functional responses to infants' cries. High quality of maternal care in childhood was associated with increased gray matter volumes in regions involved in regulation of emotions and social and sensory information processing, including the superior frontal gyrus, the OFC, the superior and middle temporal gyri, and the fusiform gyrus. Furthermore, higher levels of neural responses to infants' cry sounds were found in these same regions. The only region that was more active in mothers who reported low quality of maternal care in childhood was the hippocampus. The hippocampus is particularly rich in the glucocorticoid receptors, and critically involved in stress regulation (McEwen, 2001). Increased hippocampal activations have been observed in response to both acute and chronic exposure to stress in human and animals (Tottenham and Sheridan, 2009; van Hasselt et al., 2012). Thus, the increased activation in the hippocampus in response to infants' cries among mothers with lower quality childhood experiences may reflect greater stress responses to the cries. Therefore, the findings suggest that differences in maternal neural responses to infants are influenced by mothers' own childhood experiences, which contribute to baseline differences in terms of neural structure and functions.

Although OT plays a role in stimulating the onset and maintenance of maternal behavior, exposure to childhood adversity may result in abnormal development of the OT system in the offspring, as well as lead to poorer quality of parenting behavior later in adulthood (Champagne

and Meaney, 2001, 2007; Champagne, 2011). In rhesus monkeys, for example, non-maternal (or nursery) rearing was associated with reduced levels of cerebrospinal fluid OT for the first three years of life (Winslow et al., 2003). Similarly, cerebrospinal fluid OT levels were reduced in women who reported childhood maltreatment, and they were inversely correlated with scores of emotional abuse (Heim et al., 2009). Furthermore, in first-time mothers, the amygdala responds to infants' affect cues as a salience signal, responding more to one's own infant faces than to unknown infants (Strathearn and Kim, 2013).

Differences in classifications of adult attachments may be associated with the quality of childhood caregiving experience. Previous studies have shown that mothers with an insecure/dismissing type of adult attachment show a diminished OT response to mother–infant interaction, which is associated with reduced activation in the hypothalamus and the ventral striatum. Mothers from this attachment group also show reduced activation of the mesocorticolimbic DA system, including the ventral striatum and ventromedial PFC, when viewing images of their own versus unknown infants' faces (Strathearn et al., 2009a). Furthermore, this pattern of attachment is associated with differences in maternal behavior, including less attuned mother-to-infant vocalization at seven months postpartum (Kim et al., 2014a), and with higher rates of insecure child attachment at 14 months, based on the Strange Situation Procedure (Shah et al., 2010).

Maternal brain–behavior associations

Since fMRI techniques were first used to examine maternal neural activation for parenting, researchers have looked for specific associations between neural and behavioral sensitivity to infants, particularly during the early postpartum period when mother–infant relationships are first established. Several exciting studies have now demonstrated that individual differences in parenting behaviors may be based on variations in neural responses to infant stimuli. In one of these studies, mothers at four to six months postpartum were divided into two groups: mothers with high synchronous scores and low intrusiveness scores (synchronous mothers) and mothers with low synchronous scores and high intrusiveness scores (intrusive mothers) (Atzil et al., 2011). Synchronous maternal behaviors, including coordination of gaze, touch, and vocalizations with infants, are interpreted as more sensitive parenting behaviors and are associated with positive infant outcomes. Contrariwise, intrusive maternal behaviors include lack of coordination and more directedness with the infant, and they tend to be associated with maternal anxiety and the HPA and stress responses (Feldman, 2007). During a neuroimaging session, mothers were presented with video clips of their own infants and an unfamiliar infant. The main contrast between responses to their own versus the unfamiliar infant was greater activation in the NAcc, a key reward/motivation region, and the amygdala, a key stress and negative emotion processing area. When intrusive and synchronous mothers were compared, intrusive mothers showed greater responses in the amygdala to their own babies, whereas synchronous mothers showed greater activation in the NAcc. Furthermore, functional connectivity in the whole brain using the NAcc and the amygdala as seed regions was examined, and the intrusive and synchronous mothers were compared. In synchronous mothers, activity in the NAcc was correlated with activity in attention and social information processing regions, including the inferior frontal gyrus, the medial frontal gyrus, visual and motor areas, and the parietal cortex. Contrariwise, intrusive mothers showed greater connectivity between the amygdala and the OFC, which is characteristic of elevated anxiety. Thus, reward-related neural responses to one's own infant were associated with enhanced neural connectivity for attention and social information processing, which may further support synchronous mother–infant interactions. Anxiety-related neural responses to one's own infant were associated with more disrupted and intrusive mother–infant interactions.

In another study, the same group of researchers demonstrated that among mothers, plasma OT levels correlated positively with activations

in the ventral ACC, the left NAcc, the inferior parietal lobule, and the temporal and frontal gyri in response to videos of their own infants (Atzil et al., 2012). When mothers watched videos of various mother–infant interactions, they exhibited greater neural responses to synchronous interactions compared to abnormal interactions (such as between depressed or anxious mothers and their infants), particularly in the dorsal ACC (Atzil et al., 2014). Additionally, greater activation in the dorsal ACC in response to synchronous interactions was positively associated with mothers' own synchronous scores. The dorsal ACC is involved in integrating affective and social processes as well as regulating social pain such as social rejection. Thus, greater activation in the dorsal ACC may contribute to more sensitive processing of social cues, which may be further associated with highly synchronous behaviors among mothers interacting with their own infants.

Other researchers have found associations between parenting behaviors and greater responses to infant stimuli in neural regions important for regulating emotions and processing social information. First-time mothers and their infants at 18 months participated in structured mother–infant play interactions (free play and cleanup segments) during which maternal sensitivity and intrusiveness were assessed (Musser et al., 2012). During a neuroimaging session, mothers listened to their own infants' cry sounds as well as those of an unfamiliar infant. When neural responses to their own versus a control infant's cry were examined, the observed maternal sensitivity was associated with prefrontal activations (superior and inferior frontal gyri), regions involved in regulation of emotions. Mother–infant harmony was associated with activations in the hippocampus and the parahippocampus, as well as the precuneus, which may indicate better stress management. In another study of mothers with infants aged four to ten months, the observation of positive mother–infant interactions was associated with increased response to videos of their own infants (vs. control infants) in the putamen and the inferior and middle frontal gyri, areas involved in maternal motivation and regulation of emotions (Wan et al., 2014). Self-reported maternal warmth was associated with greater neural responses to videos of their own infants in the precuneus, visual areas, the insula, and the medial frontal gyrus. The findings suggest that positive parenting behaviors are associated with greater responses to mothers' own infants compared to unfamiliar infants in brain areas involved in social and sensory information processing.

Summary

Taken together, these findings demonstrate that during the early postpartum period, the human maternal brain exhibits great neural plasticity, both in structure and function, which supports the mother's new role. Research on variations in birth and feeding methods, exposure to stress, hormone levels, and gene expressions can significantly enhance the understanding of individual differences in the neural structure and functioning that support parenting. Furthermore, neural activations in regions involved in increased maternal motivation and regulation of emotions are particularly important for predicting sensitive parenting behaviors among human mothers. Although these activations were largely related to a normal range of individual differences, psychopathology may be associated with abnormal maternal neural and behavioral responses to infants. In the following section, we will review differences between healthy moms and those affected by psychopathology that demonstrates maladaptive plasticity, particularly in relation to the brain–OT associations.

Maternal psychopathology and neural plasticity

Postpartum depression (PPD)

PPD is a major public health concern, affecting 15 to 20% of pregnancies (Gavin et al., 2005; Gaynes et al., 2005). Risk factors for developing PPD include high-stress circumstances, minority status, younger age,

low-socioeconomic status, and reduced experience of sensitive parenting from one's own parents (Gotlib et al., 1991; Murray and Cooper, 1997a; Stowe and Nemeroff, 1995; Weisman et al., 2010). High-risk status, which includes previous major depressive episodes and abnormal stress hormone regulation, specifically cortisol and adrenocorticotropic (Marcus et al., 2011; Sexton et al., 2011; Vazquez et al., 2015), confers alarming rates of PPD as high as 50–80%, depending on the measures, postpartum timing, and definitions used (Deal and Holt, 1998; Gee and Rhodes, 2003; Hipwell and Kumar, 1996; Hipwell et al., 2005; Logsdon et al., 2005). For most women with PPD (~89%), diagnosis is made between two weeks and four months postpartum (Stowe et al., 2005) and can last for a year or more, resulting in a heightened risk for future lifetime episodes of depressive illness (Evans et al., 2001; Gotlib et al., 1989; Stowe et al., 2005; Warner et al., 1996).

Many studies show that the infant also suffers when the mother is affected by PPD, even when the mother's symptoms do not reach symptomatic severity of a major depressive disorder (McLearn et al., 2006; Murray and Cooper, 1997b; Righetti-Veltema et al., 2003). Long-term adverse effects on the child's development, emotions, and regulation of behavior (Grace et al., 2003; Halligan et al., 2007; Hay et al., 2008) cross generations through impairments in maternal care-giving sensitivity (Feldman et al., 2009; Field et al., 1988; Madigan et al., 2015; Murray and Cooper, 1997a; Stanley et al., 2004; Weissman et al., 2004) – in part via OT effects on neural circuits (Apter-Levy et al., 2013; Feldman et al., 2010). Despite the enormous personal, familial, and societal costs of these mental health disorders, progress in the study of underlying neurohormonal mechanisms that could improve identification and inform strategies for personally tailored intervention has been slow.

Existing literature points to dampened neural responses in the emotion regulation circuits among mothers with PPD. Two existing studies (Moses-Kolko et al., 2010; Silverman et al., 2007) of mothers attending to non-infant negative emotional stimuli found that PPD versus healthy status and greater PPD severity was associated with reduced activity in the amygdala to fearful and threatening faces or negatively valenced words. This finding is in apparent opposition to the increased activity of the amygdala found in non-postpartum depression (Groenewold et al., 2012). Perhaps PPD, which reduces maternal sensitivity, (Feldman et al., 2009) is associated with an amygdala shut-down not seen in other forms of depression, and plasticity in amygdala function may be a therapeutic target (see *How neuroimaging studies inform parenting intervention* section). A small study ($n = 8$) revealed reduced activity in the posterior OFC in response to negative words in women with PPD compared to healthy postpartum women (Silverman et al., 2007). Further, Laurent and colleagues (Laurent and Ablow, 2012) reported, for own vs. control sound, that depressed vs. non-depressed mothers had less activity in the medial thalamus, caudate and NA; and that the higher depressive symptoms (Center for Epidemiologic Studies Depression Scale, CESD) were associated with decreased activity in caudate, putamen, NA-medial thalamus and posterior OFC. These studies suggest reduced neural responses across an array of limbic and cortical structures to negative emotional stimuli and infant distress cues, which may be associated with increased risks for mood dysregulation and maternal insensitivity.

Little is known about within-circuit connectivity of cortical brain regions that can directly modulate limbic reactivity to infants and other emotional cues in postpartum women. In a single such study, women with PPD demonstrated an absence or disengagement of dorsomedial PFC–amygdala connectivity while viewing fearful and threatening faces, whereas healthy mothers had intact dorsomedial PFC–amygdala connectivity to fearful and threatening faces. (Moses-Kolko et al., 2010). The available data, therefore, suggest that women with PPD disengage critical cortico-limbic neurocircuitry – that is involved in emotional salience and processing a threat – during exposure to infants' and negative affective stimuli. This finding requires further examination with techniques for analyzing within-circuit regional connectivity.

An interesting exception, however, was the finding that heightened activity in the lenticular nucleus and left medial PFC to the cry of one's own baby was associated with more depressive symptoms and more anxious intrusive thoughts in a group of 12 mothers scanned on average three weeks postpartum (Swain et al., 2008). Swain and colleagues argue for a potentially adaptive function subserved by these apparent anxious/depressive symptoms in non-depressed mothers in the early postpartum phase, which are different to findings in mothers who are three or more months postpartum. Swain and colleagues, in other publications (Swain et al., under review; Swain and Lorberbaum, 2008), postulate that maternal neural responses to infants' stimuli change with time since delivery, with diminished anxiety-related subcortical and increased regulatory cortical responses to their infants' cries, among healthy mothers. Indeed, both human (Kim et al., 2010a) and rodent (Kinsley and Meyer, 2010), maternal brain research reveal postpartum structural brain growth in orbitofrontal and temporal cortices, which may reflect social learning in parents in preparation for changing baby signals over time in addition to the increasingly complex array of possible interactional scenarios. This also opens windows into domains of dysfunction when these adaptations fail to occur, leaving new parents underprepared to respond to increasingly complex situations. Therefore, postpartum duration-dependent analysis of fear/salience network activity and PFC modulatory networks is an important area in need of future investigation.

Posttraumatic stress disorder (PTSD)

PTSD is debilitating condition characterized by flashbacks, hyperarousal, hypervigilance, emotional numbing, mood lability, insomnia, and avoidance of potentially triggering situations (DSM-IV; American Psychiatric Association, 2000). It has also been associated with mild to moderate cognitive impairment, most notably, reduced concentration and difficulties associated with learning and memory (Vasterling et al., 2002). In the general population, lifetime prevalence of PTSD across the Western world ranges from 1.9% to 6.8% (Kessler et al., 2005; Wittchen et al., 2011). Neurobiological correlates in non-postpartum samples include increased insula and amygdala activity while listening to traumatic audio clips in the scanner (Hopper et al., 2007).

While PDD was associated with dampened neural response, PTSD among mothers is associated with heightened neural responses to infants in the emotion regulation circuits. Similar to non-postpartum populations, but in contrast to anxious and depressed postpartum mothers, 12–48 months postpartum mothers with PTSD secondary to adult interpersonal violence-related PTSD (IPV-PTSD) had heightened subcortical responses in the fear circuitry (Schechter et al., 2012). In this study of mothers viewing child separation vs. free play videos, IPV-PTSD mothers activated an “unrestrained” fear-circuitry that was associated with higher subjective ratings of stress. The circuitry described included heightened activity in emotion regulation and empathy regions – bilateral anterior entorhinal cortex, left caudate, left insula, and reduced frontocortical activity (superior frontal gyrus and bilateral superior parietal lobes) in women with IPV-PTSD compared to healthy mothers.

PTSD symptoms were inversely correlated with superior frontal gyrus activity and positively associated with caudate activity. Based upon behavioral data in this same population (Schechter et al., 2010), it was suggested that hyperactivity within the fear circuitry associated with IPV-PTSD might mediate reduced maternal emotional availability for coordinated joint attention during play. A further analysis with the same dataset demonstrated that dissociative symptoms, when present with or without PTSD, were associated with increased emotion regulation cortical regions (right dorsolateral PFC) and decreased limbic activity (perirhinal cortex, hippocampus, insula) to separation versus play videos (Moser et al., 2013). This is in accord with a report in other PTSD-dissociative-subtype populations viewing traumatic and non-specific negative emotional stimuli (Lanius et al., 2007). This finding is also consistent with the dampened amygdala response seen in mothers

with unresolved attachment trauma, after viewing their own (but not unknown) infant's crying faces (Kim et al., 2014b). These findings highlight the importance of the emotion regulation region and limbic activation for dissociation, PTSD symptoms and other domains of cognitive function that affect maternal sensitivity and child outcome.

Substance abuse

Drug addiction continues to be a substantial and growing public health problem in the US. Substance abuse in mothers is particularly problematic because of the negative long-term impact it may have on their children. Many women rapidly resume substance use after childbirth, with resultant adverse effects on their parenting capacity and their children's development. Addiction problems in mothers are associated with a range of major parenting difficulties, often resulting in child abuse and neglect (Mayes et al., 1997; Strathearn and Mayes, 2010).

Unlike many mothers who find engaging with their own children to be a uniquely rewarding experience, mothers with addictions may be less able to respond appropriately to their children's cues, finding them less intrinsically rewarding or salient and more stress-provoking (Rutherford et al., 2011). Current research is focusing on the ways in which drug addiction involves altered brain responses that underlie maternal behavior (Strathearn and Mayes, 2010), having previously demonstrated that infants' cues activate dopaminergically innervated brain reward circuits similar to those associated with drugs of abuse (Strathearn et al., 2008). This finding raises the possibility that drugs of abuse may co-opt the brain circuitry critical for maternal caregiving.

Likewise, drugs of abuse such as cocaine stimulate DA pathways in similar brain regions (Kufahl et al., 2005). As with other biological systems, the development of the dopaminergic system appears to be regulated by patterns of stimulation over time. For example, chronic stimulation of DA systems by drugs of abuse tends to up-regulate and desensitize DA receptors, which may lead to escalating drug use and withdrawal symptoms during early abstinence.

The pathways leading to addiction are complex and multidimensional, and they include differences in molecular and genetic expression, altered brain sensitivities to reward- and stress-related cues, and behavioral patterns that include risk-taking, social isolation, and/or trauma symptomatology. Epidemiological studies have linked addiction in adulthood to prior adverse early childhood experiences (Anda et al., 2006; Dube et al., 2003), with increased risk/severity related to the number of adverse factors experienced, such as childhood abuse, domestic violence, and parental addiction. Early exposure to low quality maternal care may also alter the development of dopaminergic pathways associated with reward-related behaviors, and response to drugs. For example, rodents who were reared in isolation showed changes in distribution of DA receptors (Gill et al., 2013), displayed more inattentive and impulsive behaviors (Lovic et al., 2011; Ouchi et al., 2013), and had an exaggerated DA response in the ventral striatum to systemic amphetamine (Hall et al., 1998). Similarly, humans with low self-reported "parental bonding" on the Parental Bonding Instrument show altered ventral striatal DA responses to psychological stress (Pruessner et al., 2004). Whereas striatal DA responses to natural rewards, such as infants' cues, may be blunted in animals exposed to lower levels of maternal caregiving (Champagne et al., 2004; Strathearn, 2011), responses to stress and stimulant drugs appear to be increased.

Current research has shown that mothers in treatment for drug addiction have almost universally experienced severe childhood trauma that remains unresolved into adulthood (98% of an addiction cohort [$n = 44$] vs. 67% of a control group [$n = 18$]) (Kim et al., 2014c). Animal models have helped to elucidate developmental pathways by which stress experienced in early life may impact neuroendocrine development and translate into behavioral patterns that increase the susceptibility to addiction. Through epigenetic mechanisms, experiences in early life appear to modify gene and receptor expression in

neuroendocrine systems, leading to changes in adult behavior, including drug seeking and addiction (Caldji et al., 2011; Champagne, 2011; Meaney et al., 2002; Sng and Meaney, 2009; Weaver et al., 2004).

Parenting difficulties that result from addiction can lead to the perpetuation of childhood abuse and neglect (Dube et al., 2003), thus continuing the cycle of childhood adversity and addiction. In fact, addicted mothers are far more likely to lose custody of their children as a result of child neglect or abuse (Minnes et al., 2008). Furthermore, growing up in a negative home environment and with childhood neglect is significantly correlated with higher levels of parenting stress in adulthood and an increased display of problematic parenting behaviors (Harmer et al., 1999). Taken together, there appears to be increasing evidence of intergenerational effects, whereby mothers who abuse drugs have often experienced grossly inadequate caregiving environments during their own childhood, perhaps further accentuating neglectful or abusive care of their children that is associated with substance abuse.

How neuroimaging studies inform parenting intervention

Our understanding on neural regions involved in parenting is still limited to inform the development of specific intervention strategies, but as the first step, the field is interested in evaluating neural changes following parenting interventions. Given the apparent plasticity of the maternal brain in adaptive mental health and psychopathological maladaptation, brain changes are likely occurring when parenting interventions are applied. The importance of such interventions is underlined by a growing body of research demonstrating that infants of mothers with mental health problems are at increased risk for developmental delays, cognitive and functional impairments, physical symptoms and injuries, as well as behavioral and emotional problems in the affected pre-school and school age children (Bagner et al., 2010; Bureau et al., 2009; Cornish et al., 2005; Feldman et al., 2009; Grace et al., 2003; Halligan et al., 2007; Hay et al., 2008; Sohr-Preston and Scaramella, 2006). Currently, mental health interventions are thus being implemented for real-world primary care treatment settings where mothers seek treatment for difficulties with parenting due to attachment, mood and anxiety disorders, and promotion of attachment security in the child. One recent study revealed that mothers with unresolved trauma, but whose attachment pattern was reorganizing toward security, were more likely to have children with secure attachment (Iyengar et al., 2014).

Specific intervention programs including the Circle of Security (Hoffman et al., 2006; Powell et al., 2014), Triple P (Positive Parenting Program) (Sanders et al., 2014), Video Interaction for Promoting Positive Parenting Programme (Van Zeijl et al., 2006), and Mom Power (Muzik et al., 2015), have been validated according to randomized clinical trial approaches. Preliminary functional imaging findings on Mom Power parenting intervention for mothers of children aged two to seven years at mental health risk due to history of psychopathology involving at least one trauma (Swain et al., 2014a) suggest brain correlates of the intervention. There were significant increases in brain-activity as a function of parenting treatment ($n = 14$), controlling for time and treatment-as-usual ($n = 15$), in response to stimuli from one's own vs. other infant, in the amygdala, precuneus, dorsal anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC) ($p < 0.001$, uncorrected). Brain regions with increased response to "your-baby-cry" versus "just-listen" included emotion regulation regions – the amygdala, the precuneus, the dorsal ACC, and the dorsolateral PFC. Brain activity for an own-child empathy task was also increased in the dorsolateral PFC and insula. Furthermore, brain activity was inversely related to parenting stress ($p < 0.001$, uncorrected) for the own baby-cry task, in empathy regions: precuneus, medial PFC and temporoparietal junction. The findings provide preliminary evidence for neural mechanisms for parenting intervention in plastic empathy circuits.

Summary

We reviewed abnormal neural regulation of parenting among mothers with psychopathology. Mothers with syndromal level depression have blunted amygdala and insula activity to negative emotional stimuli and infant distress stimuli, which is the opposite of that described in non-postpartum depressed samples. Heightened intrusive/anxious responses that accompany subsyndromal affective symptoms in very early (3 weeks) postpartum mothers, associated with medial PFC and lenticular nucleus activity to infant cry, may change over time and serve an adaptive role that fails in the development of syndromal depression. Reward-related neural responses to positive words and monetary gain are noted to be reduced in depressed mothers. Mothers, more than one year postpartum, who have PTSD, have a neurobiology which resembles that in non-postpartum populations, characterized by hyperactivity within the fear circuitry (amygdala and anterior insula) and alternatively decreased or increased (dissociative-type) voluntary ventromedial PFC/ventral ACC regulation of subcortical activity. Circuits that support social cognition/mentalization/empathy in healthy mothers are hyporesponsive to infant stimuli in mothers with insecure attachment and substance use disorders. This broad domain confers potential as a marker of impaired maternal caregiving that might benefit from greater specificity and standardization in the future. Detecting neural endophenotypes of disrupted maternal care may guide earlier interventions and improve the mental and physical health of mother and offspring.

Future directions of the field

There has been significant improvement in our understanding of the human maternal brain based on a growing number of fMRI studies with human mothers. However, important questions remain unanswered. First, although most of the studies with human mothers have focused on understanding neural functions, little work has been done regarding structural changes. Although human evidence suggests that structural growth occurs in the maternal brain (Kim et al., 2010a), animal evidence suggests mixed findings on reduced neurogenesis in the hippocampus but increased synaptic density in the prefrontal cortex during the postpartum period (Leuner et al., 2010). Furthermore, current literature suggests mixed evidence in the direction of the anatomical and functional correlations. While training-induced increased gray matter volumes have been associated with increased activation in the hippocampus (Hamzei et al., 2012), decreased gray matter volumes were associated with increased activation in the amygdala among trauma-exposed individuals (Ganzel et al., 2008). Therefore, it would be important to clarify hormone-related and experienced-based anatomical changes and how they interact with neural functions among human mothers during the early postpartum period, which will provide deeper understanding of the neural plasticity of the maternal brain.

Second, prospective and longitudinal studies across important transition periods for parenting are important to map the temporal processes of neural changes in the human maternal brain. Existing findings of the human maternal brain are based primarily on studies with women during the postpartum period or the first few years of a child's life. However, measures in these studies, such as maternal mood, hormones, neural activation, and parenting behaviors, are measured cross-sectionally, providing only correlative associations that must be interpreted with caution. Thus, causal or temporal conclusions cannot be drawn on how these factors are related to each other. Therefore, prospective studies, particularly studying women during pregnancy and/or even before conception with follow-up until the postpartum periods, may help determine if hormonal changes during the pregnancy prime and enhance neural activation in response to infants during the early postpartum period, which will be further associated with more sensitive maternal behavioral responses to infants during later postpartum periods.

Third, negative environments such as living in poverty, being a single or teenage mother, and high marital conflicts are significant risk factors for maternal insensitivity toward infants and for psychopathology (Magnuson and Duncan, 2002; Sturge-Apple et al., 2006). However, little is known about whether such negative environments can increase risk for negative maternal outcomes through changes in the neurobiological processes of parenting and mood regulation (Kim and Bianco, 2014). Therefore, future research may recruit mothers in at-risk environments and examine the effects of the environmental factors on neural responses to infant stimuli.

Fourth, we have discussed findings in mothers with defined psychopathology in the previous section, including postpartum depression and substance abuse. Larger and more targeted samples may help to identify specific neural mechanisms that are most affected in specific psychopathologies. For instance, dysfunctions in the regulation of the emotion network may be associated with postpartum depression, whereas the reward/motivation network may be more associated with substance abuse. Alternatively, as proposed in the National Institute of Mental Health's Research Domain Criteria (RDoC) (Cuthbert, 2014) continuous symptom spectra, which may overlap across defined psychopathologies, may better align with neurobiological systems. Such specificity can be critical for developing targeted interventions and treatments that are more effective in preventing psychopathology and improving symptoms of psychopathology among new mothers.

Fifth, the field will benefit from continuing to move toward combining well-established paradigms known to probe certain aspects of brain function, such as executive functions and emotion response/regulation with naturalistic and personally salient infant information. At the same time, the field also lacks studies examining specific links between neural regions/networks and behaviors throughout pregnancy and the postpartum period. For example, verbal recall memory declines during pregnancy and the postpartum period (Glynn, 2010). The next step may include examining whether activation in specific neural regions/circuits such as the hippocampus and precuneus/posterior cingulate cortex, which are parts of the neural memory circuits, change over time across pregnancy and the postpartum period, and moreover, whether the neural changes in the memory circuit are associated with memory performance using standardized episodic memory tasks.

Furthermore, the field has pointed out the need to incorporate more naturalistic and personally relevant stimuli. The child may be included in forms of neuroimaging that allow for some natural movement, such as with functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG). This may yield brain-based models that reflect real-life parental planning, responding and decision-making, and perhaps avoid neuroimaging problems in other fields that have typically been difficult to replicate or relate to, perhaps because of not using personally tailored stimuli.

Finally, alternate neuroimaging methods will also be needed to incorporate brain structure, resting state and functional neural activation, and parenting behaviors. Such multimodal approaches that use machine learning methods promise diagnostic and prognostic models for healthy maternal adaptation vs. psychopathology (Orru et al., 2012) that may not be possible with any one method. Perhaps in the future, a routine brain-scan – with advanced post-processing – will provide biomarkers for earlier assessment and correction of parenting problems toward breaking trans-generational mental health problems.

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