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The Neurobiology of Postpartum Anxiety and Depression

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Abstract

Approximately 10-20% of postpartum women experience anxiety or depressive disorders, which can have extremely detrimental effects on the mother, child and family. Little is known about the neural correlates of these affective disorders when they occur in mothers, but they do have unique neural profiles during the postpartum period compared to when they occur at other times in a woman's life. Because the neural systems affected by postpartum anxiety and depression overlap and interact with the systems involved in maternal caregiving behaviors, mother-infant interactions are highly susceptible to disruption. Thus, there is an intricate interplay among maternal mental health, the mother-infant relationship, and the neurobiological mechanisms mediating them that needs to be the focus of future study.

I. Postpartum Anxiety and Depression Occur in at Least 1 in 10 women

Early motherhood is often a time when women experience a unique sense of happiness, serenity and personal fulfillment. It is abundantly clear, however, that a significant number of recently parturient women cannot attain these positive states because they struggle with elevated anxiety and depression. **Postpartum anxiety** (Glossary) does not currently have unique diagnostic criteria, so its symptom profile is most often characterized by the same symptoms involved in anxiety disorders occurring outside the postpartum period. These include excessive concern or worry that cannot be controlled (when associated with generalized anxiety disorder - GAD) and intrusive thoughts, impulses or behaviors (when associated with obsessive-compulsive disorder - OCD). Motherhood-specific concerns about the infant's vulnerability and safety also exist and peak after giving birth, but are rarely assessed. Such concerns are completely normal, and even beneficial for infant wellbeing, but at high levels they negatively contribute to maternal anxiety [1].

The symptom profile of **postpartum depression (PPD)** (Glossary) includes sad mood, restlessness/agitation, and impaired concentration, thus resembling that of a major depressive disorder (MDD) experienced at other times in adulthood. PPD is often comorbid with anxiety [6, 7], and is strongly predicted by a prepartum history of either depression or anxiety [2-5] (Box 1). While it is unclear whether PPD has any unique symptom characteristics [2, 3], both postpartum anxiety and depression are obviously unique in their timing, some of their physiological and psychosocial risk factors (Box 2), and their consequences for the mother-infant dyad if not the entire family unit [4-6]. Precise rates of postpartum anxiety and depressive disorders are very difficult to ascertain due to the heterogeneity of the disorders, differences among studies in their research populations, the many diagnostic tools and criteria used for their diagnosis, and an overall lack of screening for psychiatric symptoms in postpartum women [7-9]. Nevertheless, recent analyses indicate that at least ~8-12% of the 4 million parturient women in the United States each year suffer from a postpartum anxiety disorder, with GAD and OCD being the most common; similar rates have been reported in

Canada and Germany [10, 11]. Furthermore, at least ~10-15% of women in these and other industrialized countries are faced with PPD [7, 8, 12-14]. In developing countries, the rates of postpartum anxiety appear to be at least as high as those in industrialized nations [15-17] and postpartum depression can be 2 to 3 times higher than in industrialized countries [14, 18, 19]. When one additionally considers mothers with high, but subclinical, levels of anxiety and depressive symptoms the number of affected women and their children around the world is significant.

Evidence for whether or not these rates mean that the postpartum period is a time of elevated risk for mental health concerns compared to other times in women's lives is equivocal, but a number of compelling studies have reported higher rates of anxiety and depression in the first few weeks, months or year after parturition compared to beforehand or afterwards (e.g., [20-23]). Even if the postpartum period is not a time of elevated risk, there are few times in women's lives when the stakes of having an anxiety or depressive disorder are as high. Indeed, a postpartum psychiatric admission is a greater mortality risk for women than almost all other single causes, including heavy smoking [24, 25]! Postpartum anxiety and depression are also each associated with a host of other negative outcomes for mothers and infants including reduced breastfeeding, lack of maternal emotional and behavioral sensitivity to the infant, poor bonding, negative infant temperament, atypical neurodevelopment, and later emotional and behavioral problems for the children when they are older [26-29]. Despite its prevalence and pervasive costs for the mother and developing child, our understanding of the neural bases of postpartum emotional and mood disorders rely on only a few recent clinical studies [30] that point to a number of brain regions affected by postpartum depression at rest and in response to infant or non-infant emotional cues. Although postpartum anxiety is as equally prevalent, very few studies have investigated its neural correlates, and no work has investigated the neural basis of *prepartum* anxiety or depression. The latter point is particularly unfortunate for treatment and prevention because women who experience anxiety or depression during the postpartum period were often anxious or depressed during pregnancy: recent estimates

show that at least 10% of pregnant women have an anxiety disorder and at least 7% of them a major depressive episode [10, 31]. Given the current state of the literature, here we examine what is known about the neural basis of anxiety and depression during the postpartum period, which may inform future studies exploring the neural basis of prepartum affective disorders. Furthermore, we aim to focus on the extent to which the neural bases of postpartum anxiety and depressive disorders appear to be similar to and different from the neural basis of these disorders experienced at other times in a woman's life – that is, outside of pregnancy or the postpartum period.

II. Neural Correlates of Postpartum Anxiety and Depression

1) Findings from clinical studies

Two general research strategies involving the safe and non-invasive **functional magnetic resonance imaging** (fMRI) (Glossary) have been used to study the brain systems involved in affective disorders (or their symptoms in studies that do not use diagnostic criteria) in women during late pregnancy through 18 months postpartum. The first strategy involves analyses of women's brain resting state, or the 'default mode' brain activity that occurs without any specific external stimulation. These analyses focus on brain systems known to underlie the behavioral dysregulations that characterize depression, including those involved in self-awareness, emotional regulation and cognitive functioning in the absence of cues [32]. Although certainly best conceptualized as multiple interacting systems, core brain regions associated with resting state activation differences in depressed postpartum women can be found in individual brain sites and are often lateralized in their activation. For example, throughout the cortex (frontal, parietal, and temporal lobes, posterior cingulate cortex) there is less resting-state activity in the left frontal lobe, but increased activity in the right, in postpartum depressed women compared to healthy postpartum women [33]. Other reports investigating specific neural structures show that, at rest, women with PPD (who also had significantly elevated anxiety) have decreased corticocortical and corticolimbic connectivity [34, 35].

More specifically, the women with PPD showed significantly weaker connectivity among the amygdala (AMG), anterior cingulate cortex (ACC), dorsal lateral prefrontal cortex (DLPFC) and the hippocampus compared to non-depressed postpartum women [34, 35]. Unfortunately, resting-state imaging data have not been collected from women with postpartum anxiety alone. However, it is clear that with PPD there are significant changes in neural activity in brain regions important for self-regulation, empathy and emotion. Such neural changes are often lateralized and exist even in the absence of specific cues being presented to the mothers.

The second general strategy to study neural correlates of postpartum anxiety and depression involves using fMRI to investigate differences in mothers' brain responses to infant and non-infant cues, with the goal of understanding both the fundamental neurobiology of PPD and postpartum anxiety as well as how they alter neurobiological correlates of maternal responding to infants. These investigations typically use an emotional cue (*e.g.*, adult face, word, infant face or cry) and a non-emotional cue (*e.g.*, shape, word), with the infant cues often involving a comparison between cues from one's own infant versus those from a non-familiar infant [36, 37]. Using this strategy, research to date has shown effects of depression, anxiety, and their postpartum timing on brain functional activity in affected compared to unaffected mothers [38]. Furthermore, neural activation between depressed and non-depressed mothers also differs in response to infant and non-infant related cues, such that activity in a specific brain region will increase in response to a non-infant emotional cue but decrease in response to an infant-related emotional cue (Table 1). For example, higher scores of either depression or anxiety during the postpartum period are associated with decreased activation of the AMG, particularly the right AMG, and particularly with negative non-infant cues [36, 37, 39-41]. Furthermore, Wonch et al. (2016) recently showed that mothers with clinically determined PPD show an overall *enhanced* response in the right AMG to positive infant photos and positive non-infant photos, but a decrease in functional connectivity between the AMG and right insular cortex

[37]. This connectivity pattern is positively correlated with both depressive symptomology *and* trait anxiety.

There are a number of additional cortical and subcortical areas of the brain in depressed mothers that show altered fMRI activity in response to infant and non-infant emotional cues (Table 1; Figure 1) [37, 42-45]. Although, of course, virtually no brain area is responsible for one behavioral outcome, it is important to highlight that alterations in activation of brain areas during postpartum depression and/or anxiety likely alter key neural networks associated with women's maternal care, empathy, stress, motivation, emotional reaction to stimulus valence, learned reward [46], and executive functioning (for reviews see [30, 47]).

2) Findings from laboratory rodent models

Our understanding of the neurobiology of anxiety and depression has been extensively informed by laboratory rodent models. Unfortunately, research using animal models of peripartum affective disorders to understand their underlying neurobiology is in its infancy. Laboratory rodent models of PPD often mimic single contributing biological or psychosocial factors to PPD in women - by repeatedly applying stressors, administering exogenous glucocorticoids, administering exogenous ovarian hormones and abruptly withdrawing them, or separating mother from pups [48-56] - to induce postpartum depressive-like behaviors. In addition to often having effects on females' depression-like behaviors, these animal models are beginning to show altered neuroplasticity in the maternal brain. Recent findings show modifications in synaptic plasticity, such as synaptic density and density of synaptic proteins, in areas of the prefrontal cortex, nucleus accumbens, amygdala and hippocampus [49, 53, 54, 57-60]; all of these are areas showing altered fMRI activity in PPD mothers compared to healthy mothers. Research in the hippocampus (a brain area that has received the most attention in animal models of PPD due to its relationship with depression and high degree of plasticity in adulthood) shows alterations in its neurogenesis and dendritic plasticity after stress in the peripartum period [54, 55, 57, 61]. In line with clinical work, animal models are also pointing to

pivotal roles for central serotonergic system and the hypothalamic-pituitary-adrenal system in postpartum depression [62, 63], although much more research is needed in this area.

It may be surprising to hear that there has been much more research on the neuroscience of normal and aberrant postpartum anxiety in laboratory rodents than there has been in women. This body of work in rodents has shown important roles of areas including the medial prefrontal cortex, bed nucleus of the stria terminalis, and midbrain periaqueductal gray in mothers' anxiety [64-67]. The neurochemicals acting in these sites to modulate postpartum anxiety in postpartum laboratory rodents include norepinephrine, serotonin, and corticotropin releasing hormone [66, 68-70]. Furthermore the inhibitory neurotransmitter, GABA, and the neuropeptide, oxytocin, may have an interactive, if not a synergistic, relationship to alter maternal anxiety [71]. All of these neurochemicals are also implicated in postpartum anxiety in women, supporting the face validity of rodent models [72-75]. It is also common to assume some role for steroids in postpartum anxiety, as neurosteroids, including allopregnanalone, are positive allosteric modulators of GABA_A receptors and potently anxiolytic [76]. Indeed, neurosteroid fluctuations resulting from rapid withdrawal of exogenous ovarian steroids are anxiogenic in nulliparous female rodents [76]. However, this does not seem to be the case in naturally parturient female rats because inhibiting neurosteroid production or removing their major substrate source (the ovaries) has no effect on dams' anxiety [77, 78]. There is also no clear evidence yet for neurosteroid influences on anxiety in reproductive women [79]. Thus, further work is needed in postpartum women and animal models to determine how measures of central neurosteroid levels, their temporal change, and their effects on GABA_A receptors might or might not affect maternal anxiety.

The following section will highlight how the neurobiology of postpartum depression and anxiety are similar, but also different, from that of MDD and GAD occurring outside the postpartum period (Figure 1). Understanding these similarities and differences will aid in our understanding of emotional and mood disorders occurring in the peripartum period.

III. Is the Neurobiology of Postpartum Depression and Anxiety Different from Depression and Anxiety Outside This Period?

In contrast to the paucity of studies on PPD, there are many studies using fMRI to explore the relationship between brain activation patterns and depression in non-postpartum individuals. As mentioned previously, depressed mothers often have hypoactive resting-state neural activity in both cortical (DLPFC, ACC) and subcortical limbic regions (AMG, hippocampus) when compared to healthy postpartum controls. However, resting state studies of non-recently parturient people (both males and females) with MDD typically find hypoactivity in more lateral cognitive regions (DLPFC, posterior cingulate and precuneus/cuneus) and hyperactivity in medial affective and subcortical limbic regions (the perigenual ACC, ventromedial PFC, dorsomedial thalamus, pulvinar, ventral pallidum/putamen, ventral tegmental area, substantia nigra, tectum and periaqueductal grey) [32, 80]. Imaging studies also reveal functional abnormalities in the brains of non-parturient patients with MDD in response to emotional cues in regions involved in emotion, motivation, and stimulus salience and reinforcement. This primarily involves decreased neural activation of cortical areas (orbital frontal cortex, DLPFC and ACC), and increased activation of limbic regions (AMG, ventral striatum or nucleus accumbens) [81, 82]. This research is informative in the present context given that PPD and MDD share many symptom characteristics, with the exception of the infant/family focus and the perinatal timing of PPD, yet they have different neurobiological activation profiles (Figure 1). For example, individuals with PPD show decreased activation in the AMG and striatum in response to non-infant emotional cues, whereas individual with MDD show increased activation in the AMG and striatum in response to emotional cues [30, 36, 37, 81, 82]. Therefore, simply extrapolating conclusions from neuroimaging studies of MDD to PDD will overlook the role of brain regions (such as the AMG) known to be particularly relevant for mothering and perhaps uniquely affected by maternal mood. PPD is likely not simply an extension of MDD as traditional diagnostic classification implies.

Highlighting the differences in brain activity between populations suffering from non-postpartum anxiety and those with postpartum anxiety is also informative. Although there are exceptions, a number of functional imaging studies on GAD outside the postpartum period show significant hypoactivity in prefrontal cortical areas (DLPFC, DMPFC, ACC) and hyperactivity in the AMG and insula in response to emotional cues [83]. GAD has further been associated with decreased connectivity between the AMG and prefrontal cortical areas, but increased connectivity between the AMG and insular cortex in response to emotional cues or an emotional task [84, 85]. In contrast, higher anxiety in postpartum subjects is associated with *lower* AMG response to emotional non-infant cues and *lower* connectivity between the AMG and the insula [38, 41]. These results collectively suggest that affective disorders during the postpartum period, and potentially the peripartum period, are neurobiological distinct from these disorders at other times in one's life. Additional findings of neurobiological differences for these disorders within and outside the postpartum period may spur a reevaluation of how they may differ symptomatically, as well how they should be treated psychosocially and pharmacologically.

IV. Postpartum Depression, Anxiety, and the Maternal Caregiving Brain Network

Depression during the postpartum period not only affects the mothers' overall wellbeing, but it also affects how mothers interact with their offspring and thus how their offspring develop. There is a substantial literature showing that depression in pregnant and postpartum women has an impact, not only on maternal sleep patterns and affective state; but also on mothers' 'hedonic' responses to stimuli, executive function and cognition [47, 86]. Moreover, we know that executive function deficits have a clear impact on the quality of mothering behavior exhibited during the first postpartum year [47, 87, 88]. Depressed mothers tend to be more intrusive with and irritated by their infant (although many depressed mothers are instead detached and withdrawn), and respond less sensitively, less contingently, and more negatively to their infants compared with non-depressed

mothers [4, 6, 89]. When observed later in the postpartum period, depressed mother-infant dyads exhibit reduced mutual attentiveness, vocal and visual communications, touching interactions and smiling compared with non-depressed dyads [6, 89]. Much of the same is true for anxious mothers and their infants [77, 90, 91]. How maternal depression and anxiety are expressed in the activation pattern of the **maternal caregiving brain network** (Glossary) is an area of recent study in clinical research and research using animal models.

1) Postpartum depression and anxiety affects the maternal caregiving brain network

Given an abundance of evidence of cross-species similarity in the neural control of maternal behavior [92, 93], the neuroanatomy of maternal behavior has largely been investigated in animal models. This research in animals has provided the bases of hypotheses regarding brain areas and systems that are activated in human mothers while viewing infant stimuli. In fact, animal work on the neurobiology of mothering provides one of the best examples in literature of the value of animal models in translational research. Numan and colleagues, as well as other researchers in the field, have provided us with an exquisite description and analysis of the functional neuroanatomy of maternal behavior in the rat [93]. Most work in the area has focused on the final common path for the expression of maternal behavior, which includes the medial preoptic area (MPOA) and its downstream projections to the ventral tegmental area (VTA) and periaqueductal gray. Interconnecting with this MPOA-to-midbrain system are multiple sensory, limbic, and cortical systems. The MPOA contains receptors for all steroid and peptide hormones that activate maternal behaviors [93]. Neurons projecting to and from the MPOA are involved in other behaviors relevant to postpartum caregiving, including mothers' affect (projections from the AMG, bed nucleus of the stria terminalis (BST), and ACC), processes associated with the salience and reinforcing properties of infant cues (projections from the ventral striatum), and attention (projections from ventral striatum and medial PFC (mPFC))[94]. Some of these sites (AMG, BST, mPFC, ACC) also contain hormone receptors and are susceptible to hormonal influences on mother's behavior [93, 95, 96].

Work on the neural bases of maternal behavior in humans is derived primarily from 20 fMRI studies where mothers, non-mothers, and sometimes fathers are presented with either pictures of their own or same-aged unfamiliar infants [97-99], recorded infant cries [43-45, 100], videotapes of infants [101] or emotional words [39]. All studies demonstrate that many of the same limbic and cortical sites important for emotional or social (face) processing [97, 98, 102], sites involved in dopamine-associated reward-processing [99] and regions regulating maternal behavior in other mammals [98, 102] respond to infant stimuli. In general, most of the regions of interest have focused on the emotion-regulation systems, including the AMG and cingulate cortex [36]. For example, Barrett and colleagues recently found greater activation in the AMG when mothers were viewing pictures of their own infant, consistent with previous research [36, 47]. They also found that level of AMG response was related to trait anxiety, where greater trait anxiety was related to lower AMG response. Furthermore, poorer quality of maternal experience and greater levels of distress during parenting are related to lower AMG response to own compared to unfamiliar infant faces and further changes in activation of cortical areas (right superior frontal gyrus, right lateral globus pallidus/AMG region) [44]. Additionally, increased response to infant cries in the right superior frontal gyrus and AMG at one month postpartum is associated with greater maternal sensitivity at 3–4 months postpartum [100]. These findings point to significant interplay, and overlap, between the neural regions involved in maternal anxiety or depressive disorders and mothering.

Because of its relatively small size and ventral position in the brain, fewer studies have explored the role of the hypothalamus and adjacent sites, such as the MPOA. However, because nearly all of the brain regions in the maternal caregiving network are affected by postpartum depression and/or anxiety, effects on the hypothalamus would be expected. In a recent study investigating how maternal depression and sensitivity affect neural activation in response to positive infant stimuli, depressed women were found to be less sensitive, accepting, available, and cooperative with their infant. The relationship between depression (Non-PPD vs. PPD) and maternal

sensitivity was related to the degree of connectivity between the AMG, known for its role in goal-directed maternal behavior, and the insula, known for its role in interoceptive processing [37]. Thus, in human mothers, processing of infant-related cues can be affected not just by maternal depression and anxiety, but also by the quality of mothering and individual differences in the motivation to mother.

3) Other factors influencing postpartum affect and mothering

There are a number of physiological, social, and experiential factors that have the potential to alter the course of postpartum anxiety and depression through their effects on the maternal brain and the mother-infant dyad. Imaging data is showing that birthing mode (vaginal versus c-section) or breastfeeding, both linked to a host of physiological changes in the mother and infant, can significantly alter maternal brain activity. When listening to their own infant's cry, mothers who give birth vaginally show increased blood oxygen level activity in areas such as the superior frontal gyrus, caudate, thalamus, and AMG compared to women who gave birth via caesarean section ([45], note that all women breastfed in this study). Breast-feeding mothers also show greater activation to their own infant's cry in the superior frontal gyrus, insula, striatum, and AMG compared to formula-feeding mothers within the first month postpartum [100]. Whether or not these factors play a role in the neurobiology of postpartum emotion and mood disorders have yet to be determined, but the scarce research suggests that mode of delivery may be a possible mediator of postpartum anxiety and depression [103, 104].

V. Treatment Effects on the Neurobiology of Postpartum Anxiety and Depression

1) Pharmacological

The most common treatment for maternal affective disorders during the peripartum period is the selective serotonin reuptake inhibitor medications (SSRIs) [105-107]. This is despite the fact that postpartum anxiety and depression are associated with altered functioning of many neurotransmitter

systems such as GABA, norepinephrine, serotonin, glutamate [35, 71, 108, 109], steroid and peptide hormones, and genetic variants of these and other systems (for review [110]). SSRI medication use by pregnant and postpartum women in industrialized countries (including, but not limited to, Canada, USA, Australia, Iceland, Denmark, Sweden, UK, Italy, The Netherlands, and France) are on the rise [105-107, 111, 112], with higher rates in Australia and the USA (5-13%) compared to Canada and Western Europe (2-7%) [106, 113]. These SSRI medications can help alleviate peripartum depression and anxiety in many women, and remain the recommended first-line treatment for postpartum affective disorders [114]. However, questions have been raised about their relative risk and benefits to the developing child as SSRIs can cross the placenta and are often evident in breastmilk [115-122]. It is also unclear how long the effects of SSRIs last or why some postpartum women do not benefit from them [123]

Animal models of PPD show that SSRIs may act on the maternal brain to reverse the behavioral effects of repeated stress by increasing synaptic density in the prefrontal cortex and the nucleus accumbens, and by increasing the number of immature neurons, but not synaptic plasticity, in the hippocampus [57, 58, 60]. This suggests region-specific effects of SSRIs in the treatment of PPD. In fact, brain imaging studies on treatments for anxiety disorders and MDD show that both medications and some forms of psychotherapy can regulate neural activation of brain areas that play a key role in these disorders such as the PFC, the hippocampus and AMG [124, 125]. Thus, it may be that similar ‘regulatory’ effects may be seen after pharmacological and psychotherapy treatment of anxiety and depression during pregnancy and the postpartum period.

2) Non-pharmacological

Given the questions about the effectiveness of SSRIs to treat postpartum affective disorders it is advantageous to consider non-pharmacological therapies [126, 127]; such therapies include various forms of psychotherapy, parenting classes, dietary supplements, ‘alternative’ therapies and

exercise [27, 128, 129]. It is also recommended that treatment for depression and anxiety during the postpartum period be individualized with treatment success often being evident after a combination of treatments (pharmacology, dietary, psychotherapy)[114]. It remains to be determined how any of these treatments alter the neurobiology of the maternal brain and improve maternal mental health.

A particularly intriguing non-pharmacological approach that deserves more research for its effectiveness in preventing and/or ameliorate postpartum anxiety and depression is increased physical contact with one's infant, regardless of breast-feeding. Mothers and infants spend much of their time together engaging in activities (e.g., feeding, holding, carrying, playing) that involve physical contact. Tactile inputs mothers receive from their infants regulate virtually all maternal behavioral and physiological processes [130], including anxiety and depression. Anxious or depressed mothers touch their infants less often and less affectionately compared to unaffected mothers [131, 132]. Anxious or depressed mothers are also less likely to continue breastfeeding, which precipitates a negative cycle because breastfeeding cessation in turn exacerbates women's anxiety and depression [133-135]. Studies on laboratory rodents are consistent with these human findings: Separating mothers from their litters, or exposing dams to only pup distal sensory cues (sight, sound, smell) for as little as four hours before testing, increases dams' anxiety behavior [92, 136]. It is unclear if more prolonged or a permanent separation from pups produces long-lasting increases in dams' anxiety [137-139], but such separations do increase dams' depressive-like behaviors [137, 140].

The anxiolytic and anti-depressive effects of infant contact are often attributed to lactation, but a critical question is whether the effects are due to suckling and its hormonal consequences involved in lactation, or involve non-suckling tactile inputs such as infant probing and stroking of mother's skin. These non-suckling inputs may be transmitted through unmyelinated sensory neurons containing the G-protein-coupled receptor, MRGPRB4, which strongly responds to massage-like stroking and conveys its rewarding effects [141, 142]. It would be fascinating if these receptors are

upregulated postpartum to heighten maternal tactile sensitivity. Most studies of maternal mental health and breastfeeding do not control for the amount of time women are in contact with their infants, which is lower when bottlefeeding [143]. Massage has well-known positive consequences for human emotional state and mood [28], so it would not be surprising if non-suckling infant tactile cues improve maternal mental health. In fact, women's state anxiety is equally reduced after breastfeeding or simply holding the infant on the lap [144]. Maternal state anxiety is also reduced after stroking the infants [145]. Consistent with these findings in women, preventing rat mothers from lactating and/or receiving suckling inputs from their pups has no effect on dams' anxiety, further emphasizing the importance of non-suckling touch for postpartum emotional state [92]. Touch interventions involving non-suckling "kangaroo care" potentially reduce anxiety and depressive symptoms in human mothers [146, 147], and all of these non-suckling offspring tactile effects presumably act by naturally optimizing maternal neurochemistry involved in her affective state.

VI. Concluding Remarks and Future Directions

At least 1 in every 10 postpartum women will suffer from anxiety or depression. The prevalence and pervasive effects of these disorders on the mother, child and family are significant and can affect subsequent generations [27, 148]: Yet, our knowledge of the neurobiology of these disorders is in its infancy. Research is pointing to an often distinct neurobiological pattern of these disorders when they occur during the peripartum period compared to at other times in a woman's life, and these patterns are intricately tied to the maternal brain network and subsequently the mother-infant relationship. Although fMRI research can provide information on regional changes in activation in brain regions by detecting regional changes in blood flow, continued research is needed for both pre- *and* post-partum anxiety and depression, using a variety of approaches in clinical and preclinical research, to determine the mechanisms behind the neurobiological patterns of activation and deactivation, the physiological correlates of these changes, and the interplay between peripartum

mood/emotion and mothering (see Outstanding Questions Box). Understanding the neurobiological correlates of maternal emotional and mood disorders will aid in developing effective and safe treatments for these disorders, thus improving the health and well-being of mother, child and family.

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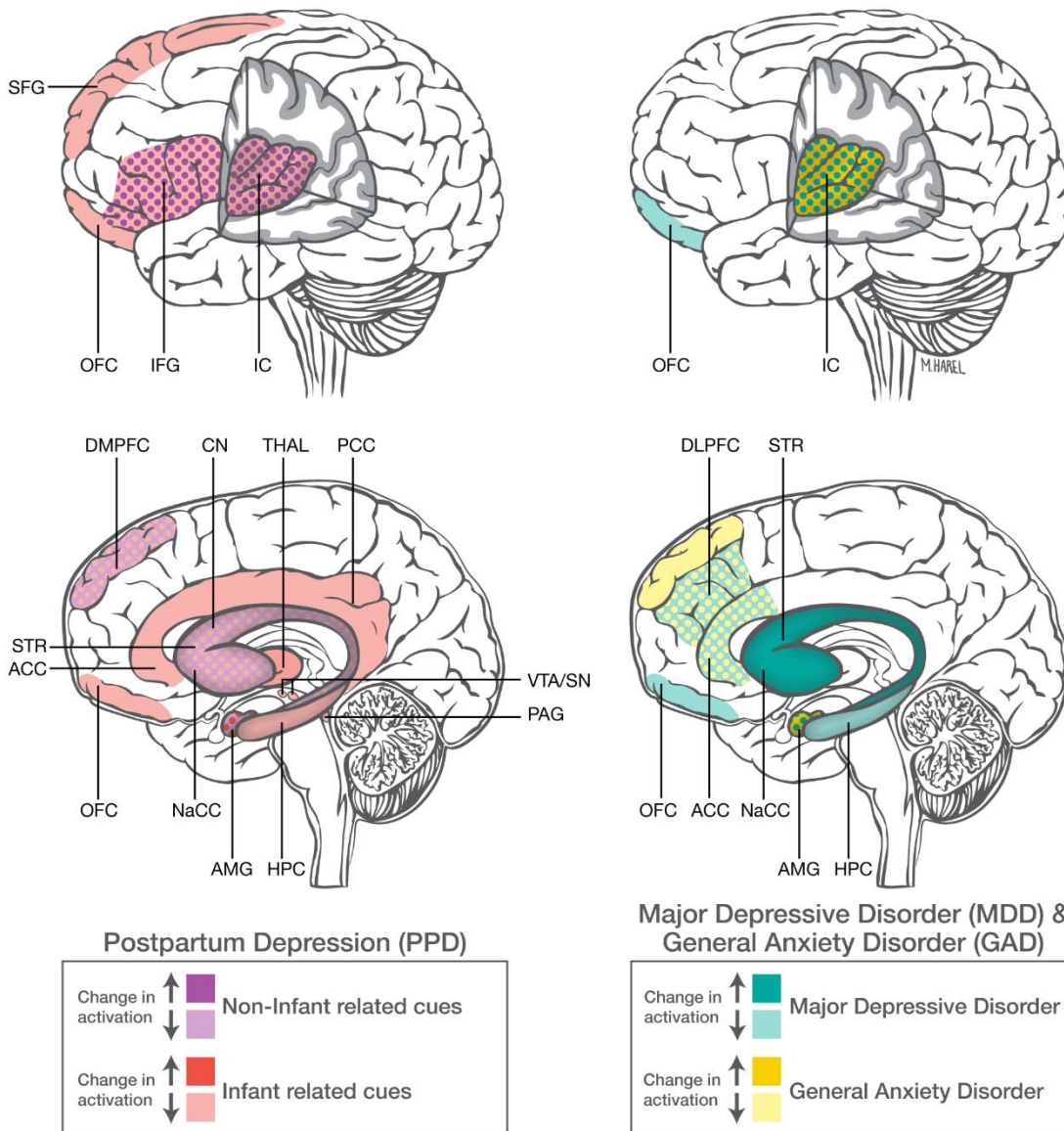


Figure 1. Representation of similarities and differences in fMRI activation patterns in key brain areas associated with Postpartum Depression (PPD), Major Depressive Disorder (MDD), and Generalized Anxiety Disorder (GAD). Dots on the left panel (PPD) indicate change in activation in response to infant or non-infant cues (e.g. AMG activation is increased in response to emotional infant cues, but decreased in response to emotional non-infant cues). Dots on the right panel (MDD/GAD) indicate that the same brain area is activated in response to an emotional cue in both disorders (e.g. AMG activation is increased in both MDD and GAD). Brain areas highlighted play key roles in neural networks associated with stress regulation, reward, motivation, sensory processing, and executive functioning so have the capacity to affect a wide range of maternal

activities. For example, prefrontal cortical areas (DMPFC, DLPFC, OFC, IFG, SFG) play important roles in executive functioning and self regulation; the insular cortex (IC) is critical for emotional processing, cognition and perception; the limbic system (ACC, PCC, HPC, AMG) is well studied for stress regulation, emotion, cognition, motivation and social responding; the striatum (STR, NaCC, CN), VTA and SN are key for learned reinforcement processing; the PAG and THAL play key roles in sensory processing (for review see [30, 47, 149, 150]). ACC – anterior cingulate cortex, AMG – amygdala, CN – caudate nucleus, DLPFC – dorsal lateral prefrontal cortex, DMPFC – dorsal medial prefrontal cortex, HPC – hippocampus, IC – insular cortex, IFG – inferior frontal gyrus, NaCC – nucleus accumbens, OFC – orbital frontal cortex, PAG – periaqueductal, grey, PCC – posterior cingulate cortex, SFG – superior frontal gyrus, SN – substantia nigra, STR – striatum, VTA – ventral tegmental area, THAL – thalamus.

	Resting State	Non-infant Cues		Monetary Reward	Infant Cues		
	(n=3)	Negative (adult face, words) (n=4)	Positive (words) (n=1)	(n=2)	Negative (cry, infant face) (n=6)	Positive (infant face) (n=4)	
Cortical areas							
Dorsal Lateral Prefrontal Cortex							[27]
Dorsal Medial Prefrontal Cortex	↓						[33, 38]
Anterior Cingulate Cortex		↓			↓		[26, 27, 36, 40]
Posterior Cingulate Cortex	↓				↓	↓	[25, 36]
Insula	↓	+			↓	+	[29, 30, 32, 36, 38 41]
Inferior Frontal Gyrus		↑ +			↓	↓	[30, 83]
Superior Frontal Gyrus		↑				↓	[40]
Medial and Middle Frontal Gyrus					↓ ^		[82]
Orbital Frontal Cortex					↓		[32, 36]
Superior Temporal Gyrus		↓			↓ ^	↓	[82]
Subcortical areas							
Amygdala		+			↓	+	[26-29, 31-33]
Striatum	↓	↓		~		↑	[32, 34, 35, 38, 40]
Thalamus			↓	↓	↓		[38, 40]
Hippocampus					↓ a		[26, 27, 41]
Substantia nigra/ VTA/ PAG	↓				↓		[38]
					↓		

Table 1. Brain area activation in depressed and/or anxious mothers postpartum. Data are results of fMRI studies. Note that not all studies investigated all brain areas or took into account postpartum anxiety. Arrow direction indicates general direction of activation. + denotes effect also with postpartum anxiety [37, 38, 41]. ~ denotes altered [151]. ‘a’ denotes women with poorer interaction with their infants[44]. ‘^’ denotes with lower income-to-needs ratio[152]. All studies used either clinical perinatal depressed (PPD) postpartum women versus healthy postpartum women [33-35, 37, 40, 41, 151] or self-rated depressed/anxious postpartum women versus healthy postpartum women, unless otherwise stated. N=17 studies [33-44, 151-155].

Glossary

Functional Magnetic Resonance Imaging (fMRI): A neuroimaging procedure that measures neural activity by detecting changes associated with cerebral blood flow; primarily indicates blood-oxygen-level dependent (BOLD) contrast. This technique relies on the fact that cerebral blood flow is most often correlated with neural activity. Thus, an increase in blood flow would indicate an increase in cellular activity within a specific brain area, and vice versa [156].

Maternal Caregiving Brain Network: Brain areas and neural systems activated or inhibited in response to offspring and important for maternal motivation and the expression of maternal behaviors. Includes areas such as the medial preoptic area, bed nucleus of the stria terminalis, amygdala, nucleus accumbens, ventral tegmental area, midbrain periaqueductal gray and other sensory, limbic, and cortical systems that project to these sites [47, 157].

Postpartum Anxiety: Elevated anxiety with a postpartum onset. At least 10% of women experience high postpartum anxiety. It occurs at higher rates than at other times in a women's life, and in some populations at rates similar to rates of postpartum depression [158]. Generalized anxiety (GAD) and obsessive-compulsive disorder (OCD) are the most common types. The relatively recently published Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) does not include a diagnosis of postpartum anxiety disorders outside the diagnoses for non-postpartum anxiety disorders. The DSM-V criteria for GAD at any time in life include the presence of excessive anxiety and worry about a variety of topics, events, or activities. This anxiety and worry is very difficult to control and occurs more often than not for at least 6 months and is clearly excessive. OCD at any time typically includes the persistent presence of obsessions and compulsions which significantly impact daily life.

Postpartum Depression (PPD): Major depression with a postpartum onset. Major depression includes at least 5 of the following symptoms that last for 2 or more weeks: persistent depressed

mood and sadness, diminished pleasure in nearly all activities, changes in sleep patterns, changes in weight, fatigue, restlessness, feelings of worthlessness, poor concentration, and reoccurring thoughts of death and suicide. Persistent depressed mood or loss of pleasure must be evident for a major depressive episode diagnosis. It should be noted that the DSM-V does not classify postpartum depression as a separate diagnosis, and it instead requires an episode of major (but not minor) depression with a peripartum onset occurring anywhere from the start of pregnancy through the first four weeks following delivery. This differs from the previous DSM-IV criteria, which involved the onset of a major depressive episode only within the 4 weeks after delivery. The broadened time frame for symptom onset can be expected to increase the rate of what is now termed “perinatal depression” [159, 160].

Box 1. Postpartum Anxiety: Overlooked Key Player in Postpartum Mental Health

While moderate maternal anxiety can facilitate attraction to young, attention to their needs, and ability to protect them [1, 161, 162], anxiety disorders affect at least 8-10% of recently parturient women and many more suffer from high, subclinical levels of anxiety [8]. Postpartum anxiety is less well known, and less scientifically studied, than postpartum depression. Accurately detecting and diagnosing anxiety in the postpartum population is very low [163, 164] and, in fact, more postpartum women are probably affected by high anxiety than they are by depression [10, 22].

Ignoring anxiety in reproductive women is a serious public health concern because a history of anxiety before or during pregnancy is one of the strongest predictors of later high postpartum anxiety or depression [9, 165-167]. Furthermore, postpartum depression is frequently comorbid with anxiety [11, 168-170], with the postpartum anxiety often preceding the onset of the depression [171, 172]. Thus, detecting and treating anxiety before or soon after parturition could often help prevent postpartum depression. It is also a concern that the commonly used Edinburgh Postnatal Depression Scale (EPDS) has latent anxiety component accounting for much of the variance in its total scores [173, 174], resulting in a poor ability to dissociate depression from anxiety [175, 176]. Because many studies of postpartum anxiety or depression do not control for comorbid symptoms, it is difficult to determine the unique contributions of each to the negative effects on mothers and children. This is also true for many of fMRI studies involving depressed and/or anxious mothers.

Box 2. Risk Factors Contributing to Postpartum Anxiety and Depression

Not all women are at equal risk for poor mental health during the postpartum period. Some of the greatest psychosocial risk factors for postpartum depression include a history of depression or anxiety before or during pregnancy, numerous sources of psychosocial stress, a history of interpersonal violence, poor relationship quality with one's partner, the lack of social support, low household income, and poor self-perceived maternal health [7, 8, 177-179]. Accordingly, psychosocial interventions can be quite effective in ameliorating postpartum depression [180]. Studies of the biological factors contributing to postpartum depression susceptibility have included (epi)genetically mediated hyper- or hypo- sensitivity to circulating ovarian or adrenal steroids, altered sensitivity to neurosteroids [177, 181], low oxytocin levels and receptor signaling [182, 183], as well as altered monoamine, neurotrophin, and immune system function [181].

Psychosocial and biological risk factors for postpartum anxiety disorders are not particularly well studied, but similar to depression, a woman's history of anxiety or depression is a very strong predictor [9, 22, 166]. Other psychosocial risk factors for high postpartum anxiety include early family history of abuse and neglect, low social support, history of trauma, current partner violence, previous miscarriage, negative childbirth experience, personality style, young maternal age, lack of education, and child temperament during the postpartum period [8, 164]. Biological correlates of high postpartum anxiety are mostly unknown, but the few studies in humans and many studies in laboratory animals suggest they include ovarian and adrenal steroids, oxytocin, prolactin, norepinephrine and serotonin [71]; all of which act on brain areas implicated in maternal mood disorders. Compared to postpartum depression, fewer studies have examined interventions or treatments for postpartum anxiety [9, 184].

Numerous barriers prevent affected postpartum women from seeking or obtaining help, including social stigma about mental health, low social support, and insufficient knowledge among

health-care providers about postpartum mental health [185]. However, this landscape seems to be changing. The past 15 years has seen a seven-fold increase in the annual number of scientific articles indexed on Medline involving the keywords “postpartum” and “anxiety” (170 vs. 25) and a four-fold increase in articles involving the keywords “postpartum” and “depression” (525 vs. 126). Furthermore, based on a recent report by O’Connor and colleagues (2016), the United States Preventive Services Task Force expanded their previous recommendation to widely screen adults for depression to specifically include all pregnant and postpartum women [186, 187]. The American College of Obstetricians and Gynecologists (2015) recently made a similar recommendation for both depression and anxiety.

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