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Chapter 5

Neurobiology of maternal mental illness

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Abstract

This chapter provides an overview of current research discoveries beginning to uncover the neurobiology of maternal mental illness. Results are described according to standard diagnostic categories (specifically, perinatal depression, perinatal anxiety and OCD, postpartum psychosis and bipolar disorder, and trauma and posttraumatic stress disorder), yet we aim to put this approach in context with the introduction of a classification model for psychiatric research, the research domain criteria, gaining traction in basic and clinical translational fields. We first review a new area of study, the neuroplasticity of the pregnant and postpartum brain, as work here has relevance for understanding the pathophysiology of mental disorders and may provide clues to changes in brain functioning that are related to compromised parenting in the context of postpartum depression. We next provide background information on neuroendocrine and immune changes during pregnancy and, to a lesser extent, the postpartum period, as alterations in these systems are significantly implicated in underlying neurobiology of mental illness for peripartum women. Our discussion of the major mental illnesses for pregnant and postpartum women includes neuroendocrine changes, neuroinflammation, and neurotransmitter alterations, as well as circuit dysfunction. Overall, remarkable progress has been made in identifying variations in neurobiology (and related systems) involved in maternal mental illness; yet, it is clear that, as classified with standard diagnostic systems, these are heterogeneous disorders and there is individual variability in the alterations in neurobiology for the same illness.

INTRODUCTION

The incidence of maternal mental illness is staggering—indeed, depression and anxiety combined are considered the most common complication of pregnancy and childbirth nationwide (Mathematica, 2019), comparable with or dwarfing rates of gestational diabetes at 6%–9% and preterm birth at 8% (Centers for Disease Control, 2019). Specifically, prevalence rates for depression (major and minor combined) are estimated at 8.5%–11% during pregnancy and 6.5%–12.9% in the first year postpartum in one study (Gaynes et al., 2005) and at 18.4% during pregnancy and 19.2% in the first 3 months postpartum in another (Yonkers et al., 2009, 2011). Across their life course, 20% of adult women in the United States will experience a major depressive episode at some point, which is twice the rate for men (Yonkers et al., 2011); accordingly, there is debate as to whether pregnancy, the postpartum, and transition to parenting periods are

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particular times of vulnerability, with some epidemiologic studies supporting this assertion (Munk-Olsen et al., 2006) and others not (Vesga-Lopez et al., 2008), except for an approximately 1.2% uptick in depression rates postpartum compared with nonchildbearing periods (Vesga-Lopez et al., 2008). This debate, and the somewhat varying prevalence statistics for depression during pregnancy and the postpartum period, reflects and highlights factors in the standard, categorical approach to diagnosing discrete mental conditions that are relevant to deciphering the neurobiology of maternal mental illness during the peripartum period: (1) There is heterogeneity in symptom profiles within the same diagnostic classification (Putnam et al., 2015, 2017) undermining reliability in diagnosing and potentially contributing to differences in who is counted as depressed (and as having other conditions); indeed psychiatric disorders are frequently comorbid, e.g., depression is often comorbid with anxiety (Simon et al., 2004) and mood disorders are also highly comorbid with alcohol use disorders (Shivani et al., 2002) and substance use disorders (Quello et al., 2005). (2) Reproductive steroids regulate mood although changes in them appear to trigger affective dysregulation in some susceptible women and not in others (Schiller et al., 2016) and at some time periods of psychobiologic transition and not others; for example, some women are depressed in pregnancy but not postpartum, others become depressed postpartum without obvious precursors in the prenatal period (Putnam et al., 2015, 2017).

With respect to anxiety disorders, such as specific phobias, social anxiety disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), panic disorder, and obsessive compulsive disorder, a 12-month prevalence was reported to be 14.9% in nonpregnant women, 13% in past year pregnant women, and 12.3% in postpartum women (Vesga-Lopez et al., 2008). Other data estimates GAD occurring in 8.5%–10.5% of women during pregnancy and 4.4%–10.8% postpartum (Misri et al., 2015). Perinatal obsessive compulsive disorder has been less well studied, but approximately 2.6% of postpartum women have been shown to meet the diagnostic criteria for OCD and 5.4% exhibited subsyndromal levels (Wenzel et al., 2003). Preexisting OCD symptoms may become exacerbated during this time (Williams and Koran, 1997; Maina et al., 1999; Labad et al., 2005; Uguz et al., 2007; Abramowitz et al., 2003; Fairbrother and Abramowitz, 2007; Forray et al., 2010; for a review, see Zambaldi et al., 2009). There is suggestive evidence that depression in the perinatal period is characterized by significant anxiety (Putnam et al., 2017), which traditional psychiatric diagnosis does not capture except as comorbid depression and anxiety. Specifically, obsessive compulsive symptoms are commonly reported in patients with postpartum depression (Wisner et al., 1999a), and high rates of postpartum depression have been observed in women with OCD (Williams and Koran, 1997; Labad et al., 2005). For example, it has been reported that 57% of women with postpartum depression exhibit symptoms of OCD (Wisner et al., 1999b). Rates of bipolar disorder and psychosis are lower: 12-month prevalence of bipolar disorder was reported in 2.3% of nonpregnant women, 2.8% of past year pregnant women, and 2.9% of postpartum women (Vesga-Lopez et al., 2008). The point prevalence rate of schizophrenia in women is 1.2% (Mcgrath et al., 2008) while puerperal psychosis incidence estimates range from 0.89 to 2.6 in 1000 women, and one study reported prevalence of postpartum psychosis in 5 in 1000 women (Vanderkruik et al., 2017).

For all of these mental conditions, social determinants of health significantly contribute to illness risk: in poverty samples, postpartum depression is nearly twice the rate as average prevalence (Chung et al., 2004; Chaudron and Nirodi, 2010) and adverse childhood experiences increase the risk of psychiatric hospitalization postpartum (Meltzer-Brody et al., 2018), underscoring the role of social factors in psychiatric conditions and the complexity of mapping their etiology on biologic as well as psychologic levels (Kendler, 2005, 2019).

In contrast to the typical practice of neurology that draws on a physical exam, standardized neurologic tests, as well as biologic measures for diagnostic specificity, MRI to identify brain lesions in MS or EEG to define seizure disorder, psychiatry primarily relies on self-report of symptoms using standardized questionnaires and patient observation in the absence of any biologically based test (except to rule out other conditions, such as blood test for hypo- or hyperthyroid functioning and, infrequently, lumber puncture for anti-NMDA receptor encephalitis). Leading psychiatrists are highly critical of the latest version of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM)-5, worrying that there is a "lack of validity" to the classification system, calling it "at best a dictionary" or even "a scientific nightmare" (Insel, 2013; Scull, 2015; Cahalan, 2019). When DSM-3, the third version, was published in 1980, it dramatically improved the reliability and hence seeming validity of the diagnostic system by more systematically cataloging symptoms and moving away from conjectures on etiology; yet, the diagnostic categories in that version, and in today's fifth, were based on consensus regarding clinical symptom constellations, given the lack of knowledge about the brain's structure and functioning (Cuthbert and Insel, 2010).

With the emergence of spectacular new neuroscience methodologies and discoveries beginning in the 2000s, psychiatric researchers viewed the DSM as hampering progress because mental illness syndromes based on self-reports of symptoms were artificially siloed and

diagnoses unmoored to discrete components of brain functioning—for example, the common dimension of cognitive control is dysregulated in eating disorders and OCD, yet studying their neurobiology happens in isolation (Marsh et al., 2009). These limitations in classification and ontology were viewed as slowing the discovery of pathophysiologic mechanisms, biobehavioral markers, risk prediction tools, and preventive/treatment interventions. In its 2008 Strategic Plan, the National Institute of Mental Health (NIMH) announced an initiative to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (National Institute of Mental Health, 2008). Dubbed the research domain criteria (RDoC), it is a research framework for new approaches to understanding and treating mental disorders. This still-evolving conceptual framework—a new kind of taxonomy for mental disorders for research—is designed to integrate various types of information across multiple levels of analysis, including genetics, molecules, cells, circuitry, behavior, physiology, and self-report, to characterize functioning across six dimensions: negative valance systems, positive valence systems, cognitive systems, systems for social processes, arousal/regulatory systems, and sensorimotor systems (National Institute of Mental Health, 2008; Insel et al., 2010; Casey et al., 2013). For example, by using an RDoC framework, instead of grouping research participants based on symptom-defined diagnostic criteria, they might be selected through an operationalized component of a dimension, such as a particular pattern of activation in reward circuitry under positive valance systems in the context of hormonal changes, which more likely will reveal mechanisms informing how cognition and behavior emerge and are constrained (Cuthbert and Insel, 2010). Importantly, the RDoC model does not privilege biology over other levels of description (self-report); it aims for integration across levels for a data-driven approach to describing psychopathology that includes knowledge of the brain, genes, behavior, and subjective experience. RDoC also does not address etiology; while variation in a brain circuit may help explain disturbed functioning, and a specific allele part of the variation, what *caused* a psychopathologic outcome, with a capital "*C*," is not considered. For etiology, development and life-course perspectives are needed. Specifically, in the words of former NIMH director Thomas Insel, "it is time to rethink mental disorders, recognizing that these are disorders of brain circuits likely caused by developmental processes shaped by a complex interplay of genetics and experience" (Insel and Wang, 2010).

In this chapter, we provide an up-to-date understanding of the neurobiology of maternal mental disorders, acknowledging that the majority of findings are the outcomes of studies using the standard diagnostic categories from the DSM or the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list developed by the World Health Organization, which is similar to DSM. As a consequence, the chapter is divided into sections based on standard diagnostic categories. When possible, we highlight research consonant with an RDoC approach, as well as at points consider etiology with a particular focus on those risk factors occurring early, across the lifespan, and related to brain–behavior outcomes. We begin with a brief overview of changes in the brain, neuroendocrinology, and immune activity during pregnancy and the postpartum periods as they inform an understanding of differences potentially related to pathology. We proceed to review research findings that are beginning to explain the neurobiology of maternal mental illness.

NEUROPLASTICITY IN PREGNANCY

Pregnancy and the transition to parenting can be conceptualized as a developmental period in adulthood involving dramatic shifts in cognition and behavior in addition to physical changes. Evidence from human and animal studies demonstrates that the brain undergoes significant changes in structure and function during the peripartum period, which are generally thought to be adaptive with respect to facilitating maternal orientation toward the mother–infant dyad (Barba-Müller et al., 2019). Methodologically, there are challenges in studying these phenomena, most notably that pregnancy is often considered an exclusion factor for research-based magnetic resonance imaging (MRI), the dominant research tool for examining brain structure and function. Nevertheless, translational studies have begun to provide a picture of the healthy human "parental brain," a necessary step to determining whether different trajectories of neural changes in the peripartum may contribute to risk or resilience for psychopathology. This section provides a brief overview of evidence related to neuroplasticity in the perinatal period.

The mammalian brain demonstrates a striking degree of plasticity in both structure and function in the peripartum, which are thought to promote caregiving-related cognitions and behaviors and enable a mother to effectively adapt to the challenges of this time (Kinsley and Amory-Meyer, 2011; Kim et al., 2016; Barba-Müller et al., 2019). Foundational studies in rodents demonstrate that neural circuits underlying maternal behavior are triggered by endocrine signals during pregnancy and subsequently maintained by experiences of caregiving for pups, with the medial preoptic area consistently identified as a key driver of caregiving behaviors (Numan, 2007; Kohl et al., 2017). Significant plasticity in the

hippocampus also occurs during pregnancy in mammals and contributes to cognitive changes across the reproductive life course (Pawluski et al., 2016). While few studies have investigated structural brain changes in humans over this period, there is emerging consensus for global and specific reductions in gray matter volume (GMV) in the postnatal period compared with prepregnancy. A comparison of structural brain changes from pre- to postpregnancy with changes in the adolescent brain revealed very similar patterns of cerebral morphometric changes, including reductions in volume and cortical thickness and surface area, as well as reductions in sulcal depth and increases in sulcal width, suggesting pregnancy and adolescence are both periods characterized by hormonally driven cortical adaptations (Carmona et al., 2019). Extending earlier findings that total brain size reduced from pre- to postpregnancy stages (Oatridge et al., 2002), a longitudinal study additionally demonstrated that pregnancy was associated with GMV reductions in particular areas (Hoekzema et al., 2017). Specifically, compared with prepregnancy, voxel-wise GMV reductions were observed in the superior temporal sulcus, medial and inferior frontal cortex, fusiform areas, and the hippocampus (Hoekzema et al., 2017). These GMV reductions were interpreted as being adaptive in terms of parenting as greater reductions were predictive of more optimal self-reported mother–infant attachment. Data from the same sample also suggests that volumetric changes in reward-sensitive brain regions occur from pre- to postpregnancy, including volume reduction in the right ventral striatum. The degree of volume reduction was associated with increased functional activation of the same region in response to infant cues, leading authors to infer that such anatomical changes over the peripartum facilitate increased responsiveness of a mother's neural reward circuit to the infant (Hoekzema et al., 2020).

Though these studies suggest a reduction in brain volume from pre- to postpregnancy, there is less certainty about whether these changes persist beyond the peripartum. Despite reductions in brain and GMV often being considered characteristics of aging, a study, interestingly, showed that maternal brains appeared significantly younger at 4–6 weeks postpartum (based on a well-validated anatomical "brain age index," calculated via machine learning) compared with 1–2 days after childbirth, suggesting a "rejuvenation" across early postpartum weeks (Luders et al., 2018). In another study, however, most observed reductions in GMV persisted until at least 2 years postpartum; only the hippocampus had returned to baseline volume by 2 years postpartum (Hoekzema et al., 2017). In contrast, Kim et al. (2010) reported increases in GMV in superior, middle, and inferior prefrontal cortex, parietal lobe, and lymbic and cerebellar structures from 2–4 weeks to 3–4 months postpartum, and also that higher degree of change was associated with more positive maternal perceptions of infants (Kim et al., 2010). These findings were replicated in another study using a whole-brain voxel-based approach across similar postnatal time points, with the additional finding of gray matter increase in the precuneus, middle occipital gyrus, and caudate (Luders et al., 2020). Together, these findings point toward a reorganization of brain tissue across the postpartum, perhaps associated with the evolving adjustment to motherhood and the development of multifarious caregiving behaviors.

In addition to structural transformations, the maternal brain has been shown to exhibit functional neuroplasticity over this time period, believed to support mothers as they transition to motherhood and cope with parenting stressors (Lonstein et al., 2015). Rodent models demonstrate that pregnancy is associated with cognitive and behavioral changes facilitating caregiving, including suppression of aversive responses to pups and improved foraging and spatial reasoning ability (Kinsley et al., 1999), promoted by enhanced plasticity in hippocampal neurons (Lambert et al., 2005), and exposure to pups additionally alters neurogenesis in the hippocampus (Pawluski and Galea, 2007). In humans, high-order social cognitive ability becomes increasingly essential during motherhood as mothers must adapt to become attuned and responsive to the needs of their new baby and for successfully raising offspring in a complex social environment (Anderson and Rutherford, 2012). Converging evidence from neuroimaging studies shows heightened emotional response and activation of theory of mind regions in healthy postpartum women (Leibenluft et al., 2004; Swain, 2011; Gingnell et al., 2015) and that inputs from these regions activate regions in the midbrain and striatum, which are critically involved in caregiving motivation. Subsequently, inputs from these regions are processed by middle and lateral prefrontal regions involved in emotion regulation and attention, suggesting their role in organizing maternal response to infant distress sounds, which includes regulating her own emotions and enabling sensitive responses to these cues (Rutherford et al., 2015; Kim et al., 2016). These brain changes confer benefits to the offspring as they facilitate sensitive caregiving by adaptive orientation in motivation and reward to be directed toward the infant; however, it is possible that the same brain changes could contribute to deleterious effects on maternal psychologic well-being for some women. Cárdenas, Kujawa and Humphreys propose a model in which hyporesponsive brain changes may be associated with decreased risk for psychopathology, and hyperresponsive changes with increased risk (Cárdenas et al., 2019).

Relatively little is known about how individual differences such as psychopathology may shape functional brain changes related to the transition to parenting, with the postpartum period of particular interest given potential downstream behavioral effects on interactions with the child. A review of the literature on neural responses to infants among depressed mothers identified only five fMRI studies, which, taken together, suggested heightened amygdala reactivity and aberrant connectivity in response to emotional infant stimuli, as well as lower connectivity between the amygdala, insula, and orbitofrontal cortex; these findings indicate that compared with healthy mothers, depressed mothers have a dampened reward response and reduced empathy to infant stimuli (Bjertrup et al., 2019). Adaptive changes to the parental brain can also be affected by maternal distress: subjective stress is associated with reduced activity in the right medial prefrontal cortex (mPFC) and bilateral midfrontal cortex in response to infant cry, and also with less positive perceptions of parenting (Kim et al., 2011).

Considering the growing evidence pointing to the emergence of a "parental brain" that underlies caregiving behavior and adaptation to motherhood, further investigation into the influence of maternal psychopathology on these neural adaptations likely will underscore the dyadic nature of maternal mental illness as affecting both mother and child (Barrett and Fleming, 2011; Werner et al., 2015). In attempting to understand how psychopathology may emerge or be exacerbated in the peripartum, consideration of the potential negative consequences of these otherwise adaptive changes to the maternal brain, as well as individual differences in the degree of brain change across this period, could reveal neural bases for perinatal mental illness.

NEUROENDOCRINOLOGY AND IMMUNE CHANGES IN PREGNANCY

Pregnancy is a time of profound physiologic changes that serve to meet the demands of this period and ensure protection of the fetus. Moreover, pregnancy, parturition, and lactation are sequential periods characterized by neuroendocrine and inflammatory changes required for the development and maintenance of the fetus and developing infant.

A coordinated sequence of neuroendocrine changes must occur to establish and successfully maintain a healthy pregnancy. These changes in hormone levels coordinate adaptive changes throughout the peripartum period, including parturition and lactation (Russell et al., 2001). In early pregnancy, there is a rapid rise in chorionic gonadotropin (Venning, 1955; Betz and Fane, 2019), which is produced by the trophoblast, specialized cells of the placenta, and functions to maintain the corpus luteum and promote the secretion of progesterone and estrogen (Venning, 1955). Progesterone levels increase during the first 3 months of pregnancy and remain elevated throughout late gestation. After delivery, the levels decline rapidly. Estrogen follows a similar pattern with levels increasing slowly during the first 3 months of pregnancy and rising more dramatically during late pregnancy (Venning, 1955).

There is also a close relationship between the hypothalamic–pituitary–adrenal (HPA) axis and the reproductive system. Initially, there is a rise in the secretion of glucocorticoids, which returns to normal levels after the first trimester and is followed by another increase during the last trimester (Venning, 1955). Typically, corticotropin-releasing hormone (CRH) is produced in neurons in the paraventricular nucleus of the hypothalamus and released into the hypophyseal portal system to trigger the release of adrenocorticotropic hormone (ACTH) from the pituitary gland and then cortisol from the adrenal cortex. During pregnancy, CRH is produced in the placenta and serves to coordinate the physiology of pregnancy and parturition. Immediately after delivery, glucocorticoid levels rapidly decline, becoming undetectable 24 h following delivery (Petraglia et al., 2010). In contrast to the negative feedback regulation of the HPA axis, glucocorticoids positively regulate CRH produced by the placenta, at the same time suppressing stress reactivity at the level of the hypothalamus during the peripartum period (Petraglia et al., 2010).

Neuroendocrine changes associated with parturition are distinct from those that occur throughout pregnancy. Oxytocin levels increase at the onset of labor, peaking at the time of delivery. However, the dynamics of oxytocin levels are a point of contention due to challenges in measurements as different approaches are used and there are other issues regarding the accuracy of the measurements (Prevost et al., 2014). Oxytocin is thought to play a role in both the initiation of labor and the expulsive phase of delivery (Blanks and Thornton, 2003; Prevost et al., 2014), and its importance in parturition is supported by the evidence that oxytocin administration is sufficient to induce labor.

Neuroendocrine changes associated with lactation are also distinct from those associated with either pregnancy or parturition. A marked neuroendocrine adaptation occurring during pregnancy involves alleviation of the mechanisms limiting prolactin secretion, resulting in hyperprolactinemia during pregnancy and lactation. Elevated prolactin levels play an important role in the development and function of the mammary gland. Prolactin secretion is stimulated by copulation and serves to protect the corpus luteum, a mass of cells that forms in the ovary and produces progesterone during early pregnancy. Prolactin secretion also increases during

mid-pregnancy, which inhibits hypothalamic prolactin release. During late pregnancy, prolactin levels rise before parturition. Following parturition, prolactin secretion is tightly linked to suckling. In addition to neuroendocrine changes responsible for the physiologic transformations associated with pregnancy, changes in hormone levels, such as those of prolactin and oxytocin, have also been proposed to play a role in maternal behaviors (Grattan and Kokay, 2008).

Pregnancy is a time marked by changes in immune function. It was initially thought to represent a time of immune suppression necessary to allow implantation and growth of the fetus. This concept was supported by the evidence that progesterone exerts immunosuppressive actions. However, we now understand that this is not the case, but rather the immune system is active and tightly controlled during normal pregnancy (Mor et al., 2011). This period is essential for the conservation of the species, and, therefore it is very reasonable to posit that the immune system would function to protect the mother and the offspring. What has become abundantly clear is that the function of the immune system is unique during the peripartum period.

Pregnancy is characterized as a period of heightened recognition, communication, trafficking, and repair (Mor et al., 2011). During normal pregnancy, a number of immune cells, including macrophages, natural killer (NK) cells, and regulatory T cells (Treg), invade the decidua and accumulate around the trophoblast. These immune cells appear to play a supportive role, since their depletion results in the termination of pregnancy due to the deleterious effects on placental development, implantation, or decidual formation in humans and animal models (Croy et al., 2000; Abrahams et al., 2004; Hanna et al., 2006; El Costa et al., 2008).

Pregnancy has been proposed to involve three distinct immunologic phases: (1) implantation, placentation, and as such the first and early second trimester of pregnancy requiring a proinflammatory response; (2) fetal growth and development requiring a supportive immune environment and an antiinflammatory state; and (3) parturition requiring strong immune support. During the first trimester when the blastocyst is implanted in the epithelial lining of the uterus, immune cells function to repair tissue and remove cellular debris (Abrahams et al., 2004; Koga and Mor, 2010); thus the first trimester of pregnancy represents a proinflammatory phase (Mor et al., 2011). The second immunologic phase of pregnancy is a period of fetal growth and development that involves cooperation between the physiology of the mother and the fetus, requiring an antiinflammatory state. Finally, the third immunologic phase of pregnancy occurs in preparation for delivery. At the time of parturition, there is a recruitment of immune cells to promote contraction of the uterus and expulsion of the fetus and placenta. Thus it is apparent that pregnancy is a dynamic period of immune function, which is tightly controlled to support the development of the fetus and result in a successful pregnancy.

The unique function of the immune system during pregnancy is evident from the fact that pregnant women have been demonstrated to respond differently to insults. For obvious ethical reasons, these studies largely rely on ex vivo stimulation measures. For example, stimulation of peripheral blood mononuclear cells with lipopolysaccharide (LPS) increases interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) during late pregnancy compared with early pregnancy, which return to prepregnancy levels postpartum (Gillespie et al., 2016). Further, many autoimmune diseases remit during pregnancy and recur postpartum, suggesting altered immune function during pregnancy. Animal models have been utilized to explore the relationship between pregnancy and inflammatory responses and have demonstrated a diminished response during pregnancy compared with nonpregnant animals (Vizi et al., 2001; Faas et al., 2003; Fofie et al., 2005; Mcclure et al., 2005; Aguilar-Valles et al., 2007; Cui et al., 2009). Thus throughout the peripartum period, the response of the immune system depends on the type of insult and stage of pregnancy.

The inflammatory changes associated with the peripartum period are partially influenced by the neuroendocrine changes, suggesting cooperation between these systems (Bränn et al., 2019). For example, progesterone is known to exert antiinflammatory effects and glucocorticoids also exert regulatory effects on the immune system. Conversely, inflammatory changes can induce neuroendocrine changes, particularly through effects on the HPA axis function. These maternal adaptations involve changes in brain function, driven by neuroendocrine and immune changes, altering stress reactivity, ingestive behaviors, emotional processing, and homeostatic mechanisms, fostering the emergence of complex maternal behaviors and, possibly, the potential for dysfunction in brain and behavior levels.

PERINATAL DEPRESSION

In DSM-5, peripartum depression is classified under the category of major depressive disorder with a specification that symptoms must occur during pregnancy or within the first 4 weeks following delivery. The symptom presentation of patients with postpartum depression resembles those of major depressive disorder and is often comorbid with anxiety disorders (Wisner et al., 2013). Although it is unclear if the symptom presentation is distinct from that of major depressive disorder, it is clear that

the symptom onset is unique, which may indicate differences in the underlying neurobiology of disease. Further, postpartum depression also exhibits unique psychosocial risk factors. The heterogeneity in perinatal depression has fueled a discussion about whether there are actually different types of perinatal depression included under this umbrella, which, as indicated previously, has complicated diagnosis, clinical trials, and potentially advancement in understanding the neurobiology of the disorder(s).

Information gained from both the clinical population and preclinical studies has provided insight into the potential mechanisms contributing to the underlying neurobiology of peripartum depression, which includes neuroendocrine changes, neuroinflammation, neurotransmitter alterations, circuit dysfunction, and the involvement of genetics and epigenetics (Pawluski, 2019; Payne and Maguire, 2019). Neuroendocrine changes, ranging from ovarian hormones to glucocorticoids, have been implicated in perinatal depression. The potential involvement of reproductive hormones in perinatal depression has received a great deal of attention, given the symptom onset at the time of hormone withdrawal and the higher incidence of depression in females relative to males (Weissman and Klerman, 1977). However, consistent changes in the levels of reproductive hormones have not been observed in women with perinatal depression (for review, see Schiller et al., 2015). This could be an indication that reproductive hormones do not play a major role in the underlying neurobiology of perinatal depression or could reflect the heterogeneity in the patient population making these associations extremely difficult to detect reliably. Interestingly, there is evidence that women with postpartum depression may exhibit altered sensitivity to gonadal steroids. A seminal study demonstrated that withdrawal from estradiol and progesterone induced depressive symptoms only in patients with a history of postpartum depression (Bloch et al., 2000). These findings suggest that, although it may be difficult to resolve absolute differences in reproductive hormone levels associated with perinatal depression, differences in sensitivity to neuroendocrine changes may be associated with perinatal depression.

Preclinical models also have been employed to examine the impact of changes in reproductive hormones on postpartum depression-like behaviors. Withdrawal from ovarian hormones (progesterone and escalating doses of estradiol) using a hormone-simulated pregnancy model has been shown to induce depression-like behaviors in rats (Stoffel and Craft, 2004). Similarly, estradiol withdrawal in an estrogen withdrawal model of postpartum depression was shown to increase anhedonia (Schiller et al., 2013). Progesterone withdrawal also has been demonstrated to induce depression-like behaviors in rodents (Beckley and Finn, 2007). These preclinical studies are useful for directly demonstrating a relationship between ovarian hormone withdrawal and depression symptoms, with potential relevance to peripartum depression.

Changes in neurosteroid levels also have been implicated in the underlying neurobiology of perinatal depression. Allopregnanolone, a metabolite of progesterone with neuroactive capabilities, has been demonstrated to exert anxiolytic and antidepressant effects (for review, see Schüle et al., 2014), and withdrawal from neurosteroids is capable of inducing depression-like symptoms in rodents (Beckley and Finn, 2007). Reduced allopregnanolone levels have been associated with the risk of developing postpartum depression (Osborne et al., 2017) and correlated with symptom severity in postpartum depression (Hellgren et al., 2014), although other studies failed to demonstrate an association between allopregnanolone levels and postpartum depression (Amin et al., 2006; Deligiannidis et al., 2013). Perhaps the best evidence of a role for neurosteroids in postpartum depression comes from the FDA approval of an allopregnanolone-based treatment for postpartum depression (Scott, 2019), which followed extensive preclinical studies.

Allopregnanolone exerts its neuroactive effects largely through positive allosteric modulation of δ subunit-containing $GABA_A$ receptors ($GABA_A$Rs). The δ subunit of the $GABA_A$R confers neurosteroid sensitivity (Belelli and Lambert, 2005) and, therefore, allopregnanolone is capable of enhancing the tonic GABAergic inhibition mediated by these receptors (Farrant and Nusser, 2005; Belelli et al., 2009). Mice that lack these neurosteroid-sensitive receptors (*Gabrd*$^{-/-}$ mice) exhibit abnormal postpartum behaviors, including depression-like behaviors and deficits in maternal care (Maguire and Mody, 2008). This preclinical model of postpartum depression-like behaviors was the first to test the therapeutic potential of positive allosteric modulators (PAMs) of $GABA_A$R δ subunit-containing receptors (Maguire and Mody, 2008). These data provided the foundation for the use of GABA PAMs for the treatment of postpartum depression (Mody, 2019).

Additional neuroendocrine changes implicated in postpartum depression involve the stress hormones, CRH, and cortisol. Stress is a major risk factor for perinatal depression (Righetti-Veltema et al., 1998; Robertson et al., 2004; O'hara and Wisner, 2014) and positively correlates with depression severity scores (Paykel et al., 1980; O'hara et al., 1984; O'hara, 1986). Previous adverse life events also are a risk factor for perinatal depression and similarly correlate with the severity

of depression symptoms (O'hara et al., 1984, 1991; Barnet et al., 1996; Guintivano et al., 2018; Meltzer-Brody et al., 2018).

Consistent with the proposed role for stress and stress hormones in the underlying neurobiology of postpartum depression, stress and stress hormones have been shown to induce postpartum depression-like behaviors in preclinical models (for review, see Perani and Slattery, 2014; Pawluski et al., 2017). Chronic stress administered throughout pregnancy induces deficits in maternal care and depression- and anxiety-like behaviors in postpartum dams (Maestripieri et al., 1991; Pardon et al., 2000; Brummelte and Galea, 2010; Nephew and Bridges, 2011; Carini et al., 2013; Murgatroyd et al., 2015; Maguire and Mody, 2016). Exogenous corticosterone administration during pregnancy or lactation is also sufficient to induce maternal care deficits and depression- and anxiety-like behaviors in preclinical models (Brummelte and Galea, 2010; Workman et al., 2013). Elevated levels of CRH during the perinatal period were proposed to form a useful diagnostic criterion for postpartum depression (Yim et al., 2009); however, other studies did not find this association using a covariate-adjusted comparison (Meltzer-Brody et al., 2011). Consistent with previous adverse life events as a risk factor for postpartum depression, early life stress in rodents induces deficits in maternal care and increases depression-like behaviors during the postpartum period (Murgatroyd et al., 2015). These data demonstrate that some of the risk factors for postpartum depression observed in the clinic can be employed to establish useful preclinical models and underscore the need for a life-course perspective when considering etiology, and potentially treatment. In a seminal paper, Nemeroff et al. showed that women with chronic depression responded differently to intervention based on childhood adversity: those with trauma backgrounds responded better to psychotherapy alone than medication alone and did not show a noticeable improvement when provided medication and psychotherapy; those without a trauma background showed the highest levels of remission with medication or medication and psychotherapy (Nemeroff et al., 2003). Similar research on treatment outcomes for women with peripartum depression has not yet been conducted; such work could lead to improved understanding of the neurobiology of peripartum depression and would be consistent with an RDoC approach by, for example, grouping pregnant or postpartum women based on trauma-related difficulties on the dimension of social processes and proceeding with biologically oriented studies related to variation in HPA axis regulation.

Inflammatory changes also have been implicated in perinatal depression. As previously described, from conception through lactation, the peripartum period involves marked changes in immune function. These changes are necessary to facilitate fetal growth and development as well as protect the mother and fetus during this critical time, and they have been implicated in peripartum depression. Altered immune function associated with postpartum depression has largely relied on changes in the expression of cytokines and the number of immune cells in women with postpartum depression. The most robust and reproducible inflammatory changes observed are increased levels of IL-6, IL-1β, and TNF-α associated with postpartum depression, which correlate with depression scores (Corwin and Pajer, 2008; Cassidy-Bushrow et al., 2012; Fransson et al., 2012; Osborne and Monk, 2013) (see Osborne et al., 2019, for some contrasting findings). Additional studies have shown a negative correlation between T cell number and postpartum depression symptoms (Hucklebridge et al., 1994) and decreased levels of IFN-γ levels and a lower IFN-γ:IL-10 ratio (Groer and Morgan, 2007). The kynurenine pathway, which, when dysregulated or overactive, can lead to immune system activation, also has been implicated in postpartum depression with increased kynurenine positively correlated with postpartum depression and depression severity scores (Maes et al., 2002). Inflammatory changes are highly variable, particularly during the peripartum period, and therefore further studies are required to definitively demonstrate inflammatory changes associated with the underlying neurobiology of postpartum depression. The lack of study in preclinical models limits the mechanistic insights that can be drawn between immune function and postpartum depression. Given the dramatic immune changes that occur throughout the peripartum period and the appreciation for inflammatory changes impacting neuronal processes, this topic warrants further investigation. Moreover, the neuroendocrine system impacts inflammatory processes and, therefore, there may be bidirectional influences between these proposed mechanisms that require additional study.

Network-level changes also have been implicated in the underlying neurobiology of postpartum depression, largely as a result of imaging studies in patients with peripartum depression. These changes represent variations in the activity in interconnected groups of neurons that coordinate activity and have been implicated in mediating transitions between behavioral states, including mood (Ochsner et al., 2009). Network activity implicated in mediating mood states have been shown to be disrupted in patients with depression, including patients with major depressive disorder as well as women with postpartum depression (Greicius et al., 2007; Kaiser et al., 2016; Brakowski et al., 2017). For example, changes in the default mode network (i.e. in the absence of external stimuli) have been observed in patients with postpartum depression, specifically, evidence of reduced connectivity of the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal

cortex (Deligiannidis et al., 2013). The amygdala has particular relevance to depression given that this region has been previously implicated in mood and emotion (Dick et al., 1996; Fossati, 2012). Further evidence suggests a role for the amygdala in depression, including the observed reduction in amygdala volume in patients with major depressive disorder (Hamilton et al., 2008) and neuroanatomical changes in the basolateral amygdala associated with depression (Rubinow et al., 2016). A reduction in connectivity between the amygdala and multiple brain regions, including the ventrolateral prefrontal cortex, insula, caudate, middle and superior temporal regions, occipital cortex, and cerebellum (Ramasubbu et al., 2014; Tang et al., 2019), and increased resting-state activity in limbic areas, including the amygdala (Drevets, 2000; Faymonville et al., 2003), also have been observed in major depressive disorder. Our current understanding surrounding the function of the amygdala in reward, anxiety, and valence processing (Janak and Tye, 2015) suggests that these pathological features involving the amygdala (summarized earlier) are associated with the primary pathology of major depressive disorder. Further, similar gene expression changes have been identified in patients and experimental models of depression (Labonté et al., 2017), including molecular changes in the amygdala, which have been implicated in vulnerability to major depressive disorder (Sibille et al., 2009). The majority of these studies have focused on network-level changes associated with major depressive disorder given that there are fewer studies specifically investigating network-level changes associated with postpartum depression. However, abnormalities in similar networks have been observed in patients with major depressive disorder and postpartum depression. For example, network dysregulation in patients with postpartum depression also involves the amygdala. Postpartum depression has been associated with reduced connectivity between the amygdala and other brain regions, including the insular cortex (Wonch et al., 2016) and the posterior cingulate cortex (Chase et al., 2014). Functional magnetic resonance imaging (fMRI) studies have also been performed to evaluate changes in neural circuits in response to infant-relevant stimuli. For example, hypoactivation of the amygdala is reproducibly observed in response to infant-relevant stimuli in patients with postpartum depression compared with healthy mothers (Moses-Kolko et al., 2010; Laurent and Ablow, 2011, 2013; Wonch et al., 2016), a finding that builds on the emerging data on the parental brain as it is moderated by individual differences in mood states. These data suggest changes in network engagement, potentially specifically related to adaptation for child rearing, associated with postpartum depression. Elucidation of the networks involved in perinatal depression may provide further insight into the underlying neurobiological mechanisms and potential therapeutic strategies to restore healthy network function. Studies are just beginning to explore network-level changes associated with perinatal depression in preclinical models informed by the RDoC approach, which is essential for establishing the mechanisms of network dysfunction associated with perinatal depression and treatment strategies targeted at restoration of healthy network function.

Finally, it is worth noting that in addition to the neuroendocrine, inflammatory, and network-level changes highlighted in this chapter, aberrant plasticity in neurotransmitter systems and genetic and epigenetic changes also have been proposed to contribute to peripartum depression (Pawluski et al., 2017; Payne and Maguire, 2019).

PERINATAL ANXIETY AND OCD

Peripartum anxiety is similar to GAD in that symptoms include excessive, uncontrollable worry and it is associated with three or more of the following six symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, or sleep disturbance; these symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. However, peripartum anxiety also has unique features, including commonly held worries that revolve around fears of fetal well-being, maternal wellness, illness in the partner, and/or parental mortality (Misri et al., 2015). One of the limitations in the diagnosis of peripartum GAD is that the physical symptoms of GAD, including fatigue, irritability, difficulty concentrating, tension, and insomnia, may be mistaken for normal consequences of pregnancy and/or new parenthood. Despite the high incidence of anxiety during the peripartum period, the DSM specifier "with peripartum onset" is currently only designated for mood disorders. The lack of a perinatal-specific screening tool for GAD is a significant barrier to diagnosis and treatment. For example, the DSM criteria for GAD specify that symptoms occur for 6 months, which may not be an appropriate time frame for perinatal anxiety, and it has been suggested that 1 month may be more appropriate (Misri et al., 2015).

OCD is an anxiety disorder involving obsessions or compulsions in which recurrent and persistent thoughts or impulses are intrusive and/or inappropriate and cause anxiety or distress. OCD symptoms during the postpartum period commonly involve obsessive and intrusive thoughts about harming the newborn (Sichel et al., 1995; Jennings et al., 1999) and associated checking compulsions (Sichel et al., 1995; Arnold, 1999).

The etiology of peripartum anxiety and OCD are not well understood but are thought to involve genetic, environmental, immunological, and hormonal factors (Brandes et al., 2004). Similar to peripartum depression, the timing of symptom presentation has implicated neuroendocrine factors in the underlying neurobiology of peripartum anxiety and OCD, including rapid changes in oxytocin, estrogen, and progesterone (Stein et al., 1993; Leckman et al., 1994; Young et al., 2001; Bartz and Hollander, 2008); in particular, oxytocin has been implicated in postpartum anxiety given the evidence that it reduces this anxiety (Lonstein et al., 2014).

Due to the timing of symptom onset, changes in neurosteroids have been implicated in postpartum anxiety based on the dramatic alterations in neurosteroid levels during the peripartum period and their well-established anxiolytic effects (Smith et al., 2007). Further, steroid hormone withdrawal increases anxiety-like behaviors in preclinical models (Smith et al., 1998, 2004, 2006; Bitran and Smith, 2005) (for review, see Pawluski, 2019). Imaging studies in postpartum women with OCD symptoms show differential activation of the superior and inferior temporal gyri, orbital frontal cortex, insula, and the mPFC during a psychosocial stressor task (Lord et al., 2012). Preclinical studies have provided information about potential brain regions involved in postpartum anxiety, including the mPFC, bed nucleus of the stria terminalis, and periaqueductal gray (Figueira et al., 2008; Smith et al., 2013; Sabihi et al., 2014; Klampfl et al., 2016). Preclinical and clinical studies have demonstrated changes in GABAergic, norepinephrine, serotonin, CRH, and oxytocin signaling associated with postpartum anxiety (Toufexis et al., 1999; Figueira et al., 2008; Sekiyama et al., 2013; Smith et al., 2013; Stuebe et al., 2013; Klampfl et al., 2014, 2016; Lonstein et al., 2014; Sabihi et al., 2014; Deligiannidis et al., 2016).

Similar to peripartum depression, stress is a risk factor for peripartum anxiety and OCD (Mckeon et al., 1984; Britton, 2008; Dennis et al., 2016), and women with postpartum OCD exhibit increased stress reactivity (Lord et al., 2012). Stress-based preclinical models have been shown to induce anxiety-like behaviors during the postpartum period (Maestripieri et al., 1991) (for review, see Hillerer et al., 2011). For example, chronic restraint stress throughout pregnancy has been shown to increase anxiety-like behaviors in postpartum dams (Maestripieri et al., 1991).

Neuroimaging studies implicate the cortico-striato-thalamo-cortical circuits, which control movement selection and initiation, reinforcement, and reward, in the pathophysiology of OCD. Thus these imaging studies in patients demonstrate unique features compared with peripartum anxiety. However, to our knowledge, imaging studies have not been performed to specifically investigate brain regions involved in perinatal OCD. Abnormalities in the dopaminergic system also have been suggested to play a role in OCD based on the proposed role for the basal ganglia (Welter et al., 2011). Further, serotonin has been implicated in the underlying neurobiology of OCD due to the successful treatment of some individuals with SSRIs (Koran and Saxena, 2000; Kellner, 2010; Pittenger and Bloch, 2014). Glutamatergic signaling also has been specified in OCD processes, largely supported by mutations in the glutamate transporter gene SLCL1A1 identified in association with OCD (Stewart et al., 2013) and treatment with glutamatergic agents (Coric et al., 2005; Grant et al., 2007; Kushner et al., 2007; Wilhelm et al., 2008; Haghighi et al., 2013). As indicated, similar to other peripartum mood disorders, neuroendocrine changes have also been implicated in the underlying neurobiology of peripartum OCD. In particular, ovarian hormones have been implicated in peripartum OCD due to the evidence of symptom manifestation related to alterations in the hormonal profile in women (Maina et al., 1999; Abramowitz et al., 2003; Labad et al., 2005). Although OCD is more challenging to study in preclinical models, compulsivity, stereotypy, and perseverance have been applied as a useful outcome measure with potential relevance to OCD (Alonso et al., 2015), an approach very consistent with RDoC research. However, to our knowledge, no preclinical studies on peripartum OCD have been undertaken to date, which is necessary to understand the underlying neurobiology.

The limited number of studies in animal models is beginning to provide mechanistic insights into postpartum anxiety and OCD. However, the lack of clinical and preclinical studies hinders our understanding of the underlying neurobiology of these disorders. The differences in symptomology suggest that there may be unique features of peripartum anxiety and OCD. To fully appreciate the mechanisms contributing to peripartum anxiety and OCD, additional clinical and preclinical studies are required.

POSTPARTUM PSYCHOSIS AND BIPOLAR DISORDER

In the perinatal period, severe mental illness may occur either as a continuation of preexisting illness or as a new disorder with onset following childbirth. Although not recognized by the DSM or ICD classification systems, “postpartum psychosis” or “puerperal psychosis” are terms commonly used in clinical practice to refer to severe episodes of mania, psychotic depression, or psychosis in the postpartum. Primiparity is a consistently

reported obstetric risk factor for postpartum psychosis (Blackmore et al., 2006; Bergink et al., 2011a, 2018), suggesting sensitivity to immune and endocrine changes, as well as psychosocial stress associated with the transition to parenting.

Dysregulated immune activation is associated with acute first-onset psychosis. These patients show elevated monocyte levels but not the normal elevation of T cells seen in healthy postpartum women (Bergink et al., 2013). There is an association between first-onset postpartum psychosis and preeclampsia, a common condition in pregnancy with immune-related pathology (Bergink et al., 2015), as well as autoimmune thyroiditis (Bergink et al., 2011b, 2018).

There also is a clear association between childbirth and onset of bipolar disorder (Munk-Olsen et al., 2012). For women with established bipolar disorder prior to pregnancy, there is a very high risk of relapse and severe mood episodes in the immediate postpartum (Di Florio et al., 2013), with an estimated 35% relapse rate in the postpartum overall and higher rates among those who were medication-naïve during pregnancy (Wesseloo et al., 2016). As with postpartum psychosis, risk for bipolar affective episodes is higher among primiparous women (Blackmore et al., 2006; Di Florio et al., 2014; Munk-Olsen et al., 2014), a finding that remains significant after accounting for the possibility that women experiencing a postpartum episode could be less likely to choose to have additional children (Di Florio et al., 2014). In addition to assisting in the identification of higher-risk women, this finding has implications for candidate neurobiological pathways that may explain associations between parity and severe mood episodes, with endocrine and immunological changes related to first childbirth being potential triggers.

Some women with bipolar disorder may be especially sensitive to the rapid hormonal shift that takes place in the immediate peripartum (described earlier in this chapter), with the role of estrogen being a particular area of interest. In a small study, the occurrence of affective psychosis following childbirth was associated with increased sensitivity of dopamine receptors in the hypothalamus, mediated by the decline in estrogen following parturition (Wieck et al., 1991). The role of estrogen in bipolar affective episodes is further evidenced by converging results of several small studies in nonpregnant women demonstrating that tamoxifen, a selective estrogen receptor modulator, significantly reduces manic symptoms (Meinhard et al., 2014).

Though not extensively studied, oxytocin also may play a role in bipolar affective episodes in the postpartum. Noting commonalities between bipolar disorder and endometriosis, including comorbidity, personality traits, and dysregulated oxytocinergic activity, Dinsdale and Crespi (2017) hypothesize that oxytocin jointly contributes to both conditions. It is highly elevated during parturition, and elevated oxytocinergic activity has been reported in bipolar disorder, particularly during manic episodes (Turan et al., 2013; Lien et al., 2016), and the possibility that oxytocin contributes to bipolar affective episodes in the postpartum is an avenue for future research.

As part of a broader effort to characterize genetic risk for psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), evidence has emerged for heritability of postpartum psychiatric illness. It has been hypothesized that the occurrence of a psychiatric episode in the peripartum could be a marker of a more heritable form of bipolar disorder (Jones and Craddock, 2007), supported by studies showing familial aggregation of postpartum psychiatric episodes in bipolar disorder patients (Payne et al., 2008) and those with psychiatric disorders in general (Bauer et al., 2019). Moreover, there is no difference between bipolar patients with and without histories of postpartum psychosis on psychological factors generally associated with bipolar disorder, including cognitive style, temperament, or personality characteristics (Perry et al., 2019). Although there is currently insufficient evidence for the use of genetic risk scores as a clinical tool, there is evidence for shared genetic mechanisms among postpartum psychiatric disorders. A multinational study applying polygenic risk scores to postpartum depression showed that genetic risk factors for postpartum depression overlapped with those for bipolar disorder, a stronger association than that seen between bipolar disorder and major depression (Byrne et al., 2014). However, a study using data from Danish population-based registers did not show an association between bipolar disorder polygenic risk scores and postpartum psychiatric episode (defined by hospital admission or prescribed psychotropic medication; predominantly depressive episodes) (Bauer et al., 2019). Further research into genetic risk scores specifically for postpartum psychiatric illness, including bipolar disorder, may help efforts to identify women most at risk.

There are few neuroimaging studies of postpartum affective psychosis. In a study of women at risk for postpartum psychosis (defined as having a diagnosis of bipolar disorder, schizoaffective disorder, prior history of postpartum psychotic episode, or postpartum psychosis in a first-degree relative), structural brain differences were reported between those who did experience an episode of postpartum psychosis. Specifically, there was reduced volume of the parahippocampal gyrus, anterior cingulate cortex, postcentral gyrus, and superior temporal gyrus, patterns of morphology that are largely consistent with general vulnerability to psychosis (Fusté et al., 2017). Comparing these findings with GMV in

the peripartum in healthy women, the authors hypothesized that when the typical brain changes occur in the postpartum (Kim et al., 2010) (increase in GMV of frontal lobe and midbrain areas), this could have a protective effect against postpartum psychosis episodes among those at risk. Overall, this is an area in need of further investigation.

TRAUMA AND POSTTRAUMATIC STRESS DISORDER

Altered neurobiology in those with PTSD could be an underlying risk factor for general psychopathology in the peripartum. History of exposure to traumatic events is one of the most common predictors of perinatal psychiatric disorders (Vesga-Lopez et al., 2008). Pregnancy may be a particularly stressful and even traumatic experience for some women, especially those who have significant histories of past trauma (Seng et al., 2010; Muzik et al., 2016). In the United States, risk factors for PTSD during pregnancy include African American racial identity, teen pregnancy, and socioeconomic factors such as education up to the high-school level or less and living in poverty (Seng et al., 2009). During pregnancy, the odds of meeting the criteria for a PTSD diagnosis were highest when the most severe trauma was abuse, followed by prior reproductive trauma (Seng et al., 2009).

Conceptually, childbirth is distinct from other kinds of traumatic events because it is viewed by many women as a positive experience. However, the stress of childbirth itself can be a trigger for PTSD symptoms, possibly more so when the past trauma was interpersonal and thus likely reactivated in the anticipation or engagement of parenting an infant (Moleman et al., 1992; Muzik et al., 2016). A meta-analysis of global studies showed the main vulnerability factors for pregnancy-related PTSD were subjective negative birth experiences, depression during pregnancy, operative birth, fear of childbirth, health complications in pregnancy, prepregnancy history of PTSD, and lack of social support (Ayers et al., 2016). Another systemic review confirmed these vulnerability factors and additionally identified postpartum depression followed by perceived quality of interpersonal interactions with treating medical staff as having the largest association with risk for postnatal PTSD (Grekin and O'hara, 2014). Although preexisting psychopathology is generally a risk factor for PTSD in the postpartum, Muzik et al. (2016) reported only a subset (25%) of women with a lifetime PTSD diagnosis experienced worsening of symptoms in the postpartum; the most salient predictors of this trajectory were negative birth experiences and labor anxiety. The remainder of the sample either experienced no change in PTSD symptoms or, in some cases, it even improved.

Research regarding the neurobiology of PTSD specifically in the peripartum is scarce. The mechanisms of associations between traumatic birth experiences and PTSD symptomatology may differ from those occurring outside of pregnancy due to the physiological changes following childbirth, such as those in the neuroendocrine and immune systems, as well as alterations in oxytocin regulation. The possible therapeutic use of oxytocin for nonpregnant PTSD patients has been examined (Kirsch et al., 2005; Olff et al., 2010), and intranasal administration has been shown to boost treatment response (Koch et al., 2016). Oxytocin may contribute to the extinction of traumatic memories (Sack et al., 2017), which could partially explain the observed temporary memory changes and adaptive extinction of aversive memories seen following childbirth (Brett and Baxendale, 2001). However, a systematic review suggests that this effect of oxytocin, and its anxiolytic properties, may exist only in cases of less severe emotional trauma; for victims of recent traumatic events and/or more severe trauma history, oxytocin may even increase anxiety (Donadon et al., 2018); this is consistent with the heterogeneity of responses to childbirth among PTSD patients (Muzik et al., 2016).

Estrogen also may influence neural reactivity to threat, with elevated estrogen outside pregnancy being associated with greater fear processing in an fMRI study (Hwang et al., 2015). However, lower estrogen levels have also been associated with altered fear inhibition and extinction (Glover et al., 2012, 2013); together, these findings raise the possibility of an inverted U-shaped relationship between estrogen and risk for PTSD (Stevens et al., 2016), although further studies are needed to examine this and determine the role of estrogen in the etiology of PTSD in the peripartum.

DISCUSSION

Science is moving rapidly in its understanding of the neurobiological substrate of maternal mental illness. These new discoveries will lead to new interventions, and, importantly, some of them may not be direct pharmacological agents. For example, Bhattacharyya et al. identified disturbed bioenergetics as a component of major depressive disorder and differences in metabolomic change patterns in those who remitted versus those who did not in response to cognitive behavioral therapy (Bhattacharyya et al., 2019). With greater knowledge of the neurobiology of maternal mental illness, a precision medicine approach, what works for whom and when, will be possible. An initiative to collect a global sample of women with postpartum depression via an app-based platform and thereby ensure sufficient power for genome-wide association studies will greatly contribute

to a precision medicine knowledge base (Guintivano et al., 2019). There also is a relevant policy discussion: a call to action and NIH task force focused on how to ethically include pregnant and lactating women in more research (PRGLAC, 2019) with a specific initiative at the National Institute of Child Health and Development (https://www.nichd.nih.gov/About/Advisory/PRGLAC), sometimes known as "Protect Pregnant Women through Research, Not from It." This plan for culture and compliance changes should lead to more research and scientific breakthroughs related to the neurobiology and treatment of maternal mental illness.

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