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Pathophysiological Mechanisms Implicated in Postpartum Depression

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Abstract

This review aims to summarize the diverse proposed pathophysiological mechanisms contributing to postpartum depression, highlighting both clinical and basic science research findings. The risk factors for developing postpartum depression are discussed, which may provide insight into potential neurobiological underpinnings. The evidence supporting a role for neuroendocrine changes, neuroinflammation, neurotransmitter alterations, circuit dysfunction, and the involvement of genetics and epigenetics in the pathophysiology of postpartum depression are discussed. This review integrates clinical and preclinical findings and highlights the diversity in the patient population, in which numerous pathophysiological changes may contribute to this disorder. Finally, we attempt to integrate these findings to understand how diverse neurobiological changes may contribute to a common pathological phenotype. This review is meant to serve as a comprehensive resource reviewing the proposed pathophysiological mechanisms underlying postpartum depression.

Keywords

Postpartum depression; stress; HPA axis; allopregnanolone; GABA; epigenetics; neuroinflammation; circuit dysfunction; oscillations

1. Overview of postpartum depression

Postpartum depression is a serious psychiatric disorder that is understudied (both clinically and experimentally) and underdiagnosed. Postpartum depression, the most common complication of childbirth negatively impacts the mother, with suicide accounting for approximately 20% of postpartum deaths [1]. Further, maternal depression also has adverse effects on infant behavioral, emotional, and cognitive development [2; 3; 4; 5; 6; 7; 8; 9]. Thus, understanding the underlying neurobiological mechanims contributing to this

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devastnig disorder is imperative. Here we provide an overview of postpartum depression (Section 1), discuss potential biomarkers (Section 2), and delve into what is known about potential contributing factors to the underlying neurobiology of postpartum depression, including a review of the current genetic (Section 3) and epigenetic (Section 4) factors, and biochemical factors, such as neuroendocrine (Section 5), neurotransmitters (Section 6), and neuroinflammatory (Section 7) changes associated with postpartum depression. Finally we review newer avenues of research focused on circuit-level changes contributing to postpartum depression (Section 8). This review attempts to generate a comprehensive resource for the potential underlying neurobiological mechanisms of postpartum depression, however, given the broad scope of this review, it is impossible to delve deeply into each topic. Thus, where appropriate we make reference to other reviews that discuss each of these areas in depth including: biological processes [10; 11; 12], potential endocrine mechanisms [13; 14; 15], the immune system [16; 17] genetic factors [18], as well as a useful review of the diverse neurobiological factors in postpartum depression [19]. Further, this review is focused on postpartum depression and, therefore, largely discusses studies in females although findings in males are included where appropriate.

1.1 Incidence

Depression, historically termed melancholia, has been classified as a mental disorder dating back to the 1800s when the first efforts were made to collect statistical information about the incidence of mental illnesses. Since then, major depression has been included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) since its inception in 1952, whereas, postpartum depression is not recognized as a unique diagnostic category. Postpartum depression was initially classified as a subtype of major depression, listed as “Major Depressive Disorder, with postpartum onset” in DSM-IV and is now classified as “Major Depressive Disorder, with peripartum onset” in the DSM-5, given that symptom manifestation begins during pregnancy in about a third of patients with postpartum depression [20]. Diagnosis of major depression requires the presence of five or more of the following symptoms: depressed mood, diminished interest or pleasure in activities, change in body weight (more than 5% in one month), insomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, decreased ability to concentrate, or recurrent thoughts of death or suicidal ideation. The criteria for the peripartum specifier listed in the DSM-5 stipulates that symptom onset must occur during pregnancy or within the first four weeks following delivery. The four week time-period remains somewhat controversial [21] and there has been a push to increase this window to 6 months following delivery. Notably, however, genetic studies indicate that only depressive episodes that begin within the first four weeks after delivery display familiality [22; 23].

The incidence of major depressive disorder is higher in males than females [24] and the peripartum period is thought to be a particularly vulnerable period for the manifestation of mental health issues, including depression. However, many studies examining the incidence of postpartum depression do not compare the rates to nonpregnant control groups and given the evidence that depression goes undiagnosed to a greater extent in pregnant women compared to nonpregnant women [25], comparisons across studies is difficult. Several

studies that have attempted to examine the overall rates of depression in the postpartum time-period compared to a non-pregnant (non-postpartum) control group have not found compelling evidence for increased rates of depression associated with the postpartum period [26; 27; 28]. Although these studies demonstrated that the overall rate of depression may not be vastly different at 6 months compared to controls [27], the rate of onset of depression was found to be 2–3-fold higher [26; 27] and the symptom levels were higher in postpartum women compared to nonpregnant controls [28]. In contrast, a large study attempting to directly measure the incidence of psychiatric disorders in pregnant and postpartum women demonstrated an elevated risk of depression during the postpartum period compared to nonpregnant women [29]. Overall, the evidence suggests that that the peripartum period is a vulnerable time for the manifestation of depression.

The prevalence of postpartum depression is thought to be approximately 10–20% [30; 31], however, the prevalence varies widely across cultures [32; 33] and based on the income levels of the countries studied [34]. Thus, it has been proposed that the estimated incidence of postpartum depression of 10–20% may be an underestimate of the global problem, with the lower reports resulting from differences in screening rates or screening measures, socio-economic environments, cultural norms, social support structure, and mental health perceptions/stigma world-wide. In fact, it has been found that postpartum depression is often un/underdiagnosed [35; 36] with some estimations that over 50% of women with postpartum depression go undiagnosed [37; 38], for review see [33]). There has been a plea for increased mental health screening during the peripartum period [39] and recent studies suggest that mental health issues may be more prevalent in postpartum women than previously appreciated.

1.2. Environmental risk factors

Environmental factors, such as previous adverse life experiences, history of depression and anxiety disorders, sociocultural roles, psychological attributes, and coping skills, are known to influence the risk for major depressive disorder in both males and females, but may also contribute to the disparities in the incidence between males and females [40]. Numerous environmental risk factors for postpartum depression have been identified and include prenatal depression, prenatal anxiety, impaired infant-mother interactions, lack of social support, financial and/or marital stress, and adverse life events [21; 41; 42]. Many of the risk factors for postpartum depression fall under the umbrella of stress. Until recently, many studies examining the role of stress have focused on life stressors during the peripartum period, which is predictive of postpartum depression and positively correlated with depression severity scores [43; 44; 45], for review see [46]). Consistent with this notion, women with postpartum depression had three times higher Everyday Stressor Index (ESI) scores compared to healthy controls [47]. Further, there is a significant association between stressful life events and the severity of depressive symptoms [48; 49; 50]. Adverse life events as a risk factor for postpartum depression has recently received a great deal of interest [47; 51]. Women who experienced multiple adverse life events, including childhood sexual abuse or adulthood sexual abuse, were found to be at an increased risk of postpartum depression, and were three times more likely to have postpartum depression compared to those that did not experience any adverse life events [47].

In accordance with the clinical evidence for stress as a risk factor for postpartum depression, many of the animal models used to study postpartum depression utilize exogenous corticosterone- or stress-based models (nicely reviewed in [52]). Exogenous corticosterone during pregnancy or lactation is sufficient to increase depression- and anxiety-like behaviors and induce deficits in maternal care in rodent models [53; 54]. Chronic stress during pregnancy also induces depression- and anxiety-like behaviors in postpartum dams and induces deficits in maternal care [53; 55; 56; 57; 58; 59; 60]. Further, repeated maternal separation, which is thought to mimic the impaired infant-mother relationship associated with postpartum depression, has been utilized to model postpartum depression in rodents [61]. Finally, consistent with the evidence that previous adverse life events are a risk factor for postpartum depression, early life stress has also been shown to increase depression-like behaviors during the postpartum period and induce deficits in maternal care [58]. These studies demonstrate the ability to model clinically-relevant risk factors in animal models to study postpartum mood disorders.

2. Proposed biomarkers

A number of biomarkers have been proposed to be useful identifiers for patients at risk for postpartum depression, including neuroendocrine (see Section 5), epigenetic (see Section 4), and neuroinflammatory (see Section 7) biomarkers. However, many of these biomarkers have not been replicated across studies, which may be due to heterogeneity in the patient population. We posit that useful information can still be gleaned from these biomarker studies despite this lack of confirmation in that integration of these findings may point to potential common pathways. Please note that this section will focus only on biomarkers implicated specifically in postpartum depression, not those inferred from studies on major depressive disorders. Further, we will provide a concise summary of biomarker findings since this topic is reviewed in greater depth elsewhere [62]. It is also important to acknowledge the challenges of biomarker identification, such as the heterogeneity in the patient population, limited access to samples (largely limited to circulating factors in the blood), and lack of control over the experimental conditions in the clinic.

2.1. Levels of reproductive hormones

Given the timing of symptom onset, altered levels of reproductive hormones are obvious candidates for potential biomarkers. However, consistent changes in reproductive hormone levels have not been observed in association with postpartum depression (for review see [19]). Interestingly, there is evidence that women suffering from postpartum depression may be differentially sensitive to the effects of gonadal steroids, since withdrawal from supraphysiologic doses of estradiol and progesterone increased depressive symptoms only in patients with a history of postpartum depression [63]. Further, lower levels of oxytocin have been shown to be a predictor of postpartum depression as well as severity of symptoms [64]. However, another study demonstrated that oxytocin levels only predicted postpartum depression symptoms in patients with a history of major depressive disorder [65].

2.2. Levels of stress hormones

Placental corticotropin releasing hormone (CRH) was shown to be a strong predictor of postpartum depression in one study and was proposed as a useful diagnostic criteria for postpartum depression [66]. However, a follow-up commentary based on this report warned that the recommendation for the use of CRH as a diagnostic marker for postpartum depression is premature [67]. In fact, an independent study found an inverse relationship between placental CRH levels and depression scores, but found that this association was not maintained in a covariate-adjusted comparison, suggesting that placental CRH was not directly associated with an increased risk of postpartum depression and, therefore, not a useful biomarker [68]. The role of neuroendocrine factors, including HPA axis dysfunction, in postpartum depression is discussed in greater detail in Section 5.

2.3. Neurosteroid levels

The neuroactive steroid allopregnanolone, a metabolite of progesterone, has also been suggested as a potential biomarker for postpartum depression. Allopregnanolone has been demonstrated to exert anxiolytic and antidepressant effects (for review see [69]), making it a good candidate as a biomarker for postpartum depression. Further, neurosteroid levels rise during pregnancy and fall precipitously during the postpartum period, alloprenanolone levels are decreased in major depressive disorder, and are increased following antidepressant treatment [70; 71; 72; 73]. Several studies have documented reduced allopregnanolone levels associated with the risk of developing PPD [74], a reduction in women experiencing postpartum blues [75], and a negative correlation of serum allopregnanolone with symptoms of postpartum depression [76]. However, it is important to note that other studies have not observed a decrease in circulating levels of allopregnanolone in patients with postpartum depression [77; 78] though the timing of the blood sample (for example 2^{nd} versus 3^{rd} trimester) may play a role in differing results. Thus, the association between allopregnanolone levels and postpartum depression remains unclear. Alterations in neurosteroid levels in postpartum depression are further discussed in Section 5.3. Further, given the ability of neurosteroids to modulate GABAergic signaling, this topic is also addressed in Section 6.1.

2.4. Other factors

Several other factors have also been investigated as biomarkers for postpartum depression. For example, higher levels of β-endorphin [79], a reduction in platelet serotonin levels [80], increased monoamine oxidase-A density [81], low omega-3 levels [82], and lower vitamin D levels [83] have all been associated with a greater risk for developing postpartum depression but have yet to been replicated.

Genetic polymorphisms and epigenetic modifications associated with postpartum depression have also been proposed to be useful biomarkers postpartum depression and have been suggested to contribute to the underlying neurobiology of the disorder. These will be discussed in greater detail in the following Sections 3 and 4.

3. Genetics of postpartum depression

There is evidence for a genetic influence in postpartum depression, based on twin [84] and family studies [22; 23] (for review see [18; 85]). Genome-wide association studies have also identified individual candidate genes as well as potential pathways involved in postpartum depression. Candidate gene studies have largely focused on genes previously implicated in major depressive disorder, such as the serotonin transporter, tryptophan hydroxylase-2 (TPH2), Catechol-O-methyl transferase (COMT), Monoamine Oxidase (MAO), and Brain Derived Neurotrophic Factor (BDNF). Interestingly, pathway analyses based on candidate genes or unbiased screens point to estrogen signaling and the hypothalamic-pituitary-adrenal (HPA) axis involvement. In fact, a recent study identified 44 risk variants in patients with major depression, with one of the strongest candidates having known involvement in the regulation of the CRH response to stress [86]. Genetic studies face the same limitations as the search for potential biomarkers in postpartum depression insofar as the heterogeneity of the patient population makes identification of common genes or common biomarkers challenging. It has been estimated that to adequately power a genome-wide association study for major depression would require five times more patients than for schizophrenia, the "flagship" adult psychiatric disorder for genomics research [86]. Despite these challenges, several studies have identified polymorphisms in specific genes or pathways associated with postpartum depression. The following section will focus only on studies which show a positive association between genetic variations and postpartum depression and does not include studies which were negative such as was the case for candidate gene association studies of Brain-Derivied Neurotrophic Factor [87; 88].

3.1. Estrogen receptor

The estrogen receptor alpha gene (ESR1) plays a role in mediating hormonal changes during the peripartum period, making it an interesting candidate for genetic association studies in postpartum depression. Polymorphisms in ESR1 have been associated with symptoms of postpartum depression in two studies [89; 90], though not all polymorphisms remained significant after correction for multiple testing. Further, an unbiased screen of transcripts associated with postpartum depression demonstrated an enrichment of transcription binding sites on ESR1 [91]. Further examinination of ESR1 polymorphisms is warranted. Estrogen has been further implicated in postpartum depression, a topic which is discussed in Section 5.1.1.

3.2. 5-HTT

Emerging evidence links mutations in the serotonin transporter (5-HTT) with postpartum depression (for review see [82]). For example, polymorphisms in the serotonin transporter gene, 5-HTT, is predictive of depression in the early post-partum period [92; 93; 94]. Interestingly, more recent studies have demonstrated that polymorphisms in 5-HTT predict symptoms of postpartum depression only in patients with associated adverse life events [95], demonstrating an interaction between genes and environment as well as between two risk factors for postpartum depression.

3.3. MAOA

Monoamine oxidase A (MAOA) is an enzyme involved in the oxidative deamination of amines, including dopamine, norepinephrine, and serotonin. Polymorphisms in the gene encoding for MAOA have also been identified in association with postpartum depression [93] and variants of MAOA have been correlated with severity of postpartum depression scores [93]. Interestingly, genetic and epigenetic alterations in MAOA in adult women with adverse life experiences were found to have a higher risk of developing depression [96] and increased cortisol levels [97], again pointing to an interaction between genes and environment as well as known risk factors for postpartum depression.

3.4. COMT

Similar to MAOA, Catechol-O-methyltransferase (COMT) is an exzyme that degrades catecholamines, including dopamine, epinephrine, and norepinephrine. Polymorphisms in the gene encoding for COMT have also been shown to be a risk factor for postpartum depression and also positively correlate with depression scores in women in the immediate postpartum time-period [87; 93; 98]. It is interesting to note that similar studies, investigating polymorphisms in COMT associated with major depressive disorder in general, have generated conflicting results (discussed in [99]). Further investigation into the role of COMT mutations in postpartum depression may benefit from including environmental risk factors.

3.5. TPH2

Tryptophan hydroxylase 2 (TPH2) catalyzes the first, rate-limiting step in the synthesis of serotonin. Genetic variants for the TPH2 gene have been shown to have an interesting association with postpartum depression, with specific variants associated with depression symptoms at specific times points during the peripartum period. For example, polymorphisms in the promoter region have been associated with depression symptoms during pregnancy and up to 6–8 months postpartum [100], whereas, polymorphisms in the intron 8 region was only associated with depression symptoms during pregnancy, not during the postpartum period [100]. A potential interesting interaction between genes and environment is the evidence that TPH2 gene expression is negatively regulated by glucocorticoid receptors [101]. However, the interaction between stress, HPA axis, adverse life events, and THP2 expression remains to be fully explored.

3.6. OXT/OXTR

Single nucleotide polymorphisms (SNPs) in the gene encoding for oxytocin (OXT) or the oxytocin receptor (OXTR) have also been studied in postpartum depression [102; 103]. Interestingly, a SNP in OXT was predictive of both variation in breastfeeding duration and postpartum depression scores, whereas, an interaction between a SNP in OXTR and adverse life events did not correlate with maternal behaviors, but was predictive of depression scores prepartum [103]. Further, an interaction between a SNP in the OXTR gene and methylation state was detected in association with postpartum depression [104]. This topic will be discussed later under a review of epigenetic changes associated with postpartum depression.

3.7. HMNC1

In a genome-wide linkage and association study, the Hemicentin 1 gene (HMNC1) had the strongest association with postpartum depression [105] though the association was not significant after correction for multiple testing. Though it's exact function remains unclear, HMCN1 is highly expressed in the hippocampus, which has been shown to be altered in rats by a postpartum drop in estrogen levels [106], and contains four experimentally determined estrogen binding sites [107]. To further explore the relationship between HMNC1 and postpartum depression, a candidate gene approach was taken which confirmed the HMCN1 polymorphism in association with postpartum depression [108] in a small sample of Brazilian women. Further research is required to understand the role of HMCN1 in the underlying pathophysiology of postpartum depression.

3.8. HPA pathways

There are a number of findings that implicate HPA axis involvement in postpartum depression. Variants in the MAOA and COMT genes, both of which have been implicated in postpartum depression, are also associated with sex-specific differences in cortisol responses to a social stressor [97]. Protein Kinase C beta type (PRKCB) has been shown to be a regulator of the HPA axis indirectly through glucocorticoid receptors (GR) and corticotropin-releasing hormone (CRH) signaling and mutations in this gene have also been associated with postpartum depression [90]. Further, polymorphisms in GRs and corticotropin-releasing hormone receptor 1 (CRHR1) have also been associated with postpartum depression [109]. A polymorphism in CRHR1 also positively correlated with severity of depression symptoms [109]. These efforts are beginning to untangle the interactions between genes and the environment on biochemical changes associated with postpartum depression. These genetic changes have implications for the neuroendocrine abnormalities associated with postpartum depression (discussed in Section 5.2). Future studies along these lines will enable us to elucidate the neurobiological underpinnings of postpartum depression.

There are two take-away points from these collective studies examining the genetic basis of postpartum depression: 1) A number of studies have demonstrated the importance of the environment, particularly stress and adverse life events, in the genetic risk for postpartum depression, and 2) Timing is important. Many studies show gene associations related to a specific time frame of onset of depression during the postpartum period, suggesting that assessments at different time points may be a factor contributing to contradictory findings.

4. Epigenetic mechanisms of postpartum depression

The previous section reviewed the heritability of postpartum depression, focusing on candidate genes and potential pathways associated with the risk and extent of depressive symptoms during the postpartum period. In addition to these genetic factors, it is likely that epigenetic factors, which refer to changes in gene expression unrelated to changes in DNA sequences, but rather to changes in chromatin structure (methylation or histone modifications) that affect gene transcription, also play a role. Epigenetic changes in gene expression are initiated via environmental influences and represent a cross-talk between

environment and genetics. Here we review emerging evidence for epigenetic changes associated with postpartum depression.

A targeted study investigating estrogen-mediated epigenetic reprogramming using a cross-species design identified DNA methylation profiles associated with postpartum depression and cross-referenced them with estradiol-induced DNA methylation profiles in the hippocampus of estrogen treated mice [110]. The overlap between these two DNA methylation profiles suggests that individuals at risk for postpartum depression may exhibit enhanced sensitivity to estrogen-mediated epigenetic changes at two genes. The two identified genes were heterochromatin protein 1, binding protein 3 (HP1BP3) and tetratricopeptide repeat domain 9B (TTC9B), both of which have ties to synaptic plasticity as well as estrogen signalling [110]. Interestingly, HP1BP3 knock-out mice demonstrate deficits in maternal care [111]. Importantly, the ability to predict postpartum depression based on gene expression levels of HP1BP3 and TTC9B was replicated in a subsequent study [112]. Although further replication is needed, epigenetic modification of these two genes may therefore represent a biomarker of postpartum depression that can be used to predict individuals at risk.

Investigation into potential epigenetic modifications in the OXTR gene associated with postpartum depression demonstrated an interaction between genotype and DNA methylation in women that developed postpartum depression [104]. Further, an interaction between DNA methylation variation in the OXTR and previous adverse life events was observed in association with postpartum depression [113]. There was also a negative correlation between serum estradiol levels and DNA methylation in the OTXR gene specifically in patients with postpartum depression and an interaction between estradiol, OXTR DNA methylation, and the ratio of allopregnanolone to progesterone [113] (Figure 1). These data highlight the interelationship between epigenetics and neuroendocrine changes associated with postpartum depression where variations in DNA methylation of the OXTR gene are negatively correlated with serum estradiol levels (Figure 1, left panel) and the ratio of allopregnanolone to progesterone (Figure 1, right panel).

Studies on epigenetic modifications in postpartum depression are just emerging, but these studies demonstrate promise and provide insight regarding the underlying pathophysiological mechanisms. Interestingly, these studies point to an interaction between epigenetic modification and signaling by reproductive hormones and neurosteroid levels, bridging multiple mechanisms implicated in postpartum depression and bring together both environmental and biological (genetic) influences (Figure 1).

5. Neuroendocrine mechanisms of postpartum depression

The peripartum period is a time of abrupt and dramatic changes in hormone levels. This period is also a vulnerable time for the development of mood disorders and it is thought that these two processes are linked in that fluctuations in reproductive hormones may play a role in the underlying neurobiology of postpartum mood disorders, a concept which has led to the ‘ovarian-steroid-withdrawal hypothesis [63; 114], (for review see [13; 115]). Further, neuroendocrine abnormalities, such as elevated levels of stress hormones during the

peripartum period, have also been implicated in the underlying neurobiology of postpartum mood disorders. This section will focus on the evidence pointing to a role for neuroendocrine abnormalities in postpartum depression, focusing on the role of ovarian and lactogenic hormones (estrogen, progesterone, oxytocin, prolactin) as well as stress hormones (cortisol, ACTH, CRH) and their neurosteroid metabolites (Figure 2). Further, this section will highlight the interactions between reproductive hormones, which have been shown to impact HPA axis function and vice versa (Figure 2). It should be noted that thyroid hormones have also been implicated in postpartum depression [116; 117], but may be a unique population or an epiphenomenon of associated thyroid pathologies which are known to be accompanied by depression [118; 119], therefore, thyroid hormones will not be included in the current discussion.

5.1. Ovarian and lactogenic hormones

Despite the obvious relationship between changes in the levels of reproductive hormones and the onset of postpartum depression, there are no consistent changes in hormone levels, kinetics of hormone withdrawal, or larger fluctuations associated with postpartum depression [19; 50; 77; 115; 120], which is likely due, in part, to inherent variability in the patient population as well as methodological differences between studies. However, the timing of symptom onset coincident with dramatic changes in the levels of reproductive hormones make it difficult to dismiss the potential importance of these hormonal fluctuations. Although absolute hormone levels may not differ in women with postpartum depression, sensitivity to reproductive hormone fluctuations at the level of the brain may be different. A critical study demonstrated that the withdrawal of reproductive hormones (estradiol and progesterone) increases depression scores only in women with a prior history of postpartum depression [13] indicating that their brain may be differentially sensitive to times of hormonal change. Further evidence for a role of reproductive hormones in postpartum depression comes from animal experiments where these variables can be better controlled than in the clinic. In the subsections below, we will review both clinical and experimental evidence pointing to a role for reproductive and lactogenic hormones, including estrogen, progesterone, oxytocin, and prolactin, in the underlying neurobiology of postpartum depression.

5.1.1. Estrogen—Estrogen levels rise dramatically before parturition, reaching levels over 1000 times their baseline values, and then precipitously drop after delivery. Changes in absolute estradiol levels have not been consistently reported in patients with postpartum depression [63; 91; 121], although it has been suggested that women with postpartum depression may exhibit increased sensitivity to estrogen signaling based on changes in estrogen-sensitive transcript expression [91], which may involve epigenetic changes [110] or differences in estrogen signaling molecules. Further, estrogen signaling is known to impact other pathways involved in mood, such as the HPA axis (for review see [122]) (Figure 2). Estrogen signaling is known to impact HPA axis function, suggesting that dysregulation of reproductive hormones could dysregulate the levels of stress hormones, another potential biochemical mediator of postpartum depression, thereby contributing to postpartum depression (Figure 2). Interestingly, several studies suggest that estrogen treatment reduces

the risk for developing postpartum depression [123] and decreases depression symptoms during the postpartum period [124; 125; 126; 127; 128] (for review see [129]).

In experimental animal models, it is well-established that withdrawal of estradiol induces depression-like behaviors. Ovariectomized rats exhibit increased depression-like behaviors which are reversed with estradiol treatment [130; 131]. In pseudopregnancy experiments, designed to mimic the hormonal fluctuations of the peripartum period with exogenous progesterone and estradiol administration, the withdrawal of hormones in pseudopregnant mice increased depression-like behaviors [114; 132; 133] which were reduced with continued estradiol treatment [114]. These experiments demonstrate that in a controlled system, withdrawal of reproductive hormones is sufficient to induce depression-like behaviors and estrogen treatment is capable of exerting antidepressant effects in animal models of postpartum depression.

5.1.2. Progesterone—In contrast to the antidepressant effects of estrogen, progesterone treatment has been shown to increase the risk [123] and worsen depression scores in postpartum women [126]. For example, higher progesterone levels are correlated with worse depression scores in postpartum women [134]. However, other studies have demonstrated that progesterone treatment decreased the recurrence of postpartum depression in women with previous postnatal depressive episodes (for review see [135]) and lower progesterone levels correlated with increased depression scores [136]. Unfortunately, these clinical studies leave the effect of progesterone for the treatment of postpartum depression unresolved.

As mentioned above, in experimental animals, withdrawal of reproductive hormones, including progesterone, is sufficient to induce depression-like behaviors [114; 132; 133]. Interestingly, progesterone administration only induced depression-like behaviors in mice following 3 days of withdrawal [137]. The progesterone withdrawal effects on depression-like behaviors could also be mimicked by blocking progesterone metabolism with finasteride treatment, implicating decreased levels of progesterone-derived neurosteroids, such as allopregnanolone, in mediating the depression-like effects of progesterone withdrawal [137]. The role of neurosteroids in the neurobiology of postpartum depression will be specifically addressed in a subsection below.

5.1.3. Oxytocin—Oxytocin has been implicated in postpartum depression given it's well-known role in regulating emotion, social interaction, stress, and the mother-infant relationships, including delivery, lactation, and attachment [138]. Further, it has received attention in postpartum depression, largely related to oxytocin's role in lactation and breastfeeding difficulties associated with postpartum depression [139; 140; 141], which may have common neuroendocrine underpinnings [142]. Consistent with this notion, oxytocin levels during breastfeeding were shown to be inversely correlated with depression symptoms [143] and decreased plasma levels of oxytocin were shown to be predictive of the development of postpartum depression [64]. However, intranasal oxytocin treatments failed to improve maternal sensitivity measures [144] and in a separate study, exposure to peripartum oxytocin increased the risk of postpartum depression [145]. Thus, contrary to popular thought, it appears that oxytocin is not associated with improvements in mood, but might actually worsen mood in women with postpartum depression.

Numerous studies in animal models have demonstrated a role for oxytocin in mediating maternal behaviors (for review see [146]). However, very few studies have investigated the impact of oxytocin on depression-like behaviors during the postpartum period. One study demonstrated that dams that lack the oxytocin receptor (*Oxtr*$^{-/-}$) exhibit impairments/reluctance in maternal care, but is not associated with altered depression-like behaviors during the postpartum period [147]. Thus, despite the clear mechanistic relationship between oxytocin and maternal behaviors, evidence for oxytocin as a critical mediator of the underlying neurobiology of postpartum depression remains largely unsubstantiated (for review see [148]). Although, an interesting recent study demonstrated a reduction in oxytocin mRNA levels in the PVN of mice that exhibit postpartum depression-like behaviors following gestational restraint stress and antidepressant effects of oxytocin injection into the PVN [149].

5.1.4. Prolactin—Similar to oxytocin, prolactin has a well-established role in lactation and maternal behaviors (for review see [142]). A study found that women with postpartum depression were less likely to be breastfeeding and had lower serum prolactin levels [150] and in women with postpartum depression who were breastfeeding, prolactin levels were also decreased [151]. Further, decreased prolactin levels were found in women with higher postpartum depression scores and in those at an increased risk for developing postpartum depression [120]. Thus, it has been suggested that failed lactation and postpartum depression may share a common underlying pathophysiological mechanism [142].

Consistent with a role for prolactin in normal maternal care, Prolactin knockout mice (*Prlr*$^{-/-}$) have significant deficiencies in maternal behavior and lactation [152]. Interestingly, *Prlr*$^{-/-}$ mice also exhibit anxiety-like behaviors, but there is no report of changes in depression-like behaviors [152]. A recent study also demonstrated reduced nurturing behaviors in the offspring of dams with reduced prolactin levels, which could be restored with exogenous prolactin treatment [153]. These studies point towards a role for prolactin in mediating normal maternal behaviors rather than being implicated specifically in postpartum depression.

5.2. Stress hormones (cortisol, ACTH, CRH)

Dysfunction of the HPA axis has been implicated in the underlying neuropathology of postpartum depression (for review see [13; 14; 154; 155]). This is, in part, based on the fact that stress is a prominent risk factor for postpartum depression and neuroendocrine disruptions are one of the most consistent findings in major depressive disorder [156]. Consistent with a role for HPA axis dysfunction in postpartum depression, there is evidence of altered levels of cortisol, ACTH, and CRH in patients suffering from postpartum depression [13]. Elevated levels of CRH have even been suggested to be a diagnostic criteria for postpartum depression [66]. However, these assertions remain controversial [67] and involvement of the HPA axis in postpartum depression remains unproven [68]. There is evidence that the regulation of the HPA axis may be dysfunctional in women with postpartum depression, including decreased responsiveness to the dexamethasone suppression test [13] and an altered ratio of ACTH to cortisol levels [157]. Interestingly, women with a history of postpartum depression demonstrate an increase in stimulated

cortisol [158], suggesting that withdrawal from gonadal steroid levels enhances HPA axis function particularly in women with a history of postpartum depression. However, there are inconsistencies in this literature with some studies not supporting HPA axis dysfunction in postpartum mood disorders [68] and there has been a call for additional studies to resolve these conflicting reports [67].

Adverse life events are known to alter HPA axis function leading to increased vulnerability to mood disorders. Thus, evidence pointing to HPA axis dysfunction in postpartum depression could be an epiphenomenon related to the increased risk in patients with previous adverse life events. Accordingly, in experimental animal models, early life stress has been demonstrated to induce HPA axis reprogramming and has also been shown to increase depression-like behaviors during the postpartum period and induce deficits in maternal care [159; 160].

Direct evidence supporting a role for HPA axis dysfunction in postpartum depression comes from experimental evidence that chronic stress paradigms during pregnancy [57] or during lactation [55] are sufficient to induce depression-like behaviors in postpartum rodents and impair maternal behaviors. The effects are likely mediated by the stress hormone, corticosterone, since exogenous corticosterone administered during pregnancy and/or the postpartum period also induces depression-like behaviors in postpartum animals and impaired maternal behaviors [53; 57; 161]. In addition, blocking CRH signaling with Antalarmin decreases depression-like behaviors in a mouse model of postpartum depression [57].

To directly examine the role of HPA axis dysfunction in postpartum mood disorders, several experimental models have been generated which exhibit inappropriate activation of the HPA axis during the peripartum period, including genetic and viral knockdown of the K^+/Cl^- co-transporter, KCC2, on CRH neurons in the paraventricular nucleus of the hypothalamus (PVN), and inappropriate activation of CRH in the PVN neurons using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) [162]. These experimental models, which result in the inability to suppress the stress-induced activation of the HPA axis during the peripartum period, are sufficient to induce depression-like behaviors during the postpartum period and impaired maternal behaviors. These studies utilizing experimental models provide direct evidence that excessive activation of the HPA axis is capable of inducing abnormal postpartum behaviors.

5.3. Neurosteroids (focus on allopregnanolone) in postpartum depression

Metabolites of steroid hormones which exert effects in the brain are termed neuroactive steroids, or neurosteroids. The neuroactive metabolite of progesterone, allopregnanolone, has been shown to exert anxiolytic and antidepressant effects [69], which are thought to be mediated, at least in part, by the ability to allosterically potentiate $GABA_A$ receptors ($GABA_ARs$), a topic which is discussed further in Section 6.1. Further, alterations in allopregnanolone levels have been implicated in postpartum depression (for review see [69]). Diminished levels of allopregnanolone correlated with increased depression scores in women during late pregnancy [76]. Additional studies have demonstrated altered levels of GABA and neurosteroids in association with postpartum depression [163]. Increased

allopregnanolone levels have been shown to decrease the risk for developing postpartum depression [74] and a polymorphism in a gene involved in allopregnanolone synthesis, aldoketo reductase family 1, C2 (AKR1C2), which results in lower allopregnanolone levels has been shown to be associated with an increase in depression scores in pregnancy [164]. Interestingly, antidepressant treatments increase allopregnanolone levels [70; 71; 72; 73] and treatment with a proprietary formulation of allopregnanolone, brexanolone, has demonstrated significant improvement of depression scores for the treatment of postpartum depression in a double-blind, randomised, placebo-controlled trial [165].

Experimentally, blockade of neurosteroid production, with finasteride treatment, increases depression-like behaviors in experimental animal models [122; 137]. Allopregnanolone levels have been negatively correlated with depression-like behaviors [122]. Mice which lack the gene encoding for a specific subtype of GABA receptors that contain a delta (δ) subunit, which are the major site for neurosteroid action, *Gabrd*$^{-/-}$ mice, exhibit abnormal postpartum behaviors, including depression-like behaviors restricted to the postpartum period and deficits in maternal care [166]. These findings implicate disruption in allopregnanolone signaling via δ subunit-containing $GABA_A$Rs in mediating postpartum depression. Further investigation into the mechanisms mediating the abnormal postpartum phenotype of this mouse model led to the discovery that these animals have the inability to suppress the stress-induced activation of the HPA axis during the peripartum period [57]. Collectively, these studies begin to tell a compelling story regarding the role for allopregnanolone, GABAergic signaling, and HPA axis function in the underlying neurobiology of postpartum depression (Figures 2, 4, 5), discussed further in Section 6.1.

6. Neurotransmitters and postpartum depression

This section will review evidence of disruption in neurotransmission in the underlying neurobiology of postpartum depression, including a role for classical neurotransmitters (GABA and glutamate) and monoamines (serotonin and dopamine). A larger number of studies exist investigating neurotransmission dysfunction in major depressive disorder, however, for the purpose of this review, this section will focus solely on postpartum depression.

6.1 GABA

GABA is the primary inhibitory neurotransmitter in the central nervous system. Alterations in GABA signaling have been implicated in major depressive disorder (for review see [167; 168]). Therefore, there is also interest in a potential role in postpartum depression. The role of GABA in pregnancy and the postpartum period has been nicely reviewed previously [169]. Relevant to postpartum depression, GABA levels have been shown to be inversely correlated with depression scores in women at risk for developing postpartum depression [163].

Experimentally, changes in GABAergic signaling during the normal peripartum period are inferred from binding studies [170; 171] and assessment of $GABA_A$R protein and mRNA levels [166; 170; 172; 173; 174]. However, it remains unclear whether changes in GABAergic signaling play a role in postpartum depression. The promise of targeting

GABAergic signaling for antidepressant treatment largely relies on the actions of neurosteroids on specific subtypes of $GABA_A$Rs, specifically those incorporating the δ subunit. The role of $GABA_A$R δ subunit-containing receptors in mediating abnormal postpartum behaviors was already discussed above (5.3 Neurosteroids (focus on allopregnanolone) in postpartum depression).

6.2. Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system. The majority of studies investigating the role of glutamate in mood disorders have focused on imaging studies and changes in neural circuit function, which will be reviewed in depth below. Only a few studies have investigated changes in glutamate signaling in association with postpartum depression (for review see [175]). Levels of glutamate in the medial prefrontal cortex are significantly increased in women with postpartum depression compared to healthy controls [176]. However, levels of glutamate were found to be decreased in the dorsolateral prefrontal cortex (DLPFC) in women with postpartum depression [177]. Interestingly, progesterone treatment restored glutamate levels in the DLPFC [177]. Thus, hormonal fluctuations during the peripartum period may alter glutamate signaling, however, further studies are required to determine whether abnormalities in glutamatergic signaling contribute to postpartum depression and to further explore a potential interaction with reproductive hormones.

6.3. Serotonin

Monoamines, including serotonin, have been implicated in major depressive disorder [178], as is evident by the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression. Relevant to postpartum depression, SNPs in TPH2, which is an enzyme in the rate-limiting step in serotonin synthesis, has been associated with postpartum depression [100], as reviewed above (Section 3.5 TPH2). To examine potential alterations in serotonin signaling associated with postpartum depression, Moses-Kolko et al. examined 5HT1A binding potential using the ligand, [^{11}C]WAY100635. Binding at 5HT1A receptors was significantly reduced in women with postpartum depression compared to healthy controls [179]. The largest reductions in binding at 5HT1A receptors was observed in the anterior cingulate and mesiotemporal cortices [179].

In two independent experimental mouse models with reduced expression of 5HT (*Pet-1*$^{-/-}$ and *TPH*$^{-/-}$), robust deficits in maternal behaviors were observed [180; 181], which were rescued by restoring serotonergic signaling [181]. These findings clearly point to a role for serotonergic signaling in mediating abnormal maternal behaviors, however, it remains unclear whether serotonin plays a role in depression-like behaviors during the postpartum period.

6.4. Dopamine

The monoaminergic hypothesis of depression has largely focused on serotonin, but there is also evidence pointing to a role for dopamine signaling in depression (for review see [182]). Potentially relevant to postpartum depression, mutations in DR1 in humans have been

associated with the specific behavior of maternal orienting away from the infant, whereas, mutations in DR2 have been associated with maternal infant-directed vocalizing [102].

It is well-established that dopamine plays a role in the reward pathway, providing the framework for the hypothesis that, conversely, deficits in this pathway may also play a role in depression (for review see [183]). A recent, elegant study by Tye et al. demonstrated that bidirectional control of midbrain dopamine neurons alters depression-like behaviors following chronic stress: inhibiting midbrain dopamine neurons increased depression-like behaviors while activating midbrain dopamine neurons decreased depression-like behaviors in rodents [184], pointing to a direct role for dopamine in depression. There is evidence in the literature for a role for dopamine in maternal behaviors. For example, there is an increase in dopamine release in the nucleus accumbens in postpartum and hormone-treated dams upon pup interaction [185]. In response to pup stimuli, only postpartum and hormone-treated females had increased dopamine release compared to basal release. Dopamine levels increase in the nucleus accumbens of lactating rats during pup licking/grooming [186]. Interestingly, high licking/grooming dams exhibit an increase in the levels of dopamine and a decrease in dopamine transporter binding [186]. Treatment with a dopamine transporter antagonist increased pup licking/grooming in low licking/grooming dams [186]. Further, dysregulated dopamine signaling has been observed in mice which naturally exhibit maternal neglect [187]. These data suggest that dopamine signaling can influence both depression-like behaviors and maternal care.

7. Neuroinflammatory mechanisms in postpartum depression

Inflammatory responses can be broadly divided into two groups: proinflammatory and anti-inflammatory. Changes in inflammatory responses occur throughout normal pregnancy and neuroinflammatory changes are emerging as influential factors in the neurobiology of postpartum depression (for review see [188]). The following section will focus on reviewing the evidence supporting neuroinflammatory changes in postpartum depression.

Altered immune system function during the perinatal period and the link to depression, led to the hypothesis that neuroinflammation may play a role in the vulnerability to mood disorders during the peripartum period. However, few studies have directly investigated the role of the immune system in postpartum depression. T cell number has been shown to be negatively correlated with depression symptoms during the postpartum period [189]. There are conflicting reports regarding levels of IL-6 in patients with postpartum depression [190; 191]. Levels of IL-6 and IL-1β have been shown to be significantly and positively associated with depressive scores in postpartum women [192]. Another study demonstrated elevated levels of IL-6 and TNF-α at delivery were associated with depressed mood postpartum [193]. Increased levels of IL-6 and the IL-6 receptor was found to be correlated with postpartum depression [194] and another study confirmed increases in IL-6 and IL-8 but only in mothers who delivered preterm [195]. Decreased IFN-γ levels and a lower IFN-γ:IL-10 ratio has also been implicated in postpartum depression [150]. However, other studies did not find a relationship between IL-6 and TNF-α levels and depression symptoms in postpartum women [16; 191], although they did find a positive interaction between the levels of these cytokines and previous adverse life events [196], linking neuroinflammation

with a well-established risk factor for postpartum depression. Increased levels of IL-1β was also shown to be associated with depression scores during the postpartum period [16].

The kynurenine pathway has also been implicated in postpartum depression. Increased kynurenine was associated with postpartum depression and kynurenine levels are positively associated with depression scores [197]. It has been proposed that higher levels of kynurenine suggest inflammation-induced degradation of tryptophan, which limits serotonin production and contributes to depression in women with postpartum depression.

As is evident from these summarized studies, there are conflicting reports of inflammatory changes associated with postpartum depression and the limited number of reports makes it difficult to determine whether there is a role for neuroinflammation in the underlying neurobiology of postpartum depression. Further study is warrented.

8. Circuit mechanisms of postpartum depression

The following subsections will review evidence of altered activity within and between specific networks associated with postpartum depression, altered white matter connectivity, and changes in network neuronal oscillations in women with postpartum depression. There is substantial evidence for alterations in networks associated with major depressive disorder (for review see [198]). However, here we will focus specifically on changes associated with postpartum depression (for review see [199; 200]), highlighting changes which are similar to those observed in major depressive disorder or those known to participate in the “maternal care network.” This section will also limit its focus to functional, rather than structural, changes associated with postpartum depression since it is likely that postpartum depression represents a “state-dependent” disorder rather than a structural disorder.

8.1. Imaging studies in humans

Functional magnetic resonance imaging (fMRI) approaches have demonstrated alterations in the resting state functional connectivity in women with postpartum depression compared to healthy controls, including attenuated activity within the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex as well as decreased corticocortical and corticolimbic connectivity [77]. Studies investigating resting-state functional connectivity in the default mode network (DMN) involved in social cognition have demonstrated disruptions in the connectivity between the posterior cingulate cortex and the right amygdala in women with postpartum depression [201]. Studies examining regional homogeneity have also demonstrated an increase in homogeneity in the posterior cingulate gyrus, frontal lobe, parietal lobe, medial frontal gyrus, medial frontal gyrus and a decrease in homogeneity in the inferior temporal gyrus, middle temporal gyrus, superior temporal lobe, and frontal lobe in patients with postpartum depression [202]. While we do not as of yet fully appreciate the implication of these resting state connectivity changes, they are consistent with the notion that postpartum depression involves network-level changes in brain function.

Additional studies have examined changes in functional connectivity in patients with postpartum depression while performing tasks or in response to infant-relevant stimuli. Attenuated activity of the orbitofrontal cortex in response to neutral stimuli, decreased

amygdala activity in response to negative words, and attenuated activity in the striatum in response to positive words have been associated with increased depression scores in women with postpartum depression [203]. Women with postpartum depression also exhibited decreased amygdala responsiveness in response to emotionally valenced stimuli [204]. Decreased activity in the ventral striatum in a monetary reward task has also been demonstrated in women with postpartum depression [205]. Another study demonstrated that attenuated activity in the dorsomedial prefrontal cortex and the amygdala in response to negative facial expressions was associated with increased infant-related hostility in women with postpartum depression [206]. Several studies have explored changes in functional activity in response to a woman's own infant's cry or image. Postpartum women exhibiting symptoms of depression failed to show activation in a distributed network of para/limbic and prefrontal regions in response to their own 18-months-old infant's cry [207]. Further, postpartum women with depression also exhibited attenuated activation of the striatum, orbitofrontal, dorsal anterior cingulate, medial superior frontal gyrus, occipital fusiform areas, and medial thalamic activation in response to their own infant's cry [207]. Women with postpartum depression exhibited attenuated activity in the dorsal anterior cingulate cortex in response to their own infant's distress faces and reduced orbitofrontal cortex, insula, prefrontal, and insula/striatal regions in response to their own infant's joy faces [207]. A similar study demonstrated an increase in right amygdala reactivity, but decreased amygdala-insular cortex connectivity in women with postpartum depression in response to viewing images of their own vs. other infants [208]. Decreased amygdala to insular cortex connectivity was also correlated with depression scores in women with postpartum depression [208]. Similarly, reduced amygdala reactivity in women with postpartum depression was also observed in response to viewing a positive image of their own infant's face or unfamiliar positive faces [209]. Collectively, there appears to be a consensus between many of these studies, implicating altered activity in the amygdala, prefrontal cortex, cingulate cortex, and insula in postpartum depression, implicating deficits in well-known limbic regions in association with differences in processing emotionally-relevant stimuli in patients with postpartum depression.

8.2. Molecular imaging

Positron emission tomography (PET) approaches have been used to examine changes in the density of receptors, ligand transporters, enzymes, drug occupancy, or endogenous neurotransmitter release in postpartum depression. Using this approach, MAO-A density was shown to be increased in the prefrontal cortex and the anterior cingulate cortex of women with postpartum depression [210; 211], similar to observations in depressed subjects unrelated to the peripartum period [212]. PET was also used to demonstrate decreased serotonin receptor binding in the mesiotemporal cortex, anterior cingulate cortex, and orbitofrontal cortex [179], whereas, no changes were found in binding to dopamine D2/D3 receptors in the striatum [213].

Magnetic resonance spectroscopy (MRS) has been used to evaluate changes in neurotransmitter levels in the brain associated with postpartum depression (Figures 4, 5). Using this approach, it was demonstrated that glutamate levels are higher in women with postpartum depression [176]. In contrast, GABA levels have been shown to be reduced in

the occipital cortex in all groups of postpartum women, but no changes were observed in association with postpartum depression [78]. Another study found no changes in GABA levels or allopregnanolone levels associated with postpartum depression [78].

There is a scarcity of studies utilizing imaging approaches to investigate the underlying neurobiology of postpartum depression. Despite the limited information available, there appears to be a consensus in the studies available implicating altered activity in the amygdala, prefrontal cortex, cingulate cortex, and insula, which are consistent with the large body of literature available studying major depressive disorder, whereas, information on neurotransmitter changes associated with postpartum depression are much more limited.

8.3. Changes in white matter connectivity in postpartum depression

Diffusion tensor imaging is an MRI-based neuroimaging technique which makes it possible to estimate the location, orientation, and anisotropy of the brain's white matter tracts. Only recently has this approach been applied to postpartum depression. A single study demonstrated lower fractional anisotropy in the anterior limb of the internal capsule, the retrolenticular internal capsule, and corpus callosum, which was correlated with depression scores in women with postpartum depression [214]. Interestingly, women with postpartum depression do not demonstrate the decreased structural connectivity in the anterior limb of the internal capsule and the genu of the corpus collosum which has been observed in major depression [215]. These data support altered connectivity in specific neural circuits in postpartum depression, however, it remains unclear whether these structural changes are a cause or consequence of the postpartum depressive state.

8.4. Changes in neuronal oscillations during pregnancy

Experimentally, neuronal oscillations reflect coordinated functional activity which can be examined between specific neuronal networks (for review see [216]). Alterations in network oscillations have been implicated in major depressive disorder [217], however, this type of network activity has not been evaluated in postpartum depression. Thus, this section will discuss studies relevant to postpartum depression which implicate altered neuronal oscillations in postpartum depression.

Interneurons have been shown to play a critical role in the generation of neuronal oscillations (for review see [218]). GABAergic signaling, in particular tonic GABAergic inhibition, mediated by $GABA_A$ receptor ($GABA_AR$) δ subunit-containing receptors, in parvalbumin (PV)-positive interneurons have been shown to play a role in the generation of gamma oscillations [219; 220]. The expression of the $GABA_AR$ δ subunit on PV interneurons is altered during the peripartum period, with decreased expression during pregnancy [219; 220]. The altered $GABA_AR$ δ subunit expression in PV interneurons over the ovarian cycle and during pregnancy is associated with an increase in the frequency of gamma oscillations in the CA3 subregion of the hippocampus in vitro [219; 220] and in vivo [221], which can be restored with exogenous allopregnanolone treatment [219].

Relevant to postpartum depression, mice which lack the $GABA_AR$ δ subunit (*Gabrd*$^{-/-}$ mice) exhibit depression-like behaviors restricted to the postpartum period and deficits in maternal care [166]. Based on the data summarized above, the loss of the $GABA_AR$ δ

subunit is likely to alter the PV-positive interneurons' ability to generate oscillations, which has been demonstrated in the CA3 subregion of the hippocampus [219]. However, future studies are required to determine whether impairments in the ability to generate neuronal oscillations within specific networks underlies "state-dependent" changes associated with postpartum depression.

8.5. Circuit changes in the "maternal care network"

Circuits involved in reward/motivation, emotional regulation, and executive function have been implicated in the maternal care network (for review see [222]). As discussed above, imaging studies investigating functional activity in response to infant stimuli elucidated involvement of specific brain regions, such as the amygdala, cingulate cortex, prefrontal cortex, striatum, and insula in normal maternal care, and these areas have been shown to be disrupted in postpartum depression (Section 8.1. Imaging studies in humans).

The maternal caregiving network has been studied to a greater degree in experimental animals (for review see [222; 223]). These studies have focused on the medial preoptic area and projections to the ventral tegmental area and periaqueductal gray in maternal caregiving. Projections from the amygdala, bed nucleus of the stria terminalis, and the anterior cingulate cortex, have been implicated in maternal affect (for review see [223]). Recent studies have also demonstrated that connections between the medial preoptic area and ventral tegmental area are essential for pup retrieval in mice [224]. Site-specific inactivation of specific brain regions has been used to map the circuitry of maternal motivation, which identified the medial preoptic area, ventral tegmental are, medial prefrontal cortex, and anterior cingulate cortex [225] as critical.

Collectively these studies are informative for identifying specific networks involved in mediating normal maternal behaviors during the peripartum period and potentially identify networks which are corrupted in postpartum depression.

9. Conclusions

This review summarizes the numerous mechanisms implicated in the underlying neurobiology of postpartum depression, including genetic and epigenetic factors, biochemical factors, neuroinflammatory changes, as well as circuit-level changes. The heterogeneity of the patient population, including timing of symptom onset and history of adverse life events, suggests that these mechanisms may play a role in some individuals, but not necessarily others. Further, these potential mechanisms do not operate in isolation, but are highly interconnected and it is likely that numerous factors may collectively contribute to postpartum depression. Here we will attempt to integrate some of these potential pathological mechanisms (for review see [226]).

One of the predominant risk factors for the development of postpartum depression is stress and previous adverse life events. Stress and adverse life events, in turn, are associated with neuroendocrine changes found in postpartum depression, including HPA axis reprogramming and epigenetic changes, which can also influence HPA function. Epigenetic

changes during the peripartum period have also been associated with changes in known biochemical factors, including estradiol and allopregnanolone (Figure 1, Figure 5).

Epigenetic changes have also been associated with neuroinflammatory changes [227]. Specific epigenetic changes have been demonstrated in women who later develop postpartum depression at the HP1BP3 gene [228], which has also been shown to be sensitive to estradiol regulation [110] and critical to normal maternal care [111]. Therefore, there is a bidirectional relationship between epigenetic, neuroendocrine and neuroinflammatory changes which may collectively influence mood during the postpartum period (Figures 1, 3, 4, 5). For example, stress hormones are known to influence neuroinflammation and, therefore, altered HPA axis function may impact peripartum neuroimmune changes contributing to postpartum depression. Conversely, neuroinflammation can also impact HPA axis function which may also contribute to postpartum depression (Figure 3).

Further, neuroendocrine changes, such as changes in the levels of the neurosteroid, allopregnanolone, can influence GABAergic signaling [229]. GABAergic signaling is also known to be a critical regulator of HPA axis function and consequently the HPA axis can influence neuroinflammatory responses. Further, given the role for GABAergic signaling in the regulation of neuronal oscillations, this is a potential mechanism linking neuroendocrine changes to circuit-level changes in activity which may contribute to state-dependent changes in mood (Figures 4, 5). There is a complex interplay between stress, neuroinflammation, synaptic transmission and circuit network function pertinent to mood disorders. Stress hormones and neuroinflammation alter synaptic transmission, with direct impacts on circuit function, which may contribute to postpartum depression (Figure 4).

This discussion highlights that the proposed neurobiological mechanisms underlying postpartum depression are highly interrelated, which include diverse potential pathological mechanisms associated with postpartum depression, such as disruptions in reproductive/lactogenic hormones, stress and HPA axis dysfunction, neuroinflammation, epigenetics, synaptic transmission, and circuit-level changes in network communication (Figure 5). These diverse mechanisms raises the possibility that there may be numerous mechanisms mediating the development of a common pathophysiological signature associated with postpartum depression. Understanding the underlying pathophysiology of postpartum depression may not only help us understand postpartum depression but is likely to shed light on the neurobiology underlying normal maternal care and behavior.

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Highlights

- The pathological mechanisms implicated in postpartum depression are diverse, but exert influence over one another
- Stress and adverse life events are prevalent risk factors for postpartum depression
- There is a bidirectional influence between stress and epigenetics implicated in postpartum depression
- Epigenetic and neuroendocrine changes associated with postpartum depression influence neuroinflammation
- Biochemical changes are linked to circuit-level changes which may contribute to postpartum depression.

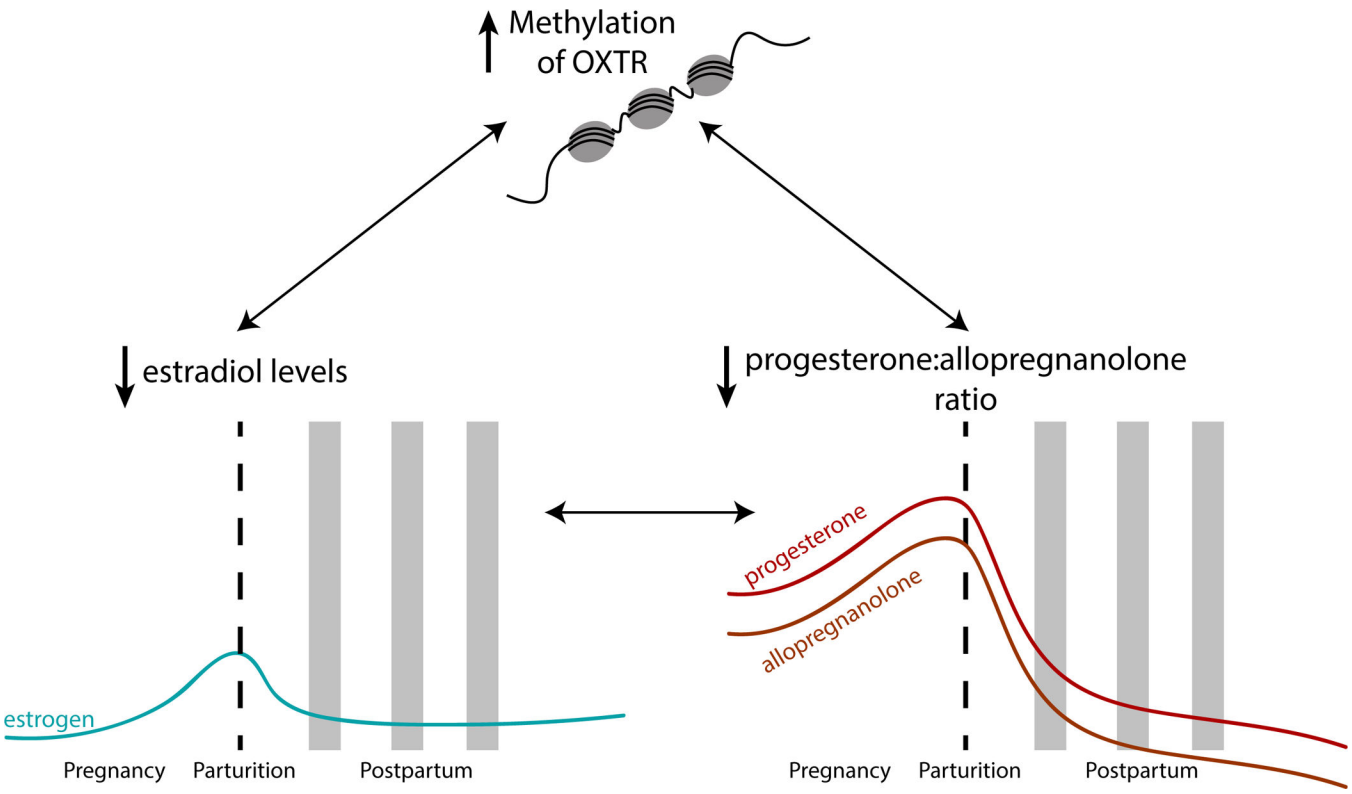

Figure 1: Epigenetic regulation of OXTR and hormonal abnormalities associated with postpartum depression.

Variations in DNA methylation of the OXTR gene in women with postpartum depression is negatively correlated with serum estradiol levels (left panel). A significant interaction between estradiol, OXTR DNA methylation, and the ratio of allopregnanolone to progesterone was also observed in women with postpartum depression. Thus, epigenetic changes can influence biochemical pathways associated with postpartum depression.

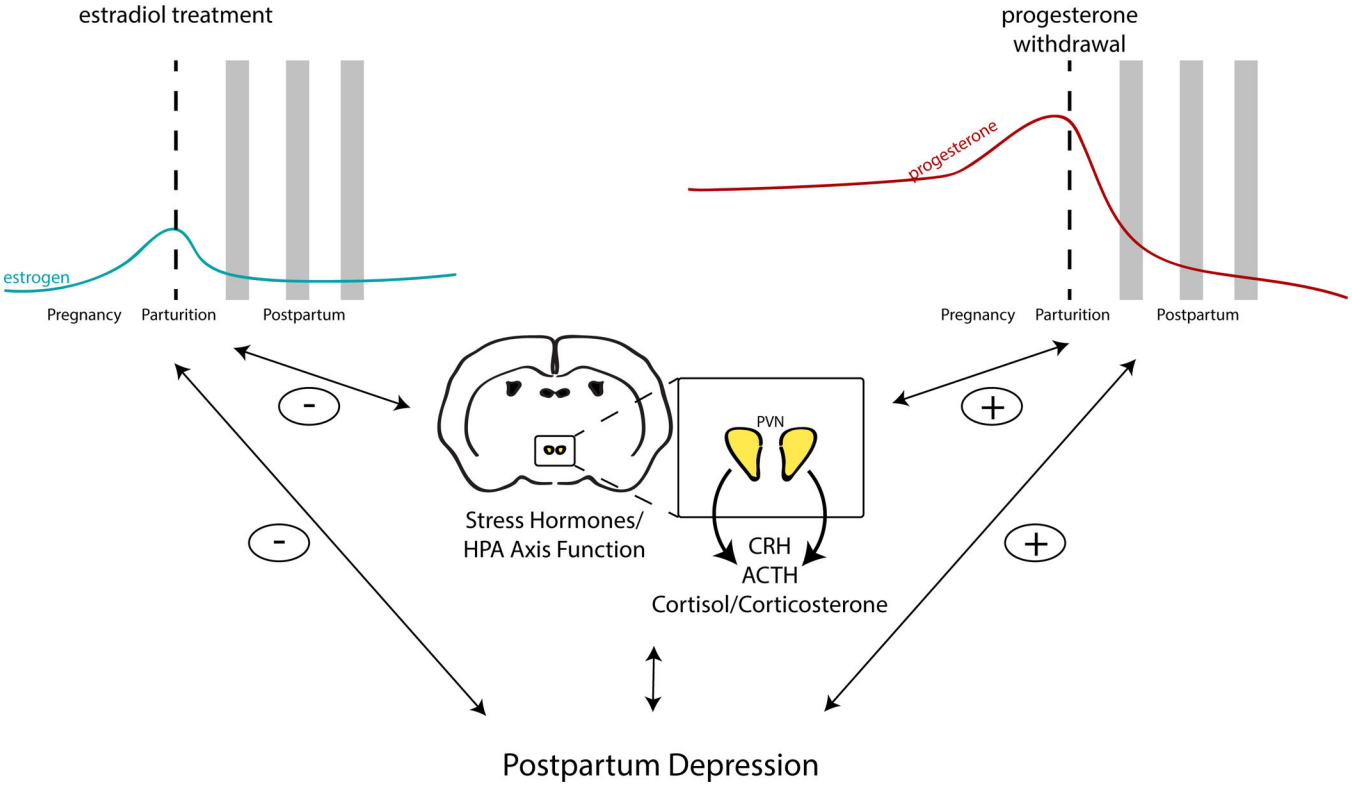

Figure 2: Crosstalk between the HPG and HPA axes in postpartum depression.

Reproductive hormones have been shown to impact HPA axis function and vice versa. For example, estrogen signaling is known to impact HPA axis function, another potential biochemical mediator of postpartum depression. Therefore, dysregulation of reproductive hormones could dysregulate the levels of stress hormones thereby contributing to postpartum depression. Similarly, disruption in HPA axis function could influence the levels of reproductive hormones also contributing to postpartum depression.

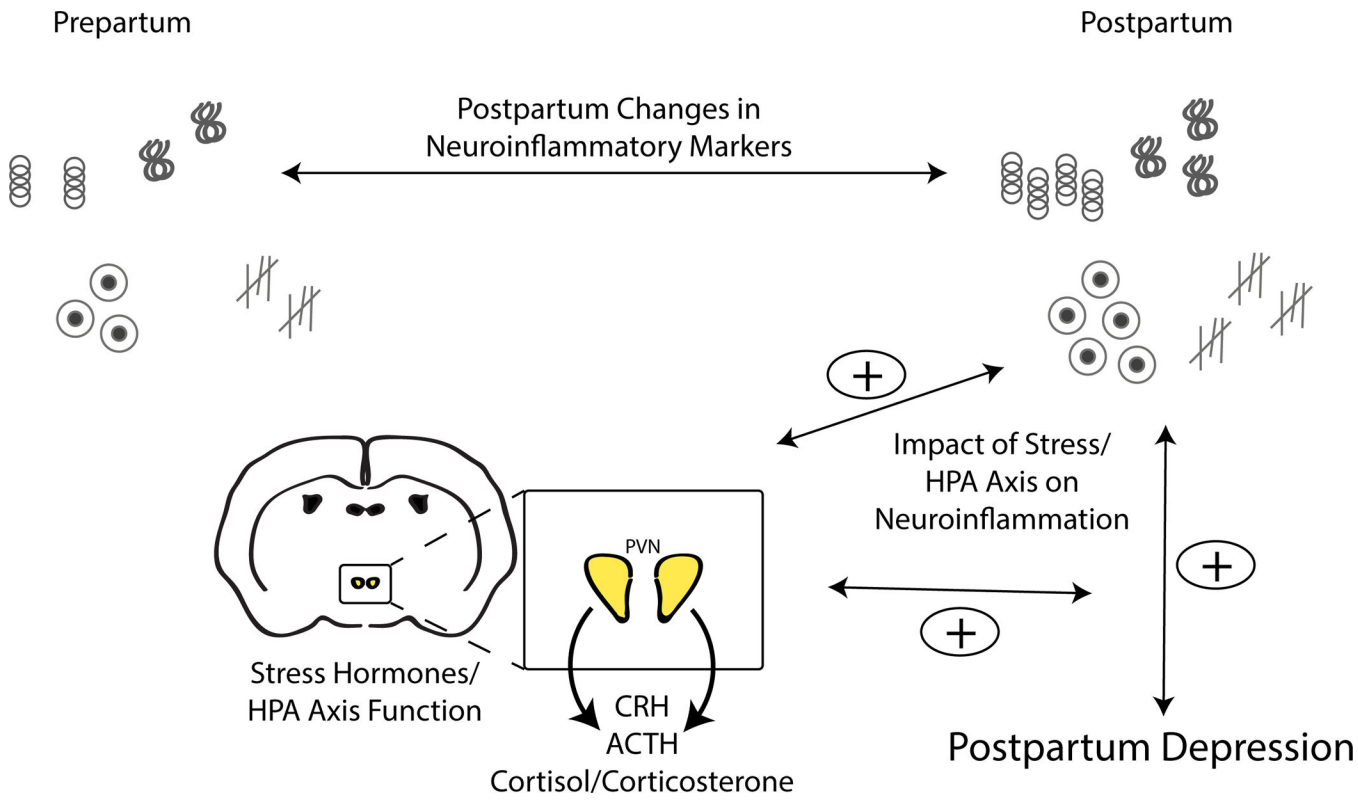

Figure 3: Stress hormones and inflammation in postpartum depression.

There are changes in neuroinflammatory markers throughout normal pregnancy. It has been proposed that disruption in these peripartum neuroinflammatory changes may contribute to postpartum depression. One potential culprit negatively impacting neuroinflammation during pregnancy is the HPA axis. Stress hormones are known regulators of immune function. Thus, disruption in HPA axis functioning and altered stress hormone levels can impact immune function. In addition, immune challenges can also activate the HPA axis, leading to altered levels of stress hormones. Thus, disruptions in the crosstalk between stress hormones and neuroinflammation may contribute to postpartum depression.

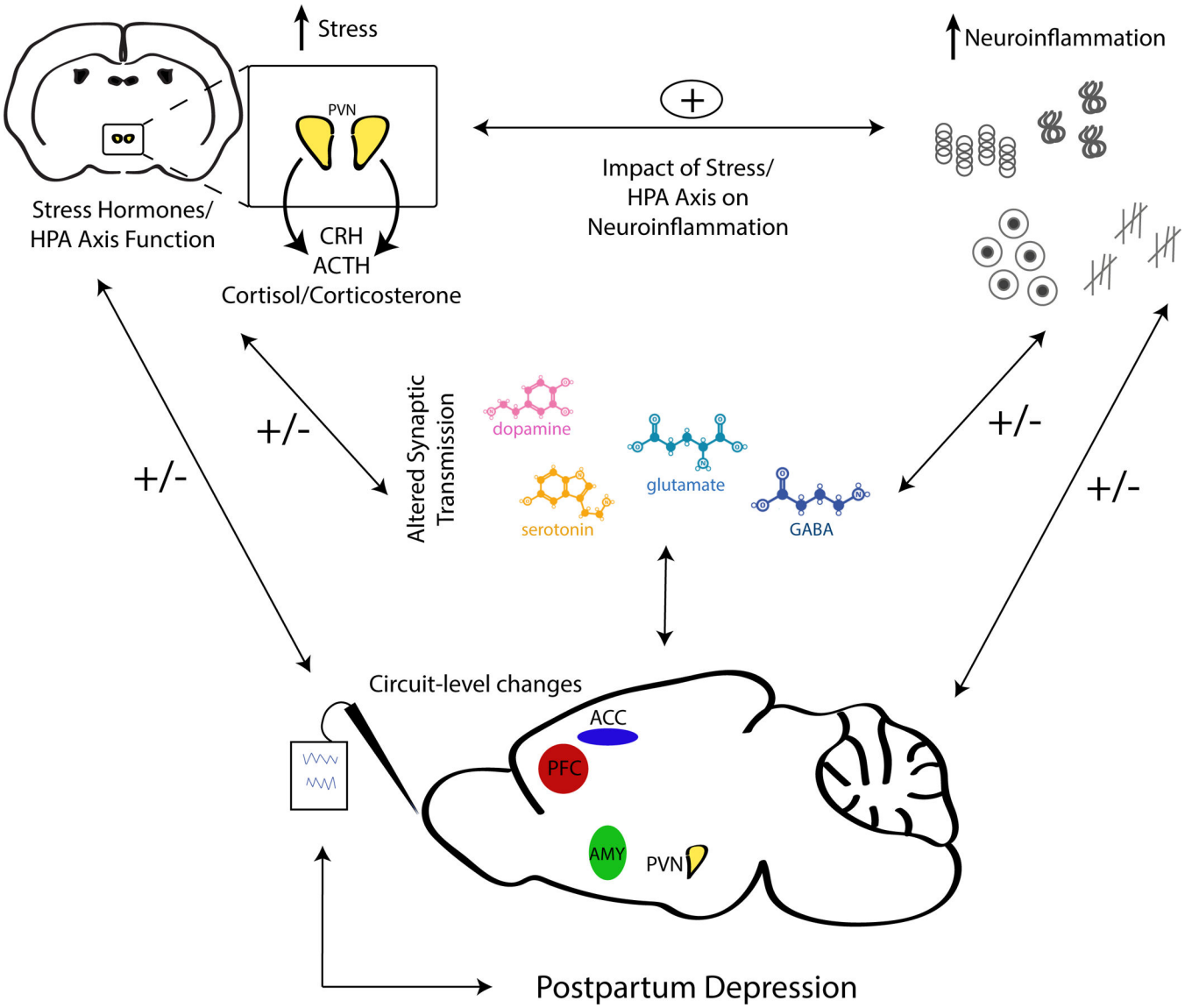

Figure 4: Environmental impacts on synaptic transmission and circuit function in postpartum depression.

There is a complex interplay between environmental risk factors for postpartum depression, including stress and neuroinflammation, on synaptic transmission and circuit network function pertinent to mood disorders. Stress hormones (and reproductive hormones not pictured here) exert profound effects on synaptic transmission, altering glutamatergic, GABAergic, and monoaminergic signaling. Similarly, neuroinflammation is associated with changes in neurotransmission. The implications for altered synaptic signaling on circuit function is clear. Thus, it is possible that stress, neuroinflammation, and altered synaptic transmission could lead to circuit dysfunction associated with postpartum depression.

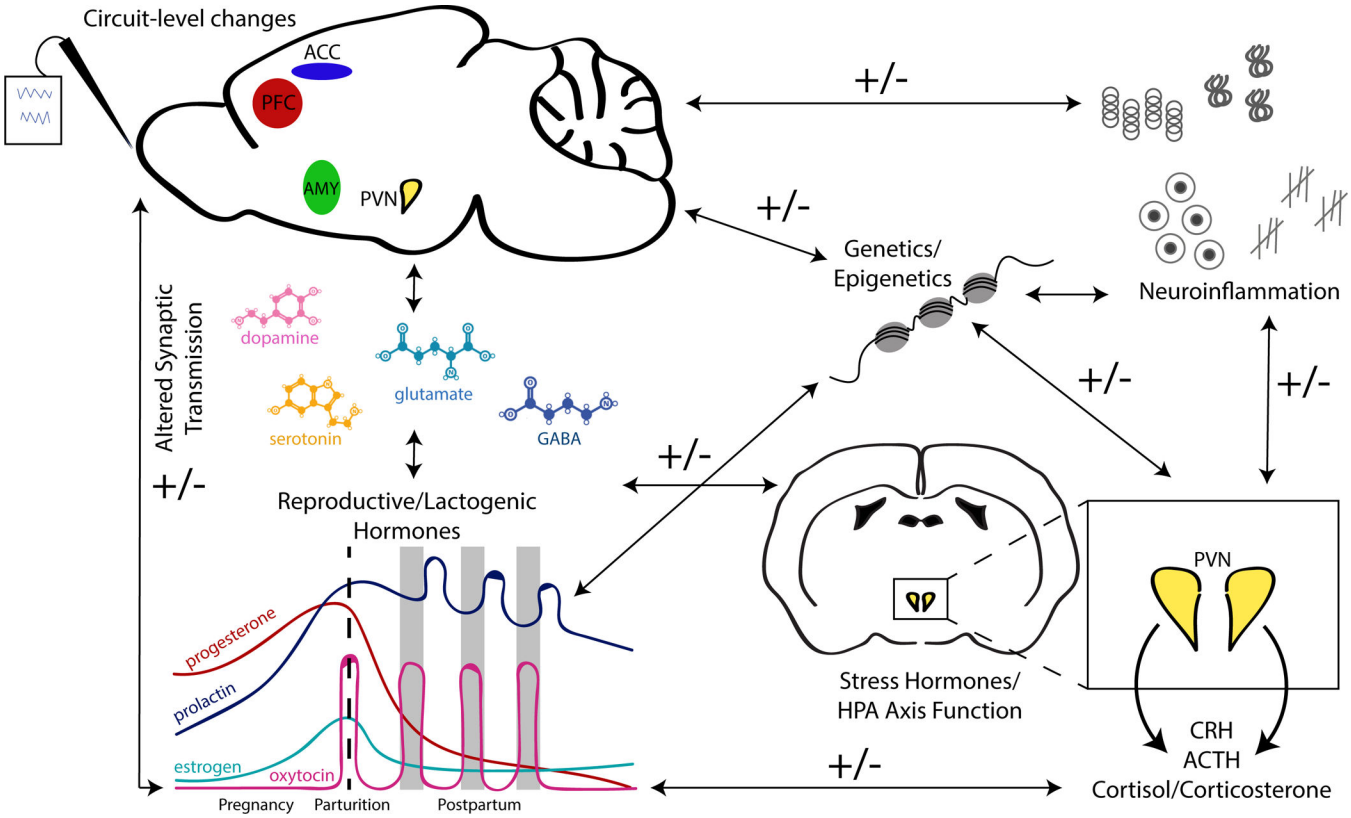

Figure 5: Complex interplay between the potential pathological mechanisms contributing to postpartum depression.

This review highlights the diverse potential pathological mechanisms associated with postpartum depression, including disruptions in reproductive/lactogenic hormones, stress and HPA axis dysfunction, neuroinflammation, epigenetics, altered synaptic transmission, and circuit-level changes in network communication in brain regions associated with mood and/or the “maternal care network”. This complex interplay between the genetic, environmental, and synaptic/network function highlights the potential diversity in the underlying neurobiology of postpartum depression. We propose that while these diverse mechanisms contribute to heterogeneity in the patient population, it is also likely that there are commonalities in the underlying neurobiological features of postpartum depression.