

Review article

Sex differences in depression: Insights from clinical and preclinical studies

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ARTICLE INFO

Keywords:

Sex steroids

Stress

Antidepressant efficacy

Transcriptional patterns

Neuroplasticity

Immune signatures

Postpartum depression

Women

Men

Estrogens

Cortisol

Hippocampus

ABSTRACT

Depression represents a global mental health concern, and disproportionately affects women as they are twice more likely to be diagnosed than men. In this review, we provide a summary of evidence to support the notion that differences in depression between men and women span multiple facets of the disease, including epidemiology, symptomology, treatment, and pathophysiology. Through a lens of biological sex, we overview depression-related transcriptional patterns, changes in neuroanatomy and neuroplasticity, and immune signatures. We acknowledge the unique physiological and behavioral demands of pregnancy and motherhood by devoting special attention to depression occurring in the peripartum period. Specifically, we discuss issues surrounding the presentation, time course, treatment, and neurobiology of peripartum depression. We write this review with the intention of highlighting the encouraging advancements in our understanding of sex differences in depression, while underscoring the gaps that remain. A more systematic consideration of biological sex as a variable in depression research will be critical in the discovery and development of pharmacotherapies that are efficacious for both men and women.

Depression is a major contributor to the global burden of disease, and the leading cause of disability worldwide (Ferrari et al., 2013; World Health Organization, 2017). Estimated lifetime prevalence rates vary across cultures (Kessler and Bromet, 2013), however a preponderance of depression in women is consistently reported (Angst et al., 2002a,b; Bromet et al., 2011; Kessler and Bromet, 2013). Recent meta-analyses of representative national samples corroborate that women are approximately twice as likely as men to be diagnosed with depression (Salk et al., 2017), an effect which emerges during puberty and remains stable in adulthood (Salk et al., 2017; Twenge and Nolen-Hoeksema, 2002). Despite ongoing research efforts, our understanding of the etiology and pathophysiology of depression remains limited, and current pharmacotherapies are efficacious for only a subpopulation of individuals (Akil et al., 2017). Here, we review sex differences across multiple facets of depression, including presentation, treatment, etiology, and pathophysiology, and we argue that advancements in this field are in part hindered by the insufficient consideration of sex as a biological factor, and/or the insufficient consideration of how the

unique physiology of women may contribute to depression. It is imperative for the purposes of this review to distinguish biological sex from gender, the latter of which is a non-biologically determined social construct. Differences in depression between men and women may be influenced by both sex and gender, however the focus of this review will be on the role of biological sex. Although depression is a uniquely human condition, animal models of depression exist and, despite their limitations, serve as valuable tools in our understanding of the disorder and its treatment. Most animal models of depression rely on stress exposure to produce depressive-like endophenotypes (Gobinath et al., 2015; Willner, 2005). There is strong construct validity to these models, as individuals with depression themselves cite stressful life events as antecedent to the disorder (Angst et al., 2002a,b; Bale, 2006). In addition, the primary neuroendocrine component of the stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, is dysregulated on a number of levels in individuals with depression (Ising et al., 2007; Lopez-Duran et al., 2009; Sher et al., 2013; Stetler and Miller, 2011) and in animals exposed to chronic stress (reviewed in Gobinath et al.,

Abbreviations: BDNF, brain derived neurotrophic factor; BLA, basolateral amygdala; CORT, corticosterone; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; DSM, diagnostic and statistical manual of mental disorders; ER, estrogen receptor; fMRI, functional magnetic resonance imaging; FST, forced swim test; GWAS, genome-wide association study; HPA, hypothalamic-pituitary-adrenal; LPS, lipopolysaccharide; MDD, major depressive disorder; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PFC, prefrontal cortex; PPD, postpartum depression; PVN, paraventricular nucleus; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

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<https://doi.org/10.1016/j.pneurobio.2019.01.006>

Received 5 June 2018; Received in revised form 21 December 2018; Accepted 28 January 2019

Available online 02 February 2019

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2015). This is evidenced by a meta-analysis indicating that cortisol, the major stress hormone in primates, is elevated in depression (Stetler and Miller, 2011), and by other findings of abnormalities in the diurnal secretion pattern of cortisol (Stetler and Miller, 2005; Vreeburg et al., 2009), and deficits in HPA negative feedback inhibition (Sher et al., 2013), with possible sex differences in presentation (Binder et al., 2009). Each of these features is observed in animal models of depression that rely on exposure to chronic stress (Mahmoud et al., 2016a; Wainwright et al., 2016a). In addition, chronic unpredictable stress exposure in animal models produces a variety of other depressive-like endophenotypes, including reductions in hippocampal plasticity, somatic disruptions such as weight loss, cognitive dysfunction, anhedonia, and alterations in coping behaviors (reviewed in Krishnan and Nestler, 2011; Vollmayr et al., 2007; Wainwright and Galea, 2013; Willner, 2017); collectively, this indicates strong face and construct validity. Whenever possible, we make connections between studies in humans and non-human animals and identify gaps in knowledge and targets for future investigation.

1. Sex differences in clinical presentation, comorbidities, and antidepressant efficacy

Depression is a heterogeneous disorder whereby clinical presentation and symptomology varies between affected individuals (Rush, 2007). There is evidence that biological sex is a factor that can explain at least some of the variability in depression presentation and comorbidities. For example, various reports indicate that compared to men, women with depression are more likely to experience higher symptom severity (Marcus et al., 2008, 2005), and the sexes show differences in the presentation of biomarkers (Labaka et al., 2018). Additionally, somatic- and cognitive-affective symptoms are more commonly reported in women than in men (Marcus et al., 2008; Penninx et al., 2013; Silverstein, 2002). Women are also more likely to present with most subtypes of depression (Bogren et al., 2017), including atypical depression, which includes characteristics such as hypersomnia, weight gain, and excessive fatigue (Angst et al., 2002a,b; Blanco et al., 2012; Marcus et al., 2005; Schuch et al., 2014). As an exception to this, depression with melancholic features, which accounts for less than 1% of cases of depression, is similarly prevalent in men and women (Bogren et al., 2017), or using within-sex percentages, more men will present with melancholic features than women with depression (Hildebrandt et al., 2003). Sex also influences comorbidities in individuals with a primary diagnosis of depression, as women have higher rates of comorbid anxiety (Schuch et al., 2014), and men have higher rates of comorbid substance use disorders (Marcus et al., 2008; Schuch et al., 2014). Importantly, some have argued that the experience of depression in men may not be captured by current Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (Addis, 2008). In a secondary analysis of a nationally representative mental health survey, men and women scored similarly on a lifetime estimate of depression when the scales included both conventional depressive symptoms, and alternative features such as aggression, risk-taking behavior, and substance use (Martin et al., 2013). The authors considered these additional features to be symptoms of depression, which has garnered criticism from others as to whether these are genuine symptoms of the disorder (Kuehner, 2014). In our view, the continued investigation of sex differences in the incidence of depression is necessary, with the recognition that men may present with other symptoms (e.g. aggression and impulsivity) that may or may not be coincident with depression. Understanding that the disease manifests differently in men versus women is a key step forward, and this will be underlined by the large sex differences seen in the transcriptional signature of depression, which we will overview in sections to follow.

Currently available antidepressants are efficacious in alleviating depression symptoms in only a subpopulation of individuals (Akil et al., 2017; Trivedi et al., 2006), and efficacy eventually declines in some

responders (Byrne and Rothschild, 1998). Indeed, biological sex is a factor that may influence antidepressant efficacy, however there is no clear consensus in the literature regarding the specific direction in which sex influences the therapeutic response to currently available antidepressants (reviewed in Sramek et al., 2016). Several studies found that women respond more favorably to selective serotonin reuptake inhibitors (SSRIs) (Berlanga and Flores-Ramos, 2006; Khan et al., 2005; Kornstein et al., 2000; Yang et al., 2011; Young et al., 2009). This effect may be more salient in younger, premenopausal women (Kornstein et al., 2000; Naito et al., 2007), perhaps pointing to synergistic effects between serotonin and ovarian hormones such as estradiol. On the other hand, men were found to respond more favorably to tricyclic antidepressants (TCAs) (Kornstein et al., 2000). Importantly, the literature on sex differences in antidepressant efficacy remains largely inconclusive, as several other reports indicate similar efficacy of TCAs and SSRIs in men and women (Kornstein et al., 2014; Parker et al., 2003; Wohlfarth et al., 2004). Few clinical studies have integrated sex as a variable in their analyses of the rapid-acting antidepressant actions of the N-methyl-D-aspartate (NMDA) antagonist ketamine, however, one study did not find sex to be associated with treatment response (Niciu et al., 2014). In general, sex differences in the pharmacokinetics and pharmacodynamics of antidepressants can lead to differences in efficacy and tolerability, and these topics are reviewed extensively elsewhere (Bigos et al., 2009; Damoiseaux et al., 2014). The continued investigation of the role of sex in the therapeutic response to currently available antidepressants is warranted in order to reconcile above-mentioned inconsistencies in the literature, with a careful controlling of age, dose and duration of treatment, as well as diagnostic scales as factors (Sramek et al., 2016). Importantly, the literature we review in later sections also suggests that biological sex should be considered in efforts surrounding the discovery and development of new pharmacotherapies for depression.

Sex differences are reported in the efficacy of several antidepressants in animal models (reviewed by Dalla et al., 2010; Saland et al., 2017; Williams and Trainor, 2018). Importantly, many animal studies administer an acute dose of antidepressants to examine drug efficacy using immobility as the behavioral readout in the Forced Swim Test (FST) or Tail Suspension Test (TST), and these studies are too often conducted in “healthy” animals that have not undergone manipulations to induce depressive-like phenotypes. Animal studies that use acute doses in healthy animals have limited translational value, as symptom alleviation is achieved only after weeks of treatment with classic antidepressants in depressed individuals (Uher et al., 2011). Nonetheless, the available evidence suggests that healthy females may be more sensitive to the acute effects of SSRIs, as lower doses of fluoxetine (Fernández-Guasti et al., 2017; Gómez et al., 2014), paroxetine (David et al., 2001), and sertraline (Kokras et al., 2015) were required to produce an antidepressant response in female rats and mice compared to their male counterparts. Extensively reviewed elsewhere (Saland et al., 2017), there are also sex differences in the antidepressant response to ketamine in animal models. In healthy animals not exposed to manipulations to induce depressive-like phenotypes, females show higher sensitivity to ketamine than males, with lower doses required to observe the antidepressant-like effect of the drug (Carrier and Kabbaj, 2013; Franceschelli et al., 2015), similar to the reported sex differences in response to SSRIs. The higher sensitivity to ketamine in females is dependent on ovarian hormones, as this effect is abolished in ovariectomized rats, but restored with estradiol and progesterone replacement (Carrier and Kabbaj, 2013). Unfortunately, studies that investigate sex differences in antidepressant efficacy using chronic drug treatment in animals with established depressive-like phenotypes are rare. Findings from our own laboratory indicate little behavioral efficacy of chronic SSRI treatment in various animal models of depression in females (Gobinath et al., 2018; Mahmoud et al., 2016a) but significant efficacy in males (Wainwright et al., 2016a,b). Findings from other laboratories also indicate SSRI efficacy in males using chronic

stress models (Bessa et al., 2009; David et al., 2009), and in males but not females in a social isolation stress model (Carrier and Kabbaj, 2012). Further, lower doses of ketamine were required to reverse the depressive-like effects of social isolation in female compared to male rats (Sarkar and Kabbaj, 2016), yet the antidepressant-like effects of ketamine were longer-lasting in male relative to female mice after exposure to chronic mild stress (Franceschelli et al., 2015). Thus, similar to the clinical literature on biological sex and antidepressant efficacy, evidence from animal models is scarce and inconclusive. Future pre-clinical research on antidepressant agents should address the above-mentioned caveats by systematically considering sex as a variable and by utilizing validated animal models of depression.

2. Potential sex differences in the etiology and pathophysiology of depression

Depression is a complex disorder with substantial heterogeneity in etiology and pathophysiology. Several theories have been posited to explain the mechanisms underlying depression, including dysfunction or alterations in monoamine neurotransmitter systems (Delgado, 2000; Hirschfeld, 2000), the glutamatergic system (Sanacora et al., 2012), stress response systems (Gold, 2015), sex steroids (Bloch et al., 2003), neuropeptides (Kormos and Gaszner, 2013; Morales-Medina et al., 2010) neuroplasticity (Wainwright and Galea, 2013), gut microbiota (Lima-Ojeda et al., 2017), immune processes (Miller and Raison, 2016), epigenetic mechanisms (Nestler, 2014), and genetic risk factors (Wray et al., 2018). With the aim of understanding the mechanisms of depression that may differ between men and women, our focus in this review will be on sex differences in depression-related transcriptional

patterns, changes in neuroanatomy and neuroplasticity, and immune signatures (Fig. 1). Further, to better understand how the physiology of females may lead to greater susceptibility to depression in a women's lifetime, we discuss female-unique factors related to pregnancy and the postpartum period that create windows of vulnerability to depression. When possible, we highlight convergent evidence and translational disconnect between clinical and preclinical studies. Beyond the focus of the current review, there are other factors that may contribute to sex differences in depression susceptibility. As such we refer the reader to other sources that discuss sex differences in neuroanatomy and the connectome (Bao and Swaab, 2011; Ingahlhalikar et al., 2014), sex differences in neural connectivity in response to negative stimuli (Lungu et al., 2015; Mareckova et al., 2017, 2016; Moriguchi et al., 2014), sex by genotype interactions affecting neural connectivity (Wei et al., 2012), sex differences in the effects of stress exposure during sensitive periods across the lifespan (Gobinath et al., 2015), and sex differences in the transgenerational effects of stress exposure (Hodes et al., 2017).

3. Sex differences in anatomical brain abnormalities in depression

Individuals with depression present with anatomical abnormalities and dysregulated network connectivity in limbic regions (Drysdale et al., 2017; Greicius et al., 2007; Koolschijn et al., 2009; Lorenzetti et al., 2009; Schmaal et al., 2016). Morphological alterations to the hippocampus are perhaps the most extensively studied in relation to depression, with several reports of reduced hippocampal volume, an effect which is corroborated by meta-analyses (McKinnon et al., 2009; Schmaal et al., 2016). Hippocampal volume reductions are observed in individuals with depression persisting longer than two years, and are

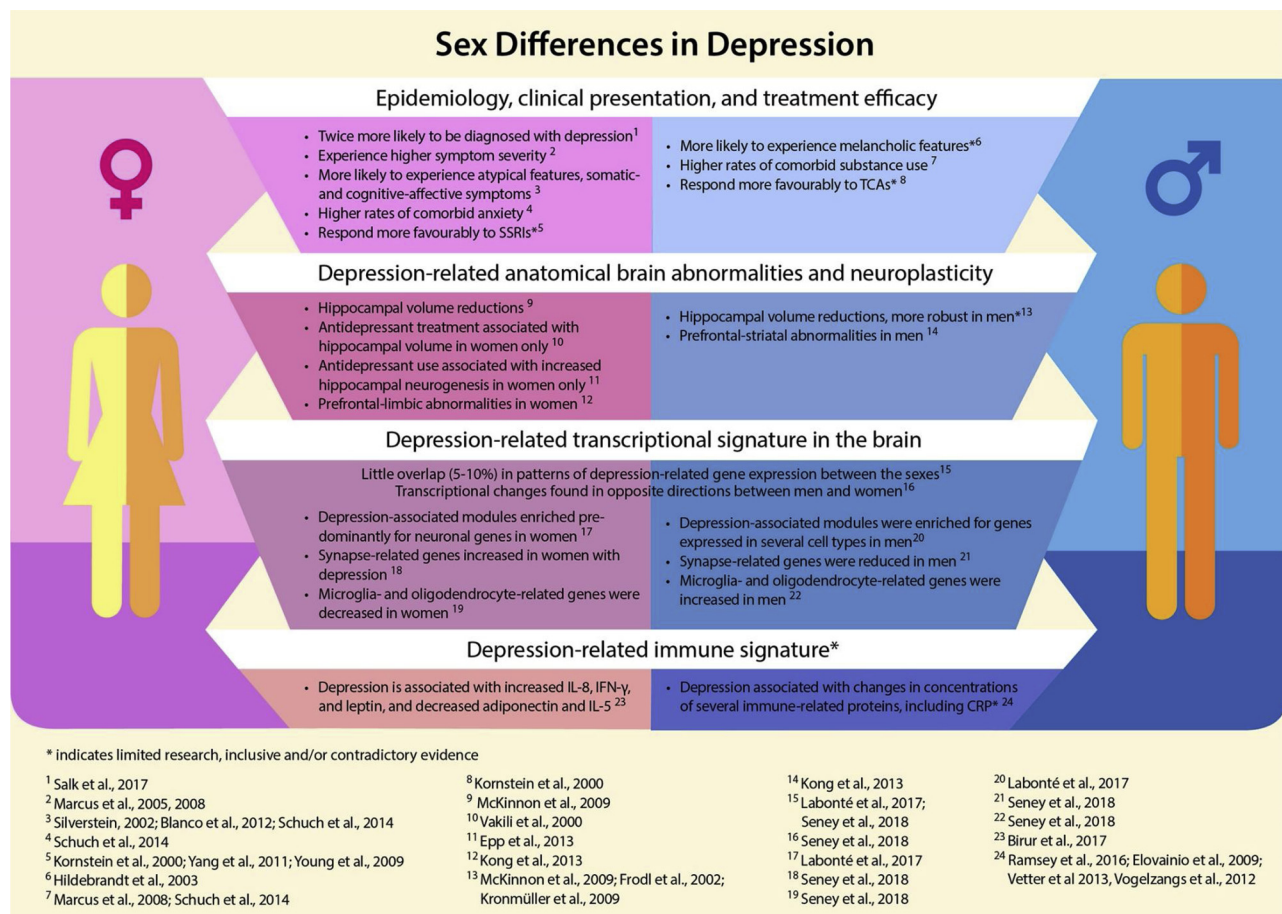


Fig. 1. Summary of clinical studies reviewed, providing evidence for sex differences spanning multiple aspects of depression. Figure created by Medical Illustrator, Vicky Earle, BSc AAM MET.

Table 1
Sex differences in rodent models of stress exposure.

Animal model	Species	Behavioral outcome	Female	Male	Neural outcome	Female	Male	References
Acute predator odor	Rat	Defensive-like behavior	↑	↑	Hippocampal cell proliferation	==	↓	Falconer and Galea, 2003
Acute foot shock	Rat	Latency to escape foot shock	Higher escape latency in males in first 5 trials		Hippocampal cell proliferation	==	↓	Shors et al., 2007
Social isolation	Rat	N/A			Hippocampal cell proliferation	↓	==	Westenbroek et al., 2004
Chronic foot shock + social isolation	Rat	N/A			Hippocampal cell proliferation	↑	↓	Westenbroek et al., 2004
Repeated restraint stress	Rat	N/A			Hippocampal cell proliferation	==	↓	Hillner et al., 2013
Repeated restraint stress	Rat	N/A			Hippocampal cell survival	↓	==	Hillner et al., 2013
Chronic restraint stress	Rat	N/A			Basal dendritic arborization, pyramidal neurons in CA3 of hippocampus	↓	==	Galea et al., 1997
Chronic restraint stress	Rat	N/A			Apical dendritic arborization, pyramidal neurons in CA3 of hippocampus	==	↓	Galea et al., 1997
Repeated restraint stress	Rat	N/A			Apical dendritic arborization, pyramidal neurons in mPFC	↑	↓	Garrett and Wellman, 2009
Repeated restraint stress	Rat	N/A			Dendritic arborization, BLA-projecting mPFC pyramidal neurons	↑	==	Shansky et al., 2009, 2010
Repeated restraint stress	Rat	N/A			Dendritic arborization, non-BLA-projecting mPFC pyramidal neurons	==	↓	Shansky et al., 2009, 2010
Sub-chronic variable stress	Mouse	Depressive-like behavior	↑	==	Dnmt3a expression in the NAc	↑	==	Hodes et al., 2015
Repeated restraint stress	Rat	N/A			Expression of opioid- and plasticity-related genes in the hippocampus	↓	==	Randesi et al., 2018
Repeated restraint stress	Rat	N/A			Expression of CRH in the hippocampus	↑	==	Randesi et al., 2018
Chronic variable stress	Mouse	Depressive- and anxiety-like behaviors	↑	↑	Gene expression in NAc and vmPFC	Small (20–25%) overlap in differential gene expression		Labonté et al., 2017
Sub-chronic variable stress	Mouse	Depressive-like behavior	↑	==	Genome-wide transcriptional analysis of the NAc	Small (3%) overlap in differential gene expression		Hodes et al., 2015

generally limited to children and middle-aged to older adults (McKinnon et al., 2009), pointing to protective factors in younger adults. Interestingly, depression-related volumetric reductions may be more apparent in men than in women (Frodl et al., 2002; Kronmüller et al., 2009), however this trend is not seen across all studies (MacQueen et al., 2003). These differences may be driven by treatment effects (discussed below) or age, as the mean age of participants was substantially younger in the study by MacQueen et al., suggesting that sex differences in the susceptibility to volumetric reductions may be more robust later in adulthood. Antidepressant treatment in individuals with depression can increase hippocampal volume or prevent hippocampal atrophy, and this may be sex-specific, as one study found increased hippocampal volume in treatment-responding women relative to non-responding women, but this effect was not seen in men (Vakili et al., 2000). Taken together, pre-menopausal women may be more resistant to hippocampal volume reductions with depression, and treatment efficacy may be more tightly linked to hippocampal volume restoration in women. Intriguingly, one study found that prescribed antidepressants were associated with increased neurogenesis in the hippocampus of women, but not men (Epp et al., 2013), suggesting a possible mechanism of volumetric restoration. Another study found sex-specific patterns of abnormalities in cortico-limbic-striatal morphology in individuals with untreated depression (Kong et al., 2013). Specifically, prefrontal-limbic abnormalities were primarily found in women, while prefrontal-striatal abnormalities were primarily found in men, pointing toward sex differences in the neuronal circuitry underlying depression (Kong et al., 2013). These findings may be of relevance to sex differences in the clinical presentation of depression; prefrontal-limbic dysfunction may be related to the higher prevalence of anxiety in

women (Etkin, 2010), while prefrontal-striatal dysfunction may be related to the higher prevalence of substance use in men (Limbrick-Oldfield et al., 2013). It is important to note that while there are inconsistencies in findings of volumetric alterations in depression, care must be taken when comparing studies with different methodology, and factors to consider when interpreting findings include insufficient statistical power, age, disease heterogeneity, and the effects of medication (Eker and Gonul, 2009). Despite these issues, the studies we reviewed provide some examples of sex differences in anatomical brain abnormalities in depression, and in particular suggest that limbic regions may be differently compromised in depression between men and women.

4. Sex differences in the effects of stress exposure or antidepressant treatment on adult hippocampal neurogenesis and dendritic remodeling

The hippocampus maintains the ability to produce new neurons throughout life in many species including humans (Boldrini et al., 2018; Eriksson et al., 1998; Gould et al., 1999), and evidence points to a role of neurogenesis in emotional processing (Anacker and Hen, 2017) and the neuroendocrine stress response (Surget et al., 2011). Reduced hippocampal neurogenesis is observed in animal models of depression (Bessa et al., 2009; Brummelte and Galea, 2010a,b; David et al., 2009; Gould et al., 1998; Green and Galea, 2008; Keilhoff et al., 2006), and factors that alleviate depressive symptoms, including chronic antidepressant treatment and exercise, increase neurogenesis in the hippocampus (Björnebekk et al., 2006, 2005; Malberg et al., 2000). In animal models of depression, hippocampal neurogenesis is required for

the efficacy of antidepressants in tests of anxiety (Santarelli et al., 2003) and to reverse HPA axis dysregulation (Surget et al., 2011), but not in a test of sucrose anhedonia or the FST (Bessa et al., 2009), although caution should be taken when interpreting these findings as the methods used to ablate neurogenesis are likely to affect other processes or brain regions. Beyond neurogenesis, other markers of neuroplasticity have proved important for antidepressant action, as the depletion of the polysialylated neural cell adhesion molecule (PSA-NCAM) inhibited the behavioral and neural efficacy of fluoxetine in male rats that had undergone chronic unpredictable stress (Wainwright et al., 2016a). Therefore, it has been theorized that adult hippocampal neurogenesis (Eliwa et al., 2017), and other neuroplastic molecules (Wainwright and Galea, 2013), are implicated in depression and its treatment. Although the exact role of new neurons in the dentate gyrus remains elusive, hippocampal neurogenesis is often utilized as a neuroplastic measure in animal models of depression.

Most animal models of depression involve exposure to stress, and sex can moderate the effects of acute and chronic stress exposure on hippocampal neurogenesis (Table 1). For example, exposure to acute predator odor (Falconer and Galea, 2003) or foot shock stress (Shors et al., 2007) reduced cell proliferation in male rats, but no such effect was observed in female rats (Falconer and Galea, 2003; Shors et al., 2007). Sex-dependent alteration in hippocampal neurogenesis are also reported in animal models of chronic or repeated stress (Hillier et al., 2013; Westenbroek et al., 2004). In individually housed rats, hippocampal cell proliferation was reduced after chronic foot-shock stress in males but increased in females (Westenbroek et al., 2004). Social isolation alone, which itself is a stressor, also resulted in differential effects on cell proliferation depending on sex, with decreased cell proliferation in females and no significant change in males; therefore, the sex differences in the effects of foot-shock stress on cell proliferation cannot be explained solely by different sensitivities to housing condition (Westenbroek et al., 2004). Another study in rats examined sex differences in the effects of repeated restraint stress on hippocampal neurogenesis, and found reductions in cell proliferation only in males, and reductions in cell survival only in females, after a stress incubation period (Hillier et al., 2013). Taken together, sex differences in the effects of stress can be observed across distinct stages of neurogenesis (i.e. proliferation and survival), and depend on the stress paradigm (acute, repeated, chronic), as well as other factors such as housing condition. As most of the reviewed studies did not examine behavioral outcomes, conclusions regarding the functional significance of these findings, especially as they relate to depressive-like behavior, are difficult to make. It is also important to note that sex hormones are potent regulators of adult hippocampal neurogenesis, a topic that we extensively reviewed previously (Mahmoud et al., 2016b), therefore some of the discussed differences in the consequences of stress exposure on neurogenesis may be influenced by sex differences in the sex hormone milieu. It is not known whether there are sex differences in depression-related changes in hippocampal neurogenesis in humans. However, one study investigated sex differences in the effects of antidepressant exposure on the density of immature neurons in post-mortem tissue from individuals with depression, and found antidepressant use to be associated with increased neurogenesis in the hippocampus of women, but not men (Epp et al., 2013). Combined with hippocampal volume studies discussed in the previous section, the findings of Epp et al. support the idea that the hippocampus may display more plasticity in response to antidepressant use in women compared to men.

Animal models of repeated or chronic restraint stress provide evidence for robust sex differences in stress-induced dendritic remodeling across multiple brain regions (Galea et al., 1997; Garrett and Wellman, 2009; Shansky et al., 2010, 2009; summarized in Table 1). In the pyramidal neurons of the CA3 region of the hippocampus, chronic restraint stress resulted in atrophy of the apical dendritic arbor in male rats, but the basal dendritic arbor in female rats (Galea et al., 1997; McLaughlin et al., 2010). Further, the effects of repeated restraint stress on the

apical dendritic arbor of pyramidal neurons in the medial prefrontal cortex (mPFC) were in opposite directions in male versus female rats (Garrett and Wellman, 2009). Specifically, dendritic atrophy was observed in males, and dendritic expansion was observed in females, and this effect in females was dependent on estradiol (Garrett and Wellman, 2009). There are also sex differences in the effects of stress on mPFC neurons that project to the basolateral amygdala (BLA; Shansky et al., 2010, 2009), a circuit that is implicated in fear and anxiety. In male rats, these neurons are resistant to chronic restraint stress-induced dendritic atrophy (Shansky et al., 2009), but interestingly, the same population of neurons displays an expansion of dendritic arbor in females rats treated with estradiol and exposed to the same stress paradigm (Shansky et al., 2010). In non-BLA projecting mPFC neurons, male rats show apical dendritic atrophy in response to chronic restraint stress (Shansky et al., 2009), but females are resistant to changes in dendritic arborization regardless of estradiol treatment (Shansky et al., 2010), somewhat consistent with the findings of Garrett and Wellman (2009). Thus, stress exposure results in sex- and circuit- specific changes in dendritic arborization, which may be represent a neural basis for sex differences in prevalence, manifestation, and treatment of stress-related disorders, including depression (Table 1).

5. Sex difference in the transcriptional signature of depression

The success of genome-wide association studies (GWAS) in identifying genetic loci that significantly contribute to depression susceptibility has been generally limited (Consortium, 2015; Flint and Kendler, 2014; Hyde et al., 2016), highlighting the genetic heterogeneity of the disorder, and the role of environmental influences. On the other hand, there is emerging evidence indicating that depression-related changes in gene expression are sex-specific (Gray et al., 2015; Labonté et al., 2017; Seney et al., 2018; Tripp et al., 2012). For example, utilizing candidate gene approaches, several post-mortem studies reported sex-specific changes in depression-related gene expression, with changes in gene expression for glutamate receptors (Gray et al., 2015), serotonin receptors (Goswami et al., 2010) and serotonergic regulators (Szewczyk et al., 2009) primarily observed in women, and more robust changes in expression for brain-derived neurotrophic factor (BDNF)-dependent genes and the BDNF receptor TrkB observed in men (Tripp et al., 2012). More recently, an RNAseq study examined the transcriptome of six brain regions from men and women with depression and matched controls (Labonté et al., 2017). Depression was associated with significant changes in transcriptional patterns across all examined brain regions in both men and women. Intriguingly, little overlap (5–10%) was detected in the pattern of depression-related gene expression between men and women across all regions (Labonté et al., 2017), highlighting that sex differences in depression extend well beyond differences in the prevalence of the disorder. Next, Labonté and colleagues employed co-expression network analyses to examine disease-associated gene modules, genes that are co-regulated in depression. The analyses identified approximately 150 depression-associated gene modules for each sex, and importantly, most of the modules were sex-specific. Interestingly, the disease-associated modules were enriched for genes expressed in several cell types in men, including neurons, astrocytes, and microglia, while in women, modules were enriched predominantly for neuronal genes (Labonté et al., 2017). These findings suggest that the transcriptional changes associated with depression may affect different cell types in the brains of men and women. In another recent study, a large-scale gene expression meta-analysis of cortico-limbic regions was performed on data from depressed individuals and matched controls (Seney et al., 2018). Largely recapitulating the findings from Labonté and colleagues, Seney et al. (2018) reported very little overlap in depression-related transcriptional changes between men and women. Moreover, a large number of transcriptional changes were found to be in opposite directions between men and women (Seney et al., 2018). Further gene-ontology analyses suggested that

synapse-related genes were reduced in men, but increased in women with depression (Seney et al., 2018). On the other hand, microglia- and oligodendrocyte-related genes were increased in men, but decreased in women (Seney et al., 2018). Collectively, there is convincing evidence that the transcriptional signature of depression is largely distinct in men versus women (Labonté et al., 2017; Seney et al., 2018). These latter findings point to sex differences in disease mechanisms, underscoring the need for the development of sex-based pharmacotherapies for depression. Sex differences in the molecular signature of depression also shed light on why men and women show differences in disease presentation and possibly treatment efficacy.

Compelling sex differences in transcriptional signatures are also observed following exposure to stress in rodent models of depression (Table 1). Notably, Labonté and colleagues (2017) complemented their findings in humans by examining behavioral outcomes and brain transcriptional responses to chronic variable stress in male and female mice. Interestingly, although this stress paradigm induced depressive-like behavior similarly in male and female mice, only a 20–25% overlap in differential gene expression was detected between the sexes in the brain regions examined (nucleus accumbens (NAc) and ventromedial PFC), corroborating their human data (Labonté et al., 2017). Using a stress paradigm that resulted in depressive-like behavior in female but not male mice, another study conducted a genome-wide transcriptional analysis of the NAc to gain insight into this sex difference in behavioral susceptibility to stress (Hodes et al., 2015). Mirroring the behavioral findings, significant sex differences were found in the patterns of gene expression following stress exposure (Hodes et al., 2015). Of particular interest was an increase in the expression of the DNA methyltransferase 3a (Dnmt3a) in the female NAc following stress, which was later demonstrated to be directly linked to the observed behavioral susceptibility (Hodes et al., 2015). In another report, chronic restraint stress resulted in gene expression changes in the hippocampus of male but not female rats, with notable downregulation of opioid- and plasticity-related genes, and upregulation of corticotropin-releasing hormone (CRH) in males (Randesi et al., 2018). Taken together, studies in rodent models of depression indicate a distinct transcriptional response to stress between males and females in instances where behavioral outcomes are distinct (i.e. when only one sex shows increased susceptibility; Hodes et al., 2015), but also when behavioral outcomes are similar (Labonté et al., 2017). These data complement human studies of sex differences in transcriptional profiles in depression (Labonté et al., 2017; Seney et al., 2018), and provide further evidence that the molecular mechanisms underlying depression may be fundamentally distinct in males and females. Thus, efforts toward the development of sex-specific pharmacotherapies that target these distinct mechanisms may lead to more efficacious treatments for both sexes.

6. Sex differences in immune dysregulation in depression and its models

There is ample evidence in support of the involvement of the immune system in depression (reviewed in Miller and Raison, 2016), and a subpopulation of individuals with depression display increased circulating concentrations of pro-inflammatory markers (meta-analyses: Dowlati et al., 2010; Haapakoski et al., 2015), and elevated markers of neuroinflammation (Rao et al., 2010; Setiawan et al., 2015; Steiner et al., 2008). Further, there is no shortage of evidence linking inflammation to depressive-like endophenotypes in animal models (Remus and Dantzer, 2016). Chronic low-grade inflammation is therefore thought to be implicated in the etiology of a subtype of depression. Importantly, sex and sex hormones moderate many aspects of immune function (reviewed in Klein and Flanagan, 2016). Despite the increased interest in the relationship between depression and inflammation, and the established sex and hormone differences in immune function, the current knowledge surrounding sex differences in inflammation and immune processes within the context of depression is sparse.

Relatively few studies to date have examined whether biological sex influences the relationship between peripheral inflammatory markers and depression. Birur et al. (2017) investigated a variety of inflammatory markers in men and women with depression, and found that compared to healthy women, depressed women had higher levels of the pro-inflammatory IL-8, IFN- γ , and leptin, and lower levels of the anti-inflammatory adiponectin, and the pro-inflammatory IL-5, but no significant differences were found between healthy and depressed men (Birur et al., 2017). These findings are in contrast with a large cohort study that reported associations between depression and a large number of immune-related proteins, including the acute phase reactant C-reactive protein (CRP), in men but not women (Ramsey et al., 2016). Indeed, several other studies also report higher CRP levels to be associated with depression in men but not women (Elovainio et al., 2009; Vetter et al., 2013; Vogelzangs et al., 2012). On the other hand, another study found that in women with depression, higher levels of CRP were associated with specific depression symptoms and greater depression severity, while no such associations were found in depressed men (Köhler-Forsberg et al., 2017). Importantly, the roles of menstrual phase and time of day were not considered in the study by Köhler-Forsberg and colleagues. Thus, the apparent inconsistencies in the literature may point to an insufficient consideration of factors such as age and steroid hormones, which can influence both depression and the inflammatory profile. For example, across the menstrual cycle, higher levels of estradiol are associated with reduced CRP levels (Gaskins et al., 2012), indicating an anti-inflammatory effect of estradiol. Both androgens and glucocorticoids also possess immunomodulatory properties (Coutinho and Chapman, 2011; Triguñaite et al., 2015) and circulating levels of androgens display circadian variation in men (Brambilla et al., 2009), as do glucocorticoids in both sexes (Dickmeis, 2009). Thus, an insufficient consideration of time of day can contribute to additional variability in the findings. By accounting for age, time of day, and menstrual cycle phase, future studies should carefully consider the role of steroid hormones in deciphering the relationship between inflammation and depression in both men and women.

Other studies in non-depressed healthy individuals have investigated sex differences in the depressogenic effects of an inflammatory challenge. In response to a bacterial endotoxin, healthy women show greater increases in depressed mood and feelings of social disconnectedness relative to healthy men (Moieni et al., 2015). Further, feelings of social disconnectedness in response to the challenge were positively correlated with IL-6 and TNF- α levels in women but not in men (Moieni et al., 2015). Another study also found that women exhibited a larger inflammatory response to a bacterial endotoxin relative to men, but this effect was not associated with larger modifications in mood or state anxiety in women (Engler et al., 2016). Thus, while it appears that women may mount a larger immune response to an acute inflammatory challenge (Engler et al., 2016; Moieni et al., 2015), whether this translates to greater alterations in mood is not clear. Circulating sex and stress hormone levels may also be at play in the effects of inflammation on depressive symptoms and therefore should be considered in future work.

Very few pre-clinical studies to date have systematically investigated whether biological sex influences the relationship between inflammation and depressive-like endophenotypes. These studies have generally investigated sex differences in the inflammatory consequences of stress (Bollinger et al., 2016; Hudson et al., 2014), or sickness behavior following an inflammatory challenge (Adzic et al., 2015; Brkic et al., 2016; Pitychoutis et al., 2009; Sens et al., 2017). Further, these studies have often investigated microglia, the resident immune cells of the brain and the primary orchestrators of the neuroinflammatory response (Kettenmann et al., 2013). Microglia are highly dynamic cells that are capable of structural remodeling in response to pathological events or environmental perturbations such as stress exposure (Kreutzberg, 1996; Walker et al., 2013), and this tight structure-function link has allowed researchers to utilize microglial morphology as a

proxy for functional or activation state (Karperien et al., 2013). A study in rats found that the effects of stress on microglial activation in the mPFC were sex-dependent (Bollinger et al., 2016). This study found that at baseline, females display more activated microglia than males, but following acute or chronic restraint stress, only female rats displayed reduced microglial activation (Bollinger et al., 2016). These findings are also of interest considering other reports, predominantly in male animals, showing the opposite trend of increased microglial activation following stress exposure (Calcia et al., 2016). Alterations in microglial function have been shown to underlie stress-induced depressive-like behavior (Kreisel et al., 2014), thus the findings of Bollinger and colleagues could have implications for sex differences in the behavioral consequences of stress. In addition, work by Luis-Miguel Garcia-Segura and his colleagues shows a number of sex differences in microglial characteristics under basal and challenge conditions. Their studies indicate that *in vitro*, microglia extracted from postnatal day 8 males showed higher migration/mobility than females (Yanguas-Casás et al., 2018). Microglia from females, however, were more phagocytic than those from males (Yanguas-Casás et al., 2018), and future studies will be examining whether these findings are similar or different in adult animals. Another study investigated sex difference in whether prior exposure to stress can prime the neuroinflammatory response to subsequent exposure to acute stress (Hudson et al., 2014). Specifically, adult CD-1 mice were initially exposed to three days of repeated variable stress, then six weeks later were acutely exposed to restraint stress. Male mice that were stressed on both occasions displayed a sensitization of IL-1 β in the hippocampus and PFC relative to male mice that were only exposed to acute restraint (Hudson et al., 2014). Interestingly, while baseline cytokine expression levels were higher in female mice, neither the initial exposure to variable stress, nor the re-exposure to acute stress had any significant effects on cytokine expression levels in the hippocampus or PFC (Hudson et al., 2014). While keeping in mind that the literature directly examining sex as a factor in the neuroimmune consequences of stress is extremely limited, the reviewed studies suggest that males and females show differential neuroinflammatory responses to stress, which may also contribute to the sex differences in stress-related disorders, including depression.

Activation of the immune system using infectious or inflammatory agents induces a host of sickness behaviors that markedly overlap with a number of depression symptoms, including reduced food intake, anhedonia, lethargy, reduced activity, and concentration deficits (Maes et al., 2012). Thus, sickness behavior is utilized as an immunological model of depression, and is generally achieved via the administration of bacterial endotoxins or inflammatory cytokines (reviewed in Remus and Dantzer, 2016). Sickness behavior can be useful in modeling depression occurring in a subpopulation of individuals in which inflammatory processes are central to the disease mechanisms, but caution should be taken in generalizing findings to other subtypes of depression. Few studies to date have examined sex differences in sickness behavior and its neurobiological correlates (Adzic et al., 2015; Brkic et al., 2016; Pitychoutis et al., 2009; Sens et al., 2017). Acute lipopolysaccharide (LPS) administration in mice resulted in increased immobility in the forced swim test and reduced sucrose consumption, indicative of increased depressive- and anhedonia-like behavior, irrespective of sex (Sens et al., 2017). However, LPS resulted in longer lasting reductions in grooming behavior and serotonergic turnover in females, and longer lasting reductions in overall food consumption in males (Sens et al., 2017), suggesting sex differences in the duration of behavioral and neurochemical alterations in response to LPS. In rats, another study reported a rather surprising finding of increased active behavior in FST following LPS treatment in female, while the behavior of males was not significantly altered (Pitychoutis et al., 2009). This was coupled with a larger increase in serotonergic turnover in females relative to males (Pitychoutis et al., 2009). In another study, male and female rats showed similar behavioral alterations following seven days of LPS treatment, including increased depressive-like behavior, reduced

sucrose consumption, and reduced activity (Adzic et al., 2015). Despite the similarities in behavioral outcomes, reduced hypothalamic BDNF was detected in females only, and increases in the inflammatory enzyme cyclooxygenase-2 (COX-2) were detected in males only (Adzic et al., 2015). Using a similar experimental design, the same group found evidence of nuclear translocation of the glucocorticoid receptor in the PFC of male, but not female rats, in response to LPS treatment, despite similar behavioral outcomes (Brkic et al., 2016). Collectively, the data do not strongly support a higher susceptibility of either sex to the behavioral consequences of inflammatory activation. However, the neurobiological mechanisms driving the behavioral consequences of inflammatory agents may differ between males and females, therefore these models can be useful in identifying targets for sex-specific pharmacotherapies in inflammation-related depression.

7. Sex hormones in depression and its treatment

Sex differences in depression point to a role of sex hormones in the disease mechanisms. Indeed, both androgens in men and estrogens in women have been implicated in depression and its treatment. In men, hypogonadism is associated with depression (McIntyre et al., 2006; Shores et al., 2005; Westley et al., 2015), and testosterone replacement therapies show some efficacy in alleviating depression, particularly in hypogonadal men (Seidman and Rabkin, 1998; Shores et al., 2009; Zarrouf et al., 2009). Preclinical research in rats corroborates the human literature, as gonadectomized male rats are more susceptible to the depressogenic effects of chronic stress than gonadally-intact males (Wainwright et al., 2011). Furthermore, testosterone shows some efficacy in reversing depressive-like phenotypes after chronic stress in castrated male rats (Carrier and Kabbaj, 2012; Wainwright et al., 2016b). In women, periods that are characterized by large reductions or fluctuations in ovarian hormones, including the postpartum period and perimenopause, are associated with a heightened risk for depression (Cohen et al., 2006; Hendrick et al., 1998; Soares, 2014). Indeed, the hormone withdrawal hypothesis of postpartum depression (PPD), which will be expanded on below, posits that the rapid drop in sex steroids after parturition underlies the etiology of the disorder, and this is supported by evidence from human and rodent studies (Bloch et al., 2000; Galea et al., 2001; Green et al., 2009). In further support of the notion that ovarian hormones are implicated in depression, pharmacologically-induced ovarian hormone-withdrawal increased depressive symptoms in healthy women, in a manner that correlates with the net reduction in estradiol (Frokjaer et al., 2015). Further, gonadectomy in female rats increases depressive-like behavior in the short term (de Chaves et al., 2009; Li et al., 2014), and increases susceptibility to the depressive-like outcomes of chronic stress exposure in the long term (Mahmoud et al., 2016a). Ovarian hormones may also be implicated in antidepressant efficacy, as some studies found SSRIs to be less efficacious in post-menopausal women compared to pre-menopausal women, and efficacy is increased in postmenopausal women prescribed hormone therapy (Thase et al., 2005). Further, estradiol shows some efficacy as a standalone or adjunct treatment in women with depression (Moses-Kolko et al., 2009; Rasgon et al., 2007). Similarly, in rats, estradiol may facilitate the antidepressant-like effects of SSRIs in the FST (Mahmoud et al., 2016a; Sell et al., 2008). Collectively, human and animal studies provide strong support for the involvement of gonadal hormones in depression and its treatment in both males and females and overall suggest that in both sexes, gonadal hormones may impart resilience against depression and enhance treatment efficacy. Further, differences in the gonadal hormone milieu between men and women may contribute to the overall sex differences in depression and possibly treatment efficacy.

8. Depression during pregnancy and the postpartum period: female-unique factors in the susceptibility for depression

Pregnancy and motherhood place unique physiological and behavioral demands on the females of most mammalian species, including humans. The peripartum period also represents a time of increased susceptibility to mood disorders in a women's life, with an estimated 15% of women developing depression during the perinatal period (O'Hara and Swain, 1996). Below, we discuss issues surrounding the presentation, time course, and treatment of perinatal depression (PND). We also review neurobiological modifications accompanying motherhood and models of PND and specifically PPD in rodents.

9. Distinguishing postpartum depression from major depression

Currently, the DSM-5 defines depression in mothers under Major Depressive Disorder (MDD), with peripartum onset as a specifier; this includes all the diagnostic criteria of MDD but occurring during pregnancy or within the first four weeks of giving birth (American Psychiatric Association, 2013). However, there are several issues with this definition. First, this definition does not categorize depression during antepartum versus during the postpartum as separate subtypes of MDD, and it does not account for the different presentation of depression between mothers and other individuals with MDD. For example, anhedonia in the case of PPD is more likely to present as loss of interest in the social domain, such as loss of interest in the infant, withdrawing from personal relationships, and other types of interpersonal difficulties (Perani and Slattery, 2014). Additionally, anxiety is more highly co-morbid with PPD in comparison to depression outside of the postpartum period in women (Hendrick et al., 2000). A specific anxiety disorder, obsessive compulsive disorder, is more prevalent in the postpartum period (Russell et al., 2013), and is also highly co-morbid with PPD in comparison to depression onset before or during pregnancy (Fisher et al., 2016). Acknowledging these differences in depression presentation could improve the diagnostic criteria of PPD, and with that the accuracy of identifying PPD cases.

Second, the current definition collapses depression occurring in pregnancy with depression occurring in the postpartum period, calling the disorder perinatal depression (PND). Timing of index depressive episode is important because depression arising in different endocrine states (i.e., before, during, or after pregnancy) may be reflective of different biological mechanisms. For example, psychosocial stress (such as history of abuse, lack of social support, and unplanned pregnancy) increased the likelihood of developing depression during gestation, whereas obstetric and infant complications increased the likelihood of developing depression in the postpartum (Altemus et al., 2012; Putnam et al., 2017). Furthermore, women with postpartum but not antepartum depression may be more vulnerable to the dramatic fluctuations in steroid hormones from gestation to parturition (see below). Indeed, women with a history of PPD endorsed more depressive symptoms after withdrawal from a hormone-simulated pregnancy (Bloch et al., 2000). These observations and others have lead to the hormone withdrawal hypothesis, which posits that with the expulsion of the placenta at the time of parturition, the withdrawal from sustained high levels of hormones during pregnancy contributes to postpartum blues and possibly depression. Additionally, in women with a previous history of MDD, prevalence rates are higher for antepartum depression than for PPD (Altemus et al., 2012), further supporting different mechanisms depending on timing of depression onset. Distinguishing timing of depression onset is also important for understanding the risk for future depressive episodes. Women with PND and a history of previous depression carry a recurrent risk for depression outside of motherhood, whereas women with index depression occurring in the peripartum period carry risk for future peripartum depression episodes but not a recurrent risk for depression outside of motherhood (Cooper and Murray, 1995). It should also be noted that delineating depression onset

during pregnancy versus postpartum will be instrumental in better understanding the effects of maternal mood on child outcome. Depression during gestation significantly influences *in utero* programming whereas PPD significantly alters maternal care and breastfeeding (including whether breastfeeding occurs as well as potentially content of the milk). The effects of PND on children is reviewed elsewhere (Hay et al., 2008; Mirhosseini et al., 2015), however it is noteworthy that improving the diagnostic criteria for PND could also improve our understanding of the effects of maternal depression on child development.

Finally, the current definition in the DSM-5 restricts the onset of depression to occur within 4 weeks of giving birth. Other major health organizations such as the World Health Organization and Centers for Disease Control and Prevention consider maternal depression to occur within 12 months of child birth (Centers for Disease Control and Prevention (CDC), 2008; Geneva: World Health Organization, 2010). While this definition is more inclusive, inconsistent temporal definitions of PPD contribute to highly variable and likely an underestimation of PPD prevalence (Hansotte et al., 2017). The 4-week restriction is also problematic because the severity of mood disturbances fluctuates substantially within the first 12 months of childbirth. The “baby blues” refers to a transient, mild mood disturbance which affects a majority of women within the first 10 days of birth and typically resolves without intervention (O'Hara and McCabe, 2013; O'Hara and Wisner, 2014). However, PPD refers to a more persistent and severe mood disturbance (O'Hara and McCabe, 2013) with greatest incidence for hospitalization occurring within the first 3 months after birth (Munk-Olsen et al., 2006). Interestingly, previous history of depression can also influence severity of PPD. De novo PPD is more severe (i.e. higher depression scores) 6 weeks after birth, but PPD as an episode of recurrent depression is more severe 1 year after birth, although depression scores are slightly elevated for the entire 12 months of the postpartum period (Fredriksen et al., 2017). These observations not only support extending the time restriction in the definition of PPD, but also support distinguishing timing of PPD as de novo or recurrent to more accurately assess PPD.

10. Neurobiology of motherhood & PPD

During pregnancy, total brain volume shrinks by 8% and returns to pre-conception volume within 6 months postpartum (Oatridge et al., 2002). A recent study showed pre- to post-pregnancy reductions in gray matter volume in areas such as the anterior cingulate cortex, bilateral temporal cortex, inferior frontal cortex, and the hippocampus, and these reductions were correlated with maternal-infant attachment (Hoekzema et al., 2017). The reductions in gray matter volume were still evident 2 years postpartum, with only a partial recovery of hippocampal volume (Hoekzema et al., 2017), demonstrating that pregnancy and motherhood are associated with long-lasting changes in brain structure. Further, the early postpartum period is associated with increased monoamine oxidase-A binding in the PFC, anterior cingulate cortex and hippocampus (Sacher et al., 2010). Preclinical models provide insight into possible mechanisms contributing to hippocampal volume reduction, such as altered hippocampal neurogenesis. Cell proliferation in the hippocampus is suppressed in the early postpartum (Pawluski and Galea, 2007; Leuner et al., 2007; Darnaudéry et al., 2007), via elevated levels of circulating corticosterone (CORT) as removing the adrenal glands from postpartum female rats restored cell proliferation in the hippocampus on postpartum day 7 (Leuner et al., 2007). Interestingly, the survival of new neurons is also suppressed in the postpartum but only in primiparous (i.e. first-time mothers) and not biparous (i.e. second-time mothers) rats (Pawluski and Galea, 2007). Moreover, reductions in hippocampal neurogenesis are still apparent in postpartum females that have had their pups removed 24 hours after parturition, indicating that these reductions in neurogenesis are related to pregnancy and not to lactation (Pawluski and Galea, 2007). There are also postpartum reductions in hippocampal dendritic branching and

Table 2

Neurobiology of motherhood, postpartum depression, and pharmacologically-induced hormone withdrawal in women.

	Findings	References
Pregnancy and Postpartum	8% reduction in overall brain volume during pregnancy, reversed by 6 months postpartum. Long-lasting reductions in gray matter volume evident 2 years postpartum. This effect was observed in regions including anterior cingulate cortex, bilateral temporal cortex, inferior frontal cortex, and the hippocampus. However, other studies find increased volume. Increased monoamine oxidase-A binding in the early postpartum, in all brain regions examined including the prefrontal cortex, anterior cingulate cortex, and hippocampus.	Oatridge et al., 2002 Hoekzema et al., 2017 Sacher et al., 2010
Postpartum depression	Increased glutamate levels in the medial prefrontal cortex of women with PPD.	McEwen et al., 2012
Hormone withdrawal	Increased depressive symptoms in women with and without a history of PPD. Depressive symptoms positively correlated with neocortical serotonin transporter binding. Depressive symptoms were associated with increased functional connectivity between the amygdala and right temporal cortex, and decreased functional connectivity between the cingulate cortex and hippocampus. Increased insula activity in response to positive and negative emotional stimuli.	Bloch et al., 2000; Frokjaer et al., 2015 Frokjaer et al., 2015 Fisher et al., 2017 Henningsson et al., 2015

spine density (Kinsley et al., 2006; Pawluski and Galea, 2006), and expression of estrogen receptor (ER) α (Pawluski et al., 2010) which may contribute to altered hippocampal volume and function in primiparous rats. In addition to volumetric changes, reproductive experience also reduces hippocampal serotonin content in postpartum female rats relative to nulliparous (i.e. no reproductive experience) female rats (Desan et al., 1988; Overgaard et al., submitted for publication). Interestingly, the dorsal raphe nucleus, an important site of serotonin production, also exhibits reduced cell survival during the postpartum (Holschbach and Lonstein, 2017). These findings and others suggest that plasticity is altered in many regions after parturition in the maternal brain, including the hippocampus and with notable reductions in serotonin (Table 3).

Reductions in hippocampal volume and neurogenesis as well as serotonin transmission have been implicated in MDD, and these neurobiological changes may increase vulnerability to depression in mothers. However, there are relatively few clinical studies directly examining the neurobiology of PPD (Table 2). One study observed that PPD was associated with increased glutamate levels in the mPFC (McEwen et al., 2012). A number of studies have investigated the effects of hormone withdrawal (via administration of gonadotrophin receptor agonist) in women, and these studies are of relevance to the postpartum period, which is characterized by a hypogonadal state following parturition (Table 2). In each of these studies women, with and without a history of PPD, endorsed greater depressive symptoms in response to ovarian hormone withdrawal (Bloch et al., 2000; Frokjaer et al., 2015). In addition, increased depressive symptoms correlated significantly and positively with neocortical serotonin transporter binding (Frokjaer et al., 2015), suggesting that hormone withdrawal and depression symptoms may be connected via altered serotonergic transmission. Furthermore, depressive symptoms were associated with increased functional connectivity between the amygdala and right temporal cortex, and decreased functional connectivity between the cingulate cortex and hippocampus (Fisher et al., 2017). In another study, ovarian hormone withdrawal increased insula activity after both positive and negative emotional stimulation in healthy young women (Henningsson et al., 2015). These observations provide insights into the neurobiological underpinnings of the hormone withdrawal hypothesis contributing to depression in women.

Rodent models of PPD (summarized in Table 3) typically involve gestational stress such as chronic restraint stress (Haim et al., 2014; Hiller et al., 2011; Leuner et al., 2014) or chronic intruder stress (Carini et al., 2013), and therefore model depression that is instigated antenatally. Our laboratory developed a rat model of depression arising selectively in the postpartum period via chronic CORT injections which reduce quality of maternal care and increase passive coping in the FST (Brummelte et al., 2006; Brummelte and Galea, 2010; Workman et al., 2013; 2016; Gobinath et al., 2018). While chronic CORT injections do

not model the psychological component of chronic stress, this paradigm minimizes maternal separation and selectively targets the mother in the postpartum period. This is advantageous because other models of postpartum stress or PPD, such as maternal separation or intruder stress, result in forced neglect (as opposed to voluntary reductions in maternal care using the CORT injections) and direct stress of the pups (as opposed to via altered maternal care). Thus, paradigms that do not involve maternal separation or direct stress of the pups and are applied in the postpartum (and not during gestation), provide a translational model closely related to PPD but not antenatal depression. Additionally, we have found that the CORT model of PPD resulted in reduced hippocampal neuroplasticity (cell proliferation, density of immature neurons) in the dentate gyrus, and reduced dendritic complexity in CA3 subfield of the hippocampus at the time of weaning, suggesting persistent reductions in neuroplasticity in the CORT-treated mother (Brummelte and Galea, 2010a,b; Gobinath et al., 2018; Workman et al., 2016, 2013). It is important to recognize that PPD is a heterogeneous disorder with differences in timing onset and symptoms, and as such different animal models of PPD can mimic various aspects of PND as discussed below.

Other models of PPD have used withdrawal after a hormone-simulated pregnancy in rats, which as stated earlier, reduced adult hippocampal cell proliferation in female rats (Green and Galea, 2008), reduced sucrose preference, and increased passive coping in the FST (Galea et al., 2001; Green et al., 2009; Stoffel and Craft, 2004). Importantly, continued treatment with estradiol or an ER β agonist throughout the simulated postpartum period prevented the development of depressive-like behavior (Galea et al., 2001; Green et al., 2009), and continued treatment with an ER β agonist prevented the suppression in cell proliferation (Green and Galea, 2008) in this model. Collectively, these findings indicate that the fall in levels of estrogens at parturition contributes to the development of PPD and its neurobiological correlates.

Other models of PND have used stress during pregnancy (Haim et al., 2014; Leuner et al., 2014; Pawluski et al., 2015), disruptions to the GABA $_A$ receptor δ subunit (Maguire and Mody, 2008) or to CRH neurons in the paraventricular nucleus (PVN; Melón et al., 2018), or manipulations of oxytocin (Wang et al., 2018). Studies by Jamie Maguire and colleagues have found that knock down of GABA $_A$ R δ subunit causes abnormal maternal care and depressive-like behaviors in the early postpartum (Maguire and Mody, 2008). These mice also showed disruptions to the HPA axis which lead these researchers to further characterize these deficits as stemming from a dysregulation of the KCC2 channels in CRH neurons the PVN of the hypothalamus (Melón et al., 2018). Intriguingly, neurosteroids show alterations with PND (Nappi et al., 2001), and recent clinical evidence suggests that the synthetic neurosteroid Brexanolone, a derivative of allopregnanolone, can reverse depression in new mothers (Kanes et al., 2017a,b). These

Table 3
Neurobiology of motherhood and postpartum depression models in rodents.

Findings		References	
Postpartum	Reduced hippocampal cell proliferation	Pawluski and Galea, 2007; Leuner et al., 2007; Darnaudéry et al., 2007	
	Reduced survival of new neurons in primiparous rats	Pawluski and Galea, 2007	
	Reductions in dendritic complexity in the CA3 and CA1 regions of the hippocampus in primiparous rats but increased spine density in the CA1	Kinsley et al., 2006; Pawluski and Galea, 2006	
	Reduced estrogen receptor α expression in the CA3 region of the dorsal hippocampus	Pawluski et al., 2010	
	Reduced hippocampal serotonin concentrations	Overgaard et al., submitted; Desan et al., 1988	
	Reduced cell survival in the dorsal raphe nucleus	Holschbach and Lonstein, 2017	
Models of peripartum depression	Behavioural Findings	Neural correlates	References
Postpartum chronic corticosterone	Maternal care deficits; increased passive-coping behaviour in the forced swim test (FST)	Reduced cell proliferation and density of immature neurons in the dentate gyrus of the hippocampus, reduced dendritic complexity in the CA3 region of the hippocampus	Brummelte et al., 2006; Brummelte and Galea, 2010; Workman et al., 2013, 2016; Gobinath et al., 2018
Withdrawal from hormone-simulated pregnancy	Increased anhedonia-like behaviour in the sucrose preference test (prevented by ER β agonist), increased passive-coping behaviour in FST (prevented by estradiol benzoate)	Reduced cell proliferation in the dentate gyrus of the hippocampus	Green and Galea, 2008; Galea et al., 2001; Green et al., 2009; Stoffel and Craft, 2004
Gestational stress	increased passive-coping behaviour in FST, maternal care deficits, impaired performance on attentional set shifting task, increased sucrose anhedonia	Reduced dendritic complexity and spine density in the NAc shell, reduced dendritic spine density and altered spine morphology in the mPFC, increased hippocampal neurogenesis and reduced CA3 glucocorticoid receptor density	Haim et al., 2014; Leuner et al., 2014; Pawluski et al., 2015
GABA $_A$ receptor δ subunit deficiency	Increased anhedonia-like behaviour in the sucrose preference test, increased passive-coping behaviour in FST, maternal care deficits	Disrupted hypothalamic pituitary adrenal axis function; deficits in GABAergic tonic inhibition in hippocampal slice preparations	Maguire and Mody, 2008
Disrupted CRH neurons in PVN	increased passive-coping behaviour in FST, maternal care deficits	Dysregulated HPA axis function in Mice lacking K $^{+}$ /Cl $^{-}$ -co-transporter (KCC2) in CRH neurons	Melón et al., 2018

data point to a role for HPA regulation and neuroactive hormones as therapeutics in PND.

The timing of depression onset in PND is paramount to a better appreciation of the diversity of PND. It is important to understand that the type of PPD being modeled within preclinical animal studies will be consequential. Animal models of perinatal depression generally utilize stress/CORT exposure either pre-gestation (Xia et al., 2016; Gemmel et al., 2018), during gestation (Haim et al., 2016; Leuner et al., 2014; Pawluski et al., 2015), or in the postpartum period (Brummelte et al., 2006; Workman et al., 2016), and all of these models are needed to explore the heterogeneity of PPD and perinatal depression. Indeed, understanding the heterogeneity of PND is important for establishing what treatment regimens may be more effective in one population versus another. One latent class analysis found that PND was the most severe in those women with antepartum onset compared to those women with a postpartum onset and those with antenatal onset were more likely to show co-morbid anxiety (Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium, 2015). Intriguingly, animal models with manipulations during pregnancy and/or pre-gestational are more likely to result in an increase in anxiety-like behaviors (Melón et al., 2018; Pawluski et al., 2012; Xia et al., 2016) while those targeting the postpartum period do not (Brummelte et al., 2006; Brummelte and Galea, 2010a,b), much like the findings of human studies (Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium, 2015).

Most models of PND have targeted disruptions in the HPA axis, but downstream targets such as oxytocin are recently being considered, as breastfeeding women with depressive symptoms show reduced levels of oxytocin and positive correlations between oxytocin and CORT, rather than negative correlations that are seen in non-symptomatic women (Cox et al., 2015). Furthermore, whereas data correlating estradiol or progesterone to PPD have been mixed (Guintivano et al., 2017), one study found oxytocin levels to be lower in women that experience PND (Lara-Cinisomo et al., 2017), although this may be related to the

experience of early life adversity in women (Lara-Cinisomo et al., 2017). In addition, a few studies have shown that perinatal depression was associated with higher methylation of the oxytocin receptor (Kimmel et al., 2016; King et al., 2017). Nursing is related to increased oxytocin and an attenuated HPA responsiveness to stress (Slattery and Neumann, 2008), and some studies have indicated a relationship between breastfeeding and resilience to depression (Pope and Mazmanian, 2016). Corroborating this notion, a recent study showed that higher nursing demand was associated with reduced depressive-like behavior in the postpartum period, as sham rats with double the nursing burden showed reduced passive coping in the FST compared to thelectomized rats (De Guzman et al., 2018). Epigenetic variations in PPD have been explored by Kaminsky's group, with findings suggesting that epigenetic changes in perinatal depression are directed toward hormone sensitivity in both estrogen-responsive genes as well as oxytocin-related genes (Osborne et al., 2016). As a word of caution for PPD models, testing for deficits in maternal care and increased depressive-like behavior are often conducted in the early postpartum, whereas the human disease often extends beyond the early postpartum period. Furthermore, testing in the early postpartum would disrupt the maternal/infant dyad, and thus findings may either be exacerbated or a consequence of this separation between dam and offspring. Thus, care must be taken to understand the role of maternal separation in these paradigms and the interpretation of findings using the different animal models of PPD.

11. Issues surrounding PPD treatment

As in the case of MDD, mothers suffering from depression during pregnancy and postpartum are also prescribed antidepressants such as SSRIs. However, there is emerging clinical evidence indicating that these prescribed antidepressants have limited efficacy during gestation or in the postpartum (systematic review: De Crescenzo et al., 2014). One clinical trial found that SSRI treatment reduced depressive scores 4

weeks into the intervention period in comparison to counseling, but this effect was not present at 18 weeks (Sharp et al., 2010). Another study found that in women with a history of depression, antidepressant use during the third trimester of pregnancy did not prevent PPD (Suri et al., 2017). Further complicating the interpretation of the postpartum antidepressant literature, few studies directly compare SSRI efficacy to placebo. Of the few studies that do, SSRI and placebo did not differ in affecting depressive scores among mothers also undergoing psychotherapy (Appleby et al., 1997; Bloch et al., 2012) or not (Wisner et al., 2015). Another trial found that SSRIs offered no significant benefit over placebo on depressive scores, but the attrition rate was high among both treatment conditions (Yonkers et al., 2008). The interpretation of other clinical studies is complicated by the lack of placebo control groups (Misri et al., 2004; Wisner et al., 2006) or baseline differences in depression scores (Hantsoo et al., 2014). More concerning, even 6 years after diagnosis of PPD, antidepressant use (during pregnancy and/or the postpartum) did not predict maternal recovery from depression or anxiety (Shankar et al., 2017). By six years postpartum, 20% of women had not recovered from anxiety or depression and there were no significant differences in depressive or anxiety scores in the women who had or had not taken SSRIs during pregnancy/postpartum (Shankar et al., 2017). Besides SSRIs, other types of antidepressants such as low doses of ketamine or transdermal estradiol did not prevent PPD (Xu et al., 2017), although more research using other doses is necessary. In addition to the questionable effects on maternal mental health, maternal SSRI use has been linked to adverse child outcomes, including increased risk for autism (Brown et al., 2017), but this remains controversial as effects of SSRIs likely depend on amount and timing of exposure, and the severity of depression in the mother (Oberlander and Zwaigenbaum, 2017). Thus, this inconclusive set of evidence emphasizes the importance of studying how antidepressants function specifically during motherhood for the well-being of both mothers and children.

Animal models are mixed in their findings on the effectiveness of SSRIs during the postpartum, and this likely depends on timing of treatment and the model of PND used. In our own model of PPD using high levels of CORT during the postpartum, we have consistently seen that SSRIs (paroxetine and fluoxetine) improve CORT-induced maternal care deficits (Gobinath et al., 2018; Overgaard et al., 2018; Workman et al., 2016), but not immobility in the FST (Workman et al., 2016; Gobinath et al., 2018; Overgaard et al., 2018), nor improvements in reduced hippocampal neurogenesis (Gobinath et al., 2018; Workman et al., 2016). We have attributed these findings to an early selective efficacy of fluoxetine and paroxetine, in which maternal care deficits are reversed in the short-term, but efficacy is not sustained with longer exposure to SSRIs as demonstrated by the inability to increase neurogenesis in the hippocampus or improve FST behavior. In our model, it is not clear what may be interfering with the ability of SSRIs to increase neurogenesis across the postpartum, as SSRIs do increase neurogenesis in other models of depression in females outside of the postpartum period (Mahmoud et al., 2016a). One possibility is that the high exogenous levels of CORT that we administer in our model of PPD may be interfering with the ability of SSRIs to influence neurogenesis, as others have shown that the ability of fluoxetine to normalize stress-induced HPA axis dysregulation depends on neurogenesis at least in male mice (Surget et al., 2011). Interestingly, we found that when coupled with voluntary exercise, fluoxetine was efficacious in reducing passive-coping behavior in the FST and increasing hippocampal neurogenesis (Gobinath et al., 2018). Lonstein and colleagues have noted changes in serotonin signaling during pregnancy and the postpartum (Holschbach and Lonstein, 2017), and these alterations likely influence the efficacy of SSRIs. Indeed, we also observe compromised serotonin signaling using our CORT-induced model of PPD (Overgaard et al., submitted for publication). Intriguingly, other models of PND utilizing stress during pregnancy do observe SSRI efficacy on FST behavior, hippocampal neurogenesis, and in prefrontal cortex remodeling with SSRIs given

either exclusively in the postpartum (Haim et al., 2016), or across both gestation and the postpartum (Gemmell et al., 2018). These studies collectively suggest that SSRIs may afford efficacy in the postpartum period depending on the nature of the model and timing of exposure to SSRIs.

12. Conclusions

It is evident from the preceding review of the literature that there are notable sex differences in depression-related gene expression, neuroplasticity, and immune signatures; these differences may account for disparities in prevalence and pathoetiology of the disease between men and women. There are sex differences reported in other biomarkers of depression (e.g. BDNF, nerve growth factor, serotonin, and dopamine), and in genetic polymorphisms associated with risk for depression, but these are beyond the scope of this review and the readers are directed to other reviews on these subjects (Labaka et al., 2018; Perry et al., 2017). To gain a better comprehension of sex differences in depression, studies need to be conducted using an animal model of depression. In clinical studies, attention needs to be paid to factors such as age and hormone fluctuations (e.g. menstrual cycle phase, and circadian fluctuations in CORT) to understand the role of biological sex within various aspects of depression. Including subjects of both sexes in depression research is critical for progress toward a better understanding of the disease and toward the discovery of novel targets for drug development, a view that aligns with others in the field (Williams and Trainor, 2018). However, it is equally important to study sex-specific factors and periods that contribute to depression vulnerability in either sex, including the peripartum period in women. This dual approach of studying sex differences and sex-unique factors may lead to important discoveries and ultimately more efficacious treatment options for both men and women.

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