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Reproductive Steroid Regulation of Mood and Behavior

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Abstract

In this article, we examine evidence supporting the role of reproductive steroids in the regulation of mood and behavior in women and the nature of that role. In the first half of the article, we review evidence for the following: (i) the reproductive system is designed to regulate behavior; (ii) from the subcellular to cellular to circuit to behavior, reproductive steroids are powerful neuroregulators; (iii) affective disorders are disorders of behavioral state; and (iv) reproductive steroids affect virtually every system implicated in the pathophysiology of depression. In the second half of the article, we discuss the diagnosis of the three reproductive endocrine-related mood disorders (premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression) and present evidence supporting the relevance of reproductive steroids to these conditions. Existing evidence suggests that changes in reproductive steroid levels during specific reproductive states (i.e., the premenstrual phase of the menstrual cycle, pregnancy, parturition, and the menopause transition) trigger affective dysregulation in susceptible women, thus suggesting the etiopathogenic relevance of these hormonal changes in reproductive mood disorders. Understanding the source of individual susceptibility is critical to both preventing the onset of illness and developing novel, individualized treatments for reproductive-related affective dysregulation.

Introduction

In this article, we pose and answer the following question: Is there evidence to support a role of reproductive steroids in the regulation of mood and behavior in women, and if so, what is the nature of that role? The primary female reproductive steroids, estrogen and progesterone, are derived from cholesterol, secreted by the ovaries, circulate in the bloodstream, and cross the blood-brain barrier. 17β-estradiol, the primary physiologic estrogen, varies over the menstrual cycle and powerfully affects behavior. More recent evidence suggests that estradiol and progesterone are not only capable of acute neuromodulatory effects (i.e., “neuroactive steroids”), but are actually synthesized in the brain, which has led to their inclusion in the group of “neurosteroid” compounds. In the first half of this article, we

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review evidence that the reproductive steroids estradiol and progesterone regulate biological systems and behaviors that are implicated in depression. This evidence is organized according to four major themes. First, the reproductive system powerfully regulates a variety of behaviors, including consummatory behavior (e.g., eating) and reproductive behavior (e.g., mate seeking, copulation). Second, both human and non-human animal studies demonstrate that reproductive steroids are potent neuroregulators from the subcellular to cellular level to neural circuits to behavior. Reproductive steroids organize and activate behavior across the lifespan, and their effects are observable across multiple units of analysis, from the most basic (e.g., cellular receptor function) to the most complex (e.g., cognition). Third, affective disorders are disorders of behavioral state. Depression, then, is not a collection of symptoms but rather represents a dysfunctional, self-organized, integrated ensemble of behaviors, perceptions, cognitions, and neurobiological characteristics (a "state"), the appearance of which reflects the activation or inhibition of specific brain cortical networks. The reproductive system is designed to powerfully regulate behavior states, as seen, for example, in the choreographing of sexual receptivity in concert with cyclic ovarian function. As such, changes in reproductive endocrine function have the capacity to precipitate a "switch" in behavioral state. Fourth, reproductive steroids affect virtually every system implicated in the pathophysiology of depression. For example, reproductive steroids regulate the neurotransmitters and neurosteroids implicated in depression as well as neuroplasticity, neuroprotection, neural circuit activity and synchronicity. They also regulate the HPA axis and immune function. Taken together, these lines of evidence suggest a role for reproductive steroids in the affective dysregulation that accompanies mood disorders in women.

In the second half of this article, we review the empirical literature on reproductive endocrine-related mood disorders, including premenstrual dysphoric disorder (PMDD), postpartum depression (PPD), and perimenopausal depression. Evidence supporting the relevance of reproductive steroids to these disorders is a focus of our review. This evidence comes from case-control studies of hormone changes and attendant mood symptoms and hormone manipulation, genetic, and neuroimaging studies. Despite accumulating evidence that reproductive steroids may trigger affective dysregulation in women susceptible to reproductive endocrine-related mood disorders, the source of individual susceptibility remains unclear. Future research in this area is critical to both preventing the onset of illness and developing novel, individualized treatments for affective disorders in women.

The Neuroregulatory Effects of Reproductive Steroid Hormones

Two key principles govern our understanding of the neuroregulatory effects of reproductive steroid hormones. The first principle is that behavior is a readout of central nervous system activity. Non-human animal studies have demonstrated that stimulation of specific brain regions and neurons affects behavior either directly or as an interactive process with other stimuli. For example, electrical stimulation of a key neuroendocrine region, the hypothalamus, in rats results in a number of hormone-mediated behaviors, including eating, drinking, and reproduction (25, 200, 212, 237), all reward-seeking behaviors. Electrical stimulation of the ventromedial nucleus of the hypothalamus facilitates the lordosis response in female rats outside the cycle phase when lordosis usually occurs (estrus) (212, 237).

Another example of how changes in the activity of specific brain regions or neurons can be shown to influence behavior involves stimulation of the neural reward circuitry. In vivo photostimulation of specific neurons that project to the ventral tegmental reward circuitry increases avoidant behavior (i.e., avoiding a chamber where shock had been delivered previously) and decreases reward (sucrose) seeking in mice (140), behavioral phenotypes that are both relevant to depression (88, 270) and modulated by estrogen (166,336).

The second principle is that, just as with any physiologic stimulus, reproductive steroid-related behavioral and neuroregulatory effects are highly context dependent (259, 261). The organizational and activational effects of reproductive steroids are time sensitive and developmental stage dependent. For example, in one study, exposure of Chinook salmon eggs to an aromatase inhibitor to prevent estradiol exposure for only 2 h during development when the gonads were bipotent created a fully functional phenotypic male from a genotypic female (238). Another example involves the initiation of hormone replacement therapy relative to the time since menopause. Some studies suggest that early initiation of hormone-replacement therapy reduces the risk of coronary heart disease (124,257), while other studies have shown that hormone replacement therapy initiated in older women with a longer time since menopause is associated with either no change in risk (123) or increased risk of coronary heart disease (256). Many effects of reproductive steroids also are sex specific (19, 69, 192). Estradiol administration followed by progesterone triggers a gonadotropin-releasing hormone (GnRH)-stimulated luteinizing hormone (LH) surge in females but not in males, leading some to conclude that the responsible hypothalamic GnRH neurons are hard-wired differently in males and females (108). Independent of differences in “wiring,” however, cells isolated from males and females may show very different responses to reproductive steroids administered in vitro (Fig. 1) (19,339,364). The target cell and tissue provide a context—estradiol, for example, increases the MAP (mitogen-activated protein) kinase signaling protein ERK1 in neurons but decreases it in glial cells in the rat brain (364, 365). The environment also determines the effect of reproductive steroids on the brain and behavior: in rats, maternal behavior (i.e., licking and grooming) increases estrogen sensitivity in the medial preoptic area of adult female offspring, which, in turn, promotes maternal behavior of the offspring (47,48). Finally, the genome clearly provides a context that determines the effects of reproductive steroids on brain and behavior. Maguire and Mody, for example, demonstrated a γ-aminobutyric acid A ($GABA_A$) receptor δ-subunit knockout mouse that displays no behavioral abnormalities until during and after pregnancy, at which time the dam exhibits depressive behavior and cannibalizes its offspring (181). Thus, hormonal states associated with reproduction may provoke affective dysregulation in the context of a genetic susceptibility. Careful attention to these contextual variables is essential for understanding the neurobiological sources of individual variation in behavior.

The reproductive system regulates behavior: from a teleological perspective, two systems that are critical for survival of the species are the appetitive (to obtain energy sources) and the reproductive systems. As such, it is critical that the behavioral repertoires for feeding and for sex be redundant, highly conserved, and compelling, as the associated behavioral outcomes are not optional (at the species level). As elegantly shown by Pfaff et al. (160, 236, 237), even “simple” reproductive behaviors like lordosis represent the complex integrative product of multiple signaling pathways, all with the intent of commandeering the attention,

motivation, social behavior, and motor behavior of the female rodent to facilitate reproduction. Given the CNS systems affected and the powerful demand characteristics of reproductive hormonal signaling (sex literally and figuratively commands our attention), it is hardly surprising that reproductive steroids play a major role in the regulation of many nonreproductive behaviors. Examples too numerous to comprehensively cite include the following:

Cognition.—Levels of estradiol determine the mode of cognition in female rats, such that females use hippocampal-sensitive strategies (i.e., use spatial cues) under conditions of high estradiol and striatal-sensitive strategies (i.e., remembering what the rat did in the last run through the maze) under conditions of low estradiol (157). Similarly, estradiol levels are associated with cognitive performance in human females. During the menstrual cycle, women show increased verbal abilities and decreased visual-spatial abilities when estradiol and progesterone levels are high and the opposite pattern when estradiol and progesterone levels are low (127), and estradiol levels are significantly correlated with neural activity in frontal and parietal areas during visual-spatial processing (278) and the left inferior frontal gyrus during verbal processing (55). Cognitive function declines during menopause (116), irrespective of age, which may result from estrogen's effects on synaptic organization of the prefrontal cortex, hippocampus, and dorsolateral prefrontal cortex (249, 319, 356, 357). Although support for estrogen's role in menopause-related cognitive decline has not been well supported by human studies, a clear role for estrogen in cognition has been demonstrated in non-human primate studies. For example, in aged non-human primates, ovariectomy induces spatial memory deficits, which are reversed with cyclic, low-dose estrogen treatment (249).

Motivation.—The tendency for humans to choose immediate rewards over larger, delayed rewards, called the "now bias," varies with frontal dopamine levels (294). Cyclic elevations in estradiol modulate dopamine levels in the prefrontal cortex, and as a result, impulsive behavior changes in response to changes in estrogen levels; as estrogen levels decrease, impulsive behavior increases (294).

Consummatory behavior.—Reproductive steroids regulate eating behavior. Food intake increases and locomotor activity decreases in certain female rodents following ovariectomy and the subsequent depletion of estradiol and progesterone, leading to eventual weight gain (354). However, estradiol replacement following ovariectomy can inhibit this weight gain (106,202,354). Moreover, eating behavior is regulated by cyclic changes in estrogen and progesterone levels in women (80,154).

Maternal behavior.—Estrogen and oxytocin modulate maternal licking and grooming behavior, pup gathering, and nest building in rodents (48). Late-follicular estrogen levels correlate with the reported ideal number of children, a measure of maternal tendency, in nulliparous women (167).

Motor behavior.—Reproductive steroids have both organizational and activational effects on motor behavior, and estrogen is necessary for the proper development of critical nervous

system sensorimotor behaviors (214). Specifically, exogenous administration of estrogen to prenatal rodents results in increased spontaneous motor activity in adulthood (77), suggesting that estrogen has organizational effects on sensorimotor development. Estrogen also has activational effects on motor behavior. In rodents, locomotor activity increases during estrus as estrogen levels rise [see (297) for a review]. Exogenous estradiol administration increases locomotion (e.g., running wheel activity) in mice, and this effect is mediated by estrogen receptor alpha (ERα) in the medial preoptic area (218). Progesterone administration similarly increases motor behavior in mice (i.e., horizontal crossings and open field entries) (100). In women, cyclic increases in estrogen are associated with increased motor coordination (128), and in postmenopausal women with Parkinson's disease, estrogen treatment improves motor abilities (327).

Sleep.—Sleep complaints are one of the most common symptoms related to the menopause transition (346). Declining estrogen levels that occur during the menopause transition are associated with more frequent awakenings and trouble falling asleep (161). Estrogen treatment, however, can improve the sleep disturbances, decrease the difficulty of initiating sleep, and decrease nocturnal restlessness and awakenings in peri- and postmenopausal women (240,320). Women who discontinue hormone therapy report an increase in the frequency of sleep problems once the therapy is suspended (326). However, further research may be needed to better understand the complex relationships between reproductive steroids and sleep, particularly during the menopause transition. Because the menopause transition is associated with numerous vasomotor symptoms, it is not clear whether the improvement in sleep quality is due to direct effects of estrogen therapy independent of the resolution of vasomotor symptoms. Additional evidence for the regulatory effects of hormones on sleep states can be found in animal studies. In ovariectomized rats, ovarian hormones affect recovery sleep differently than spontaneous sleep (66). When the rats are sleep-satiated, estradiol promotes arousal, but after sleep deprivation, both estradiol and progesterone facilitate rapid eye movement sleep (66).

Temperature regulation.—Estradiol and progesterone appear to have opposing effects on thermoregulation [see Charkoudian and Stachenfeld (49) for a comprehensive review]. In general, progesterone exposure increases and estradiol exposure decreases the thermoregulatory set point (305). Temperature regulation is perturbed during the transition to menopause. Perimenopausal estradiol withdrawal precipitates vasomotor symptoms (hot flushes) (255), and estradiol treatment alleviates these symptoms (217). Although these relationships have been well established, the mechanisms by which reproductive steroids influence thermoregulation are less clear (49).

From the subcellular to cellular to circuit to behavior, reproductive steroids are powerful neuroregulators. The classic mechanism of reproductive steroid action is genomic. Steroids are lipophilic and permeate the cell membrane to bind intracytoplasmic or intranuclear receptors. These receptors are transcription factors that can bind to response elements in the DNA and regulate gene expression, transcription, and protein synthesis. This classical view, while accurate, is hopelessly incomplete, because it is now clear that myriad other factors participate in the regulation and consequences of an activated receptor.

In addition to their intracellular location, steroid receptors exist on the cell membrane, where they rapidly regulate ion channel activity and activate signal transduction systems. Broadly labeled “nonclassical,” these activities were once regarded as of little consequence but are increasingly viewed as being of great physiologic importance, particularly with regard to understanding behavior. The particular relevance of the acute, nonclassical effects of estradiol and progesterone to behavior is twofold: First, reproductive steroids act like neurotransmitters in the brain, rapidly affecting brain function and behavior. Estradiol, for example, can be acutely and locally synthesized in nerve terminals and then released into the synapse where it can acutely mediate male rodent reproductive behavior (12). Second, estradiol and progesterone activate protein kinases that modify the steroid hormone receptor in such a way as to amplify its transcriptional effects upon further exposure or reexposure to the reproductive steroid (332, 333). As such, steroids sensitize targets to their own signal. Moreover, as a function of the role of intracellular signaling proteins in the activation of the steroid receptor, there is considerable cross talk between cellular growth factors, neurotransmitters, and steroid hormones. In some cases, neurotransmitters (e.g., dopamine) can directly activate the steroid receptor and mimic the effects of steroids even in their absence (241).

Effect of context

Adding another layer of complexity, the specific genomic and nonclassical actions of reproductive steroids are completely context-dependent. Steroid-activated receptors influence gene transcription by forming combinations with other intracellular proteins, including coregulators and cointegrators. Coregulators determine whether gene transcription is enhanced or suppressed by the activated receptor (176, 177, 223). Coregulators, of which over 350 have been identified, comprise coactivators, which associate with agonist bound receptors to stimulate gene transcription, and corepressors, which may associate with either unbound or antagonist bound receptors to inhibit gene transcription. Cointegrators allow activated receptors to regulate genomic expression through sites (e.g., activating protein [AP-1] binding site) other than the classical DNA hormone response elements by tethering the receptor to transcription factors (e.g., Jun, Fos, and ATF) that bind the DNA. Coregulators and cointegrators both contain enzymatic activity (e.g., histone acetylase) and recruit other coregulators and transcription factors to modify the chromatin structure and regulate transcription. Coregulators and cointegrators also exist in a tissue-specific fashion, and the availability of these proteins determines the transcriptional response to an activated hormone receptor, thus explaining how estrogen receptor modulators can act like agonists in some tissues and like antagonists in others (129). The diversity of hormone effects is further facilitated by the existence of different hormone receptor subtypes. The estrogen receptor, for example, has two major isoforms: ERα and estrogen receptor beta (ERβ). ERα and ERβ are encoded by separate genes, are found in different brain regions, and have different physiologic effects (133). Finally, as shown in Figure 2, reproductive steroids are synthesized from cholesterol, are highly homologous, and serve as precursors for one another. As a result, the presence and availability of enzymes that convert one steroid hormone to another markedly affect the amplitude and nature of the steroid signal. The effects of estrogen and progesterone are therefore dependent upon many factors that differ from cell to cell and tissue to tissue. These tissue-specific effects will become apparent in

our discussion of the effects of reproductive steroids on brain function and network dynamics, where the effects are dependent on the specific brain region and reproductive stage (e.g., menstrual phase or menopausal status), as well as on several other factors, including receptor density, prior exposure, and neuroregulatory milieu. Our discussion of the effects of reproductive steroids on brain tissue will focus on their relevance to regulating affective states. For additional information about steroid receptor structure, function, and distribution in the brain, the interested reader is encouraged to see excellent, recent reviews of these topics (40,188,193,196,343).

Reproductive Steroids: Regulators of Affective State

Affective and cognitive dysfunction in depression

Depression is defined by the presence of affective, cognitive, behavioral, and neurovegetative symptoms. Depressed mood and anhedonia are prominent (5). Other core symptoms include feelings of worthlessness and guilt, impaired concentration and decision-making, suicidality, insomnia, lassitude, appetite problems (i.e., appetite loss or gain), psychomotor agitation or retardation, and irritability (341). Major depressive disorder (MDD) is diagnosed when symptoms are present most of the day, nearly every day, for at least two weeks (5). Depressive disorders have an episodic course: roughly 25% of major depressive episodes (MDEs) remit within 2 months, and over 80% remit within one year, with or without treatment (54). Of those who experience remission, approximately 60% will also experience recurrence (335). Although multiple etiological models of depression exist, the most promising models account for the episodic nature of the illness. Specifically, many individuals respond to triggering events with characteristic increases in negative affect (i.e., sadness and anxiety), but for individuals with depression, these affective states are more persistent. One might therefore conclude that depression is the result of a faulty affective switch that, once triggered, gets “stuck.” According to cognitive theories of depression, this faulty switch is the result of information-processing biases: the experience of negative emotions results in the activation of critical contextual and self-evaluative thoughts, and an inability to disengage from these negative thoughts results in a persistent, depressed state (158), characterized by both heightened negative affect and suppressed positive affect. Importantly, negative and positive affect are dimensions that vary independently: negative affect can be high when positive affect is low or high (340), and the various combinations of high and low negative and positive affect are associated with different psychiatric disorders (342).

Negative affectivity is an emotional dimension of distress and dissatisfaction that contains a number of specific negative emotions, including sadness, guilt, fear, anger, and disgust. Negative affect is common to both depression and anxiety and accounts for their substantial comorbidity and sequential relation (52). Depression and anxiety disorders coexist at a much higher rate than that expected based on chance, and anxiety precedes depression just as often as depression precedes anxiety (199). Family and twin studies have shown that depression and anxiety share a genetic susceptibility to such an extent that they are indistinguishable (258). Thus, for an etiological model of depression to be useful, it must also account for

symptoms of anxiety, and as such, examining negative affectivity rather than sadness *per se* allows one to capture the range of emotional dysregulation that characterizes depression.

Anhedonia was first identified as a loss of the capacity to experience pleasure by Ribot in 1894. In the non-human animal literature, anhedonia is defined behaviorally as a deficit in hedonic behavior, including reduced intake in palatable solutions, reduced preference for palatable solutions, and reduced brain self-stimulation, which have been shown to respond to a variety of medications that treat depression in humans, including tricyclic antidepressants (e.g., desipramine) (205), selective serotonin reuptake inhibitors (SSRI) (e.g., citalopram) (310), and atypical antidepressants (e.g., mianserin) (204). In humans, anhedonia can be defined as an absence of positive affect (52), a notion that is more consistent with Ribot's original conceptualization of anhedonia than any definition since. Positive affect includes a range of positive mood states, including joy, energy, enthusiasm, interest, alertness, and self-confidence, that are diminished in patients with depression (342), schizophrenia (32), and certain personality disorders (51). However, low positive affect in combination with high negative affect is uniquely related to depression (342), and measures of positive and negative affect are sensitive to daily mood changes. Moreover, in individuals with MDD, positive affect increases following treatment with SSRIs (e.g., paroxetine) and serotonin-norepinephrine (NE) reuptake inhibitors (e.g., venlafaxine) (67), which is similar to the effects of antidepressant medication on anhedonic behavior in non-human animals.

In addition to affective dysregulation, depression is characterized by myriad cognitive abnormalities. Early cognitive theories of depression suggested that biased cognitive processing accounts for the onset, maintenance, and recurrence of depressive episodes (17, 18). In particular, depression was thought to be associated with impairments in perception, attention, and memory. Recent research in cognitive neuroscience has largely supported these theories. Depression is associated with impaired short-term (working) memory and long-term memory. In depressed mood states, the accessibility of mood-congruent material is increased, enabling those with a depressed mood to have improved memory for negatively valenced emotional material, compared with neutral material. However, while depressed individuals tend to remember negatively valenced emotional material as well as nondepressed individuals, they demonstrate impaired memory for neutral material (207). Individuals with depression have difficulty removing irrelevant negative material from their working memory (139,143,207). Furthermore, autobiographical memory specificity, or the ability to recall specific autobiographical memories of events less than one day ago, is reduced in individuals with depression (59). There is a positive relationship between depressed mood and impaired autobiographical memory specificity suggesting that as a depressed mood increases, memory impairments worsen (59).

The negative memory bias in depression can be accounted for by attentional biases (33). Mood-congruent attentional biases have been found in individuals with depression and dysphoria (114, 142, 159, 226). Individuals with depression maintain attention for negative words and mood-congruent (sad) faces and have difficulty disengaging from that negative information (114, 142, 159). This attentional bias to negative information may contribute to the continuous processing of negative information, such as rumination (159). Rumination, defined as the tendency to perseverate on negative emotions, characterizes chronic, severe

depression (216). Rumination is associated with increased interference from irrelevant negative material (143). This inability to dismiss irrelevant negative cognitions and memories may lead to difficulties with processing new information and a prolonged negative mood state.

In addition to memory and attention, depression may also influence problem solving, processing speed, reaction time, and decision-making. Depressive symptoms have been associated with impaired every-day problem-solving ability and less effective problem-solving solutions (71, 361). Induction of mild dysphoria reduces the problem-solving ability of formerly depressed individuals with a history of suicidal ideation (349). Increased depression severity is associated with reduced processing speed (191) and increased intraindividual reaction time variability (144). In addition, depressed individuals experience more decisional conflict (246) and score lower on decision-making skills (141) than those without depression. Overall, increased depressive symptoms have been associated with poor cognitive abilities and impaired executive function (15,72,191).

Effects of reproductive steroids on biological systems implicated in depression

Reproductive steroids affect virtually every system implicated in the pathophysiology of depression (260). Estradiol regulates the synthesis, metabolism, receptor concentration, and trafficking of neurotransmitters implicated in depression, including serotonin, dopamine, and NE. In animal studies, estradiol has been shown to inhibit serotonin transporter (SERT) mRNA (234), alter SERT protein levels and binding (26, 91, 194, 262, 312), increase serotonin (5-HT) 2A receptor binding and mRNA (313), facilitate imipramine-induced down regulation of 5-HT2 receptors (148), decrease activity of the 5-HT1A receptor, and increase the expression of 5-HT1A receptors (50, 323). In humans, prolactin increases following administration of the serotonergic agents meta-chlorophenylpiperazine (318) and buspirone (68) during the luteal phase compared with the follicular phase of the menstrual cycle, suggesting that reproductive hormones may modulate the serotonergic system. Further evidence comes from human imaging studies, where combined estrogen and progestin replacement is associated with increased 5-HT2A binding in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, and lateral orbitofrontal cortex (209). For a review of the possible role of these interactions in affective regulation, see Rubinow et al. (262).

Estrogens influence the synthesis, release, and metabolism of dopamine and can modulate dopamine receptor expression and function (289). However, the effects are complicated, with different studies demonstrating significant variations in the direction of effects and brain regions impacted (164). Several studies have demonstrated that estradiol increases dopamine release and receptor density in the striatum. During the rat estrous cycle, the density of striatal dopamine uptake sites is highest during proestrus (206), which coincides with peak estradiol (184) and dopamine levels (206). Also in rodents, pregnancy and lactation are associated with increased levels of dopamine and its primary metabolite DOPAC in striatal tissue (45). Ovariectomy reduces striatal dopamine receptor density (37), extracellular dopamine levels, and behaviors mediated by the striatal dopaminergic system [for a review see Becker (20)]. Estrogen treatment increases striatal dopamine receptor density (227), dopamine uptake sites in the striatum (206), dopamine release, and striatal

dopamine-mediated behaviors (20). Estradiol also modulates dopamine neuron activity in the ventral tegmental area (363), the effects of which are believed to modify the rewarding properties of reproductive states and facilitate reproductive success in female rats (20). In contrast, it is well established that estradiol exerts antidopaminergic effects on the anterior pituitary and hypothalamus. In the hypothalamus, estradiol inhibits the synthesis and activity of tyrosine hydroxylase (35, 230), the rate-limiting enzyme in dopamine synthesis, which results in decreased dopamine release to the anterior pituitary (57). Estradiol also inhibits anterior pituitary prolactin cell responsiveness to dopamine, which results in increased prolactin release (250). It has been suggested that the antidopaminergic effects of estrogen protect against schizophrenia in women of reproductive age, when the incidence is 40% lower in women than in men. Moreover, adjunctive treatment with estradiol has been shown to reduce positive and general symptoms of schizophrenia in regularly menstruating women (163).

Finally, reproductive steroids modulate noradrenergic system activity. Estradiol and progesterone influence NE synaptic communication in the hypothalamus, preoptic area, and cortex, although the effects are region-specific (89). In the hypothalamus and preoptic area, estrogen attenuates β-adrenergic and presynaptic α_2-adrenergic inhibition of NE release (89, 145, 235). Estrogen promotes NE release in the hypothalamus by stabilizing α_2-adrenenoceptor phosphorylation and uncoupling the receptor from G protein (330), rather than by regulating receptor density (89). In the cortex, estradiol regulates postsynaptic α_2-adrenenoceptors. In one study, estradiol treatment reduced cortical α_{2D}-adrenenoceptor messenger RNA by 50% compared with ovariectomized control animals, and this reduction was accompanied by a significant decrease in cortical α_2-adrenenoceptor density (146). The noradrenergic effects of estrogen in the frontal cortex are thought to explain hormonal modulation of cognitive function (146). For example, in young, ovariectomized rats, estrogen replacement amplifies the effects of stress on working memory by inhibiting the stimulation of NE α_2-adrenenoceptors (283), thus supporting a role for estrogen in both the affective and cognitive symptoms associated with depression.

Estrogen regulates the neuroplasticity processes implicated in depression. Brain-derived neurotrophic factor (BDNF) levels in the forebrain and hippocampus decrease following ovariectomy and increase with estradiol treatment (150, 302). Notably, BDNF levels decrease during periods of depression and stress and increase with antidepressant treatment (287). Estradiol treatment results in increased cyclic adenosine monophosphate response element-binding protein activity (365) and the neurotrophin receptor protein tyrosine kinase receptor type 1 (TrkA) (301) and type 2 (TrkB) (9), and it decreases glycogen synthase kinase-3 (GSK-3) beta activity (46) in rodents, similar to antidepressant medications. Estradiol increases hippocampal long-term potentiation and spine density (39), which contribute to synaptic plasticity. Of note, this regulation of hippocampal spine density is dependent on glutamate receptor (NMDA) signaling (358), which has also been implicated in the etiopathogenesis of depression (162, 183). In the amygdala, estradiol also increases BDNF, TrkB, and proline-rich receptor-like protein kinase 2 (pERK2), which is associated with decreased depressive-like behavior (101).

Estrogen plays a role in neuroprotection. Estrogen protects against oxidative damage, glutamate excess, and beta-amyloid toxicity (117,203,292,308) in hippocampal (190) and cortical neurons (43). Rapid neuroprotection by estradiol is partially mediated by G-protein-coupled receptor 30 (GPR30) and the subsequent downregulation of NMDA receptors (175). Interestingly, the neuroprotective effects of estradiol are sexually dimorphic and mediated by ERα (43). In a study of rat pups, pretreatment with 17β-estradiol protected female but not male cortical neurons from glutamate toxicity (43). Estradiol regulates cellular energetics by improving mitochondrial respiratory efficiency and prevents oxygen-free radicals that are thought to adversely affect mitochondrial energetics in depression (102, 103, 170). Estradiol can activate adenosine monophosphate kinase, an enzyme that plays a role in cellular regulation and homeostasis, through an ERβ-mediated effect (173). In mice, ovariectomy-induced loss of estrogen led to significant deficits in bioenergetics and accumulation of mitochondrial amyloid beta (Aβ), whereas estradiol treatment initiated at the time of ovariectomy prevented the deficits (360).

Depression is considered a stress-related disorder characterized by hypothalamic-pituitary-adrenal (HPA) axis hyper-activity (215). Estradiol modulates the HPA axis: estradiol regulates basal and stress-induced adrenocorticotropic hormone (ACTH) and cortisol in animals via its effects on the glucocorticoid receptor and corticotropin-releasing hormone (CRH) (266). As a result, it has been suggested that estrogen add-back therapy with the loss of ovarian function may help prevent potential HPA axis hyperactivity at menopause by decreasing ACTH and cortisol response to CRH (104). Nonetheless, unlike in rodents, it appears that progesterone rather than estradiol may be responsible for the increased HPA axis activity observed during the luteal phase of the menstrual cycle (251,252).

Depression is characterized by immune dysregulation and “inflammation.” Individuals with MDD have been shown to have higher circulating levels of proinflammatory cytokines, including tumor necrosis factor-α and interleukin (IL)-6 (73), and treatment with the cytokine interferon-alpha results in MDD in 50% of patients (245). As reviewed by Cunningham et al. (58), estradiol modulates immune system function. Estradiol regulates cytokine production and receptor expression, monocyte and macrophage function, activation of effector cells, and the number and function of dendritic cells and antigen presenting cells (58). Estradiol inhibits inflammation (178) and produces effects that are opposite to the proinflammatory immune alterations associated with depression (42,314). Further, estradiol protects against stress-induced increases in neuroinflammation in the hippocampus (244). Thus, irrespective of the molecular etiopathogenesis of depression, a possible role for reproductive steroids reasonably can be posited.

Network Neuroscience: Reproductive Steroids Regulate the Neural Networks Implicated in Depression

Affective disorders are characterized by dysregulation of mood, cognition, and behavior. There is no set of symptoms that universally and comprehensively identifies affective disorders, but certain disturbances appear with great frequency. As noted earlier, these include alterations in pleasure and in the assignment of affective “valence” to events, loss of

flexibility in changing mood state, negative self-image, disturbed interpretation of social interactions, reduced appetitive behavior, and reduced motivation for social interactions. Depressed patients see both positive events as less positive and negative events as more negative. All three domains affected by depression can be considered to result from deficient information processing, which in turn may reflect disturbed activity in or regulation of the neural networks giving rise to the neural computations underlying emergent behavioral and perceptual processes. Both structural and functional imaging studies provide strong evidence for abnormal neural processing in depression.

Brain regions often implicated in depression include the ACC, dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, amygdala, and hippocampus, which together form the frontolimbic “emotion processing” circuitry (92, 126, 155). For example, findings in depression include hypoactivity in the dorsolateral prefrontal cortex (62, 92) and hyperactivity in the subgenual ACC (75,186,187). Gray matter volumetric loss is observed in many of these same regions, including the rostral ACC and the posterior cingulate cortex, precuneus, prefrontal cortex (dorsolateral prefrontal cortex and dorsomedial prefrontal cortex), and orbitofrontal cortex (120). It is, however, the *interactions* of these and other brain regions that are the likely locus of dysfunction, and these interactions are described by structural, functional, and effective connectomics. Structural connectivity describes anatomical connections (usually of white matter and defined by diffusion tensor imaging), functional connectivity describes statistical patterns of dynamic interactions among brain regions, and effective connectivity refers to directed, causal effects. Brain regions that are functionally integrated in the service of responding to the environment constitute a network (229, 303), and these networks are degenerate; that is, one network can perform many functions, and one function can be performed by many networks (303). Examples of networks include dorsal and ventral attentional networks, frontosubcortical regulatory network [a mood regulation system (156)], central executive network (which regulates attention, decision making, working memory and involves the dorsolateral prefrontal cortex and the posterior parietal cortex) (198), mesolimbic reward circuitry, and resting state networks (60), including the default mode network (DMN) (93). Several of these networks have been described as dysfunctional in depression. First, the DMN is a resting state network that is active under nontask-driven conditions and involves the rostral ACC, posterior cingulate cortex, precuneus, medial prefrontal cortex, temporoparietal junction (inferior parietal and posterior temporal), plus, less frequently, hippocampus, medial temporal lobe, and lateral temporal cortex (93, 119, 185). The DMN has been reported to be upregulated in MDD (hyperactive during emotional processing, with increased glucose metabolism and cerebral blood flow) (119, 169, 284, 347). This upregulation would be consistent with impaired executive function and emotional regulation (seen in depression) and may be effectively targeted by deep brain stimulation, which is accompanied by symptom reduction and decreased subgenual ACC metabolism (187). The DMN is the substrate for reflective, self-referential associative thought (e.g., focus on feelings and thoughts, judging one’s own character, and rumination) (93). Increased connectivity has been observed in depression between the dorsomedial prefrontal cortex and regions of the DMN (ACC, posterior cingulate cortex/precuneus) as well as components of the Affective Network (ACC) and Cognitive Control Network (dorsolateral prefrontal cortex)—each of

which is implicated in emotional dysregulation and depression (285). This increased connectivity may represent the pathological linking of networks, resulting in the attentional shifts, excessive self-focus, cognitive interference, and autonomic dysregulation that characterize depression. Of note, although resting-state functional connectivity between the subgenual ACC and the hippocampus is increased in depressed patients, structural activity is decreased, suggesting that the functional changes may be compensatory (165). Further, many of the regions in the DMN showing significant changes in activation in depressed patients (e.g., ACC, posterior cingulate cortex, middle frontal cortex, and precuneus) are highly connected hubs, the most influential nodes responsible for regulating information transfer within and between networks. In contrast to the increased functional connectivity within the DMN, the central executive network shows significantly decreased functional connectivity in depressed patients, and response to treatment has been associated with modulating the connectivity between these and other networks implicated as dysfunctional in depression (174). Finally, synchronized neuronal oscillations in the alpha frequency (8–12Hz), which coordinate cortical:cortical and cortical:subcortical connectivity (and specifically modulate connections among the dorsal ACC, anterior insula, anterior PFC, and thalamus (264)), are increased in depression, consistent with the increased functional connectivity seen in the DMN and other resting state networks (119,122,171,366).

Reproductive steroids regulate many of the networks implicated in depression. The majority of research in this area focuses on the influence of reproductive steroids on brain function in adult women, and that will be the focus of our review of neural networks. Aside from activational effects of reproductive steroids, however, there are also organizational effects, although they have been less studied in relation to mood disorders. The classical organizational-activational model of hormone effects on brain development and function is being replaced by a parallel model that includes multiple sex-specific signals and pathways that unfold across the lifespan (189). Permanent differentiating (organizational) effects of reproductive steroids on neural systems have been studied in mouse models. The majority of these studies have shown that in the perinatal period of hormone sensitivity estradiol is masculinizing (albeit estradiol derived locally in the brain from testosterone) and exerts region-specific effects that include neurogenesis, neuroprotection, and apoptosis (189). Permanent differentiating effects of reproductive steroids may also occur at puberty and contribute to mood disorders in women (293); however, because systematic study of these effects in humans is not possible, these effects are not well understood.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of euthymic women have demonstrated that reproductive hormones modulate the neural circuits involved in normal mood states. Not surprisingly, these studies, which in general have small sample sizes, differ in their results, potentially as a function of differences in study design, sample age and reproductive status, means of varying hormone exposure (menstrual cycle phases vs. exogenous administration), length of hormone exposure, nature of hormone evaluated, exact timing of imaging relative to reproductive condition, levels of hormones achieved, nature of the stimulus (e.g., cognitive vs. affective), imaging methods, nature of imaging analysis (e.g., activation vs. connectivity), etc. Nonetheless, one can say the following: (i) in regional activation studies across the menstrual cycle, reproductive steroids impact the reactivity of the same brain regions

identified as dysfunctional in depression. For example, high-estrogen menstrual cycle phases have been associated with increased activation in the amygdala, medial orbitofrontal cortex, ACC (albeit inconsistently), medial frontal gyrus, inferior frontal gyrus, and hippocampus (7, 8, 16, 56, 111, 279, 345, 362). In a study by Protopopescu et al. (242), women showed increased activation of the medial orbitofrontal cortex and decreased activation of the lateral orbitofrontal cortex during the luteal phase compared with the follicular phase, which suggests the ability to evaluate behavioral responses on the basis of reward value may be regulated by reproductive hormones and impaired in the days prior to the onset of menses (81). Modulatory effects have also been observed during experimentally created hormonal states. A PET study of asymptomatic women showed decreased activation of the dorsolateral prefrontal cortex, inferior parietal lobule, and posterior inferior temporal cortex during leuprolide-induced hypogonadism, whereas the expected pattern of cortical activity returned following either estradiol or progesterone add-back (23). Studies of the effects of combined oral contraceptives have identified increased activity in the medial prefrontal cortex, ACC, dorsolateral prefrontal cortex, and inferior frontal gyrus (1,239,263), and decreased activity in posterior cingulate cortex, medial frontal gyrus, inferior frontal gyrus, and insula (1,109).

Effects of ovarian steroids on circuit function have been examined with studies of both neural functional connectivity and measurements of the coherence of network activation. Changes in connectivity on fMRI have been observed, again across the menstrual cycle or following hormonal intervention. Findings vary between studies, in part as a presumed consequence of differences in both probes (e.g., spatial vs. verbal tasks) and analytic methods. In comparisons between menstrual and luteal phases, functional connectivity between right temporal lobe and left inferior parietal lobe is higher in the luteal phase (344), while that between the right middle frontal gyrus and the left inferior parietal cortex is stronger (more negative; i.e. greater lateralization) during menses (322,345). Despite inconsistencies, data suggest that interactions within and between hemispheres and between cortical and subcortical regions vary as a function of menstrual cycle phase (322). These altered functional relationships may be reflected in the observation that alpha asymmetry, observed as disturbed in several mood disorders, is altered by menstrual cycle phase (although again contradictory results exist). Further, at a circuit level, reproductive hormones regulate neural reward circuitry in humans, with increased activity in the superior orbitofrontal cortex and amygdala during reward anticipation and in the midbrain, striatum, and left ventrolateral prefrontal cortex during reward delivery in the follicular phase (compared with the luteal phase) (74). Changes in connectivity following exogenous administration of reproductive steroids include the following: estradiol-induced increased effective connectivity between the right hippocampus and both the right superior and medial PFC (225) as well as between the amygdala and both temporal and prefrontal cortices (224); progesterone-induced decreased connectivity between the amygdala and fusiform gyrus and increased connectivity between the amygdala and the ACC (350); and estrogen-induced increased connectivity between the thalamus and basal ganglia (149).

While the canonical circuits described earlier are often investigated hemodynamically via blood-oxygen-level-dependent imaging (219), parallel electroencephalography (EEG) research aims to understand the temporal association and dissociation of circuits and their modulation by sex steroids. EEG is used to create a visual representation of the brain's

endogenous electric fields, which are dynamic in nature and influenced by circuit-level activity (99). Similar to fMRI, EEG is capable of implicating circuits in processes of cognition, emotion, and in the case of many mood disorders and pathological affective states (151, 213, 338). The best characterized patterns of activity, or oscillations, are within the alpha band, which spans the frequency of 8 to 12 Hertz (Hz) and is related to attentional modulation (153). Aberrant oscillations have been identified as potential biomarkers for affective disorders (321), and EEG-recorded cortical activity is dynamic with respect to ovarian hormonal milieu (41).

Though the data are far less abundant than that of fMRI, varying activation patterns across the menstrual cycle have also been observed using EEG (27, 41, 195, 253). Due likely to lack of hormonal confirmation of phase and variance of tasks, the results of these studies are somewhat conflicting. Nonetheless, cortical dynamics may be altered at specific time points in the menstrual cycle, as indicated by interhemispheric transfer time (131), attentional blink (138) and resting state alpha oscillation (41). Of these observations, the latter is particularly compelling, as hemispheric asymmetry in the alpha band has been identified in numerous psychiatric conditions, including depression (63, 134), social anxiety disorder (208), panic disorder (352), and PMDD (10, 172). A model by Davidson (61) describes this phenomenon as a result of lateralization of emotion processing, wherein positive emotions activate the left PFC, and negative emotions the right. In support of this model, both individuals with depression and those with PMDD show greater alpha oscillation power in the left hemisphere than the right (10, 134). The relationship between alpha oscillation and neural activation is inverse, such that the left-skew of power (greater alpha oscillations in the left hemisphere) in individuals with depression represents decreased activity in the left hemisphere, which has also been demonstrated via fMRI (121). Further, alpha asymmetry induced in healthy controls viewing footage of disaster returns quickly to baseline, but more pronounced asymmetry predicted mood deterioration during the following week (228). Alpha asymmetry can be used to differentiate those in remission from depression from those who were never depressed (4, 63, 113, 135, 307), suggesting its potential as a depression biomarker.

The ability of reproductive hormone changes to provoke depressive symptoms may occur as a result of the affect regulatory effects of neurosteroids. Neurosteroids are steroid hormone metabolites that are synthesized in the brain and modulate the inhibitory and excitatory neurotransmitters GABA and glutamate, respectively. Neurosteroids identified as most relevant to depression are dehydroepiandrosterone (DHEA) and allopregnanolone (ALLO). Blunted DHEA secretion is associated with MDD (112, 137, 197, 274, 359), and DHEA administration has antidepressant effects (271,355). ALLO, a progesterone metabolite, also has been implicated in depression and is particularly relevant to reproductive mood disorders. Several lines of evidence suggest a role for ALLO in triggering affective dysregulation. In rodents, ALLO regulates the GABA receptor (182) and has anxiolytic effects (29,30,348). ALLO withdrawal results in anxiety behaviors and insensitivity to benzodiazepines (298,299). In humans, depression is associated with decreased circulating ALLO levels, and successful antidepressant treatment is associated with increased ALLO (87,254,280,282,311,331). ALLO has been shown to regulate the basic neurobiological systems that are dysregulated in MDD, including the HPA axis (14,147,231,232), the

immune system (132), and neuroprotection (70, 267). ALLO also modulates the limbic system (3,31), which, as described previously, has been implicated in MDD.

The Role of Gonadal Steroids in Reproductive Mood Disorders

Reproductive mood disorders are characterized by affective dysregulation and functional impairment that occur during specific reproductive states (e.g., the premenstrual phase of the menstrual cycle, pregnancy, parturition, and the transition to menopause). Dysregulated affect in reproductive mood disorders includes increased negative affect (i.e., irritability, anger, sadness, and anxiety), decreased positive affect (i.e., anhedonia), and affective lability (233,329), while functional impairment is defined by clinically significant distress or disability in social, occupational, or other important activities (6). Reproductive mood disorders include PMDD, PPD, and perimenopausal depression.

Premenstrual dysphoric disorder

Diagnosis—PMDD is a reproductive mood disorder that affects 2% to 5% of women and is characterized by a recurrent, predictable pattern of distressing emotional and somatic symptoms that begin during the mid- to late-luteal phase of the menstrual cycle, when estradiol and progesterone levels are relatively high, and remit after the onset of menses, when estradiol and progesterone levels are relatively low and stable (86). In research conducted by our team, PMDD diagnosis required prospective daily assessment of mood symptoms over the course of three consecutive menstrual cycles. PMDD was defined by a 30% increase (relative to the range of the scale employed) in mean negative mood symptoms during the week before menses compared with the week after menses, a more stringent criterion than that of the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (5). For the purpose of this review, we will use the term PMDD to refer to both premenstrual dysphoria (the term used prior to DSM-5) and DSM-5 PMDD.

The effect of cyclic changes in gonadal steroids on mood in PMDD—The physiology of the hypothalamic-pituitary-gonadal (HPG) axis, which regulates the menstrual cycle, is well understood (94) and illustrated in Figure 3. In brief, under the control of the hypothalamic GnRH, both follicle-stimulating hormone (FSH) and LH are released from the pituitary. During the first “half” of the menstrual cycle—the follicular phase—FSH stimulates the progressive growth of ovarian follicles. One follicle becomes dominant and, toward the end of the follicular phase, releases dramatically increased levels of estradiol. This “spike” of estradiol exerts positive feedback on the pituitary and results in a peak of LH, which is followed by the release of an egg from the mature follicle, ovulation. Following ovulation, the remaining part of the mature follicle undergoes “luteinization” and, under control of LH, secretes progressively increased levels of progesterone and estradiol. About midway through the luteal phase, which lasts for 14 ± 2 days, the corpus luteum involutes, progesterone (and estradiol) levels drop, which signals the shedding of the endometrium (uterine lining) or menstruation, which lasts for approximately five days. By convention, the onset of menses is designated the first day of the menstrual cycle. (If fertilization occurs, the corpus luteum is sustained by human chorionic gonadotropin and menses does not occur.) Because PMDD symptoms occur in predictable patterns relative to

menses (i.e., heightened symptoms during the week before menses compared with the week after menses), many have speculated that estrogen, progesterone, or their combination trigger mood symptoms. As a rule, basal hormone studies of PMDD, and of reproductive mood disorders in general, have been singularly unrevealing, with no consistently observed differences between patients and controls. Indeed, there is virtually no convincing evidence for a hormone abnormality in PMDD. Reproductive steroids can, nonetheless, be demonstrated to trigger affective dysregulation, albeit in the context of an antecedent susceptibility.

In a study employing GnRH agonist-induced ovarian suppression and hormone add-back, Schmidt et al. (276) demonstrated that elimination of the menstrual cycle eliminated PMDD symptoms, while estradiol and progesterone add-back precipitated symptom return. The same hormone manipulation had no mood effects in women lacking a history of PMDD (Fig. 4). Thus, ovarian steroids triggered PMDD symptoms, but only in a group of women that were otherwise susceptible to the mood destabilizing effects of estradiol and progesterone. Finally, in a recently completed study employing ovarian suppression and continuous hormone add-back for three months, Schmidt et al. (unpublished data) demonstrated that it was the change in hormone and not the hormone level itself that was the critical signal in precipitating affective symptoms in women with a history of PMDD. While the precise mechanisms by which the change in hormone levels provokes affective symptoms in PMDD remain unclear, studies in rodents demonstrate that dramatic behavioral changes can be precipitated by acute changes in levels of neurosteroids (286,300).

Neurosteroid regulation of mood in PMDD—The majority of neurosteroid research in PMDD has focused on the progesterone metabolite ALLO, a potent GABA receptor regulator. For comprehensive reviews of the role of neurosteroids and neuroactive steroids in affective disorders see (76) and (281). Researchers have examined abnormalities in circulating ALLO in PMDD with varying results. Although several investigators observed decreased serum ALLO levels in women with PMDD compared with controls on menstrual cycle day 26 (248), during the luteal phase only (201), or during the follicular phase only (28), women with PMDD in two of these studies (28, 201) had lower progesterone levels, which likely accounts for their lower ALLO levels. This explanation is supported by Girdler et al.'s (110) observation that women with PMDD had both higher progesterone and ALLO levels than controls during the luteal phase. Successful treatment with antidepressant medication was associated with reduced ALLO levels in a study by Freeman et al. (97), but it is unclear whether baseline differences in ALLO or progesterone may account for this finding. Other studies showed neither diagnosis-related differences in ALLO or pregnanolone (277,337) nor any difference in ALLO levels in women with PMDD before and after successful treatment with citalopram (315). The use of different assays, antibodies, and methods of extraction across studies may account for some the variability in findings. Nonetheless, there is no reliable evidence that peripheral ALLO levels distinguish those with PMDD from those without.

In the absence of consistent basal neurosteroid abnormalities in PMDD, researchers have examined the response to various challenges, including the administration of neurosteroids, benzodiazepines, and mental stress. One reliable neurophysiologic measure of $GABA_A$

receptor sensitivity is saccadic eye velocity, which characterizes the speed of eye movements that bring the retinal image being viewed onto the fovea. Saccadic eye velocity is correlated with self-reported sedation and suppressed by benzodiazepines (316). Women with PMDD show differences from controls in pregnanolone-modulated saccadic eye velocity and sedation in the luteal phase (316), although these differences may be attributable to saccadic eye velocity response to vehicle in those with PMDD and blunted sedation in controls during the follicular phase. Patients with severe PMDD show blunted saccadic eye velocity and sedation responses to the $GABA_A$ receptor modulators pregnanolone and midazolam compared with women with less severe PMDD (316, 316), which may indicate an altered profile of $GABA_A$ receptor subunits. Midazolam insensitivity, in particular, could suggest increased expression of the α-and/or δ-subunits (317). However, neurosteroid levels were not reported for women with more or less severe PMDD, making it difficult to draw conclusions about whether the effects may have been attributable to variation in baseline hormone levels, given the risk of increased sampling variability with small samples ($n = 6$). Although women with PMDD also show a blunted ALLO response to stress (110), as mentioned earlier, the lack of an expected increase in ALLO following stress may be attributed to elevated progesterone and ALLO levels at baseline in the women with PMDD compared with controls. Similarly, women with PMDD demonstrate altered metabolism of progesterone to ALLO (152), although women with PMDD had an elevated ALLO/progesterone ratio at baseline, and women with PMDD and controls showed the same pattern of results following progesterone administration (152). The concept of altered steroidogenesis conferring vulnerability to reproductive-related illness is supported by research in polycystic ovarian syndrome, which is characterized by enhanced peripheral 5α-reductase activity and results in hyperandrogenism (90) and attendant behavioral symptoms, including depression and anxiety (64). Steroid synthesis may be similarly altered in PMDD such that mood symptoms result from decreased enzymatic conversion of progesterone to ALLO by 5α-reductase and 3α-hydroxysteroid dehydrogenase (3α-HSD) (Fig. 1). One potential mechanism that could account for differential enzymatic metabolism of progesterone to ALLO is suggested by Borolato et al. (36). They demonstrated that early life stress reduces the expression of 5α-reductase isoforms in the rat nucleus accumbens and medial prefrontal cortex, thereby reducing the synthesis of ALLO from progesterone.

Finally, possible ALLO abnormalities in PMDD also have been examined through inspection of the timing of symptom onset or exacerbation relative to changes in ALLO levels. As with progesterone, circulating ALLO levels fluctuate over the course of the menstrual cycle because ALLO is a progesterone metabolite. As such, plasma ALLO concentrations are highest during the mid-luteal phase, decline to low levels in the premenstrual phase and follicular phase, and are correlated with progesterone levels in healthy women (107, 277). Because of the potent anxiolytic effects of ALLO, one would expect decreased mood symptoms during periods of elevated progesterone and ALLO levels (i.e., the mid-luteal phase of the menstrual cycle). However, PMDD symptoms emerge during the mid-luteal phase (during elevated ALLO concentrations) and remit after the onset of menses (during decreased ALLO concentrations) (233). Other hypothesis-contradicting observations include the following: progesterone administration is either ineffective or exacerbates affective symptoms in women with PMDD (95, 96, 265, 276, 324); and drugs

that prevent ovulation, and thus prevent the subsequent increase in progesterone and ALLO levels, prevent PMDD symptoms (276).

Although the timing of symptom onset and response to progesterone administration in PMDD seemingly conflict with the literature on the anxiolytic effects of ALLO, an animal model of ALLO function in PMDD explains how increasing circulating progesterone levels may trigger affective dysregulation in susceptible women. Smith et al. (300) demonstrated that under certain hormonal and behavioral conditions ALLO exerts anxiogenic effects. ALLO withdrawal followed by ALLO administration results in anxiogenesis in response to an aversive stimulus. This effect is mediated by an increase in $GABA_A$ receptor α4 expression, which is associated with insensitivity to the benzodiazepine agonist lorazepam (300). Thus, ALLO withdrawal modifies the $GABA_A$ receptor such that the reintroduction of ALLO, in combination with an aversive stimulus, triggers hippocampal excitability rather than inhibition, resulting in an amplified stress response. One possible cellular mechanism for the abnormal response to ALLO administration after ALLO withdrawal is presented by Shen et al. (286), in which a particular configuration of subunits (α4β2δ) of $GABA_A$ receptors, a configuration induced by changes in ALLO levels, reverses the effects of ALLO from enhancing to inhibiting GABA-gated current. Thus, ALLO released as a result of an aversive stimulus during the luteal phase (and following the rise in ALLO post ovulation) may paradoxically increase negative mood symptoms. These findings may help explain the timing of affective symptom onset during the luteal phase of the menstrual cycle and during pregnancy, the negative mood effects of progesterone administration in both PMDD and PPD, and the salutary effects of ovulation suppression in women PMDD.

Consistent with these models, women with PMDD show abnormalities in cortical inhibition and GABA levels across the menstrual cycle. Cerebral cortical inhibition increases during the luteal phase in healthy control women, a presumed effect of increased ALLO levels and a finding that is absent in women with PMDD (295,296). Women with PMDD show reduced GABA levels in the occipital cortex during the follicular phase and increasing levels from the follicular to the luteal phase, whereas healthy controls show decreasing levels from the follicular to the luteal phase (84). Healthy control women also show a significant negative association between ALLO and cortical GABA levels, whereas women with PMDD do not (84), suggesting a luteal phase-specific reduction in GABA receptor function. Taken together, these findings are consistent with an abnormal response to ALLO in women with PMDD.

Reanalysis of existing data from our prior studies also supports the role of ALLO in PMDD. We examined ALLO levels and depressive symptoms in a previous study of ovarian suppression with depot leuprolide acetate (a GnRH agonist) and subsequent progesterone add-back in women with PMDD (276). During progesterone add-back (i.e., when progesterone levels were held steady), ALLO levels declined significantly in those with PMDD but not in controls (269). In addition, the change in ALLO was negatively associated with premenstrual symptoms in women with PMDD but not in controls, which suggests that declining levels of ALLO worsened symptoms in those with PMDD.

ALLO acts on $GABA_A$ receptors (29), which are present throughout the cortex and limbic system (38,136). Infusion of ALLO into the amygdala has antidepressant effects in rodents (83, 288). In healthy, euthymic women, progesterone administration increases amygdala connectivity to the dorsomedial prefrontal cortex similar to antidepressant medication (351). Pregnenolone administration (leading to increased ALLO levels) reduces amygdala and insula activity, increases dorsomedial prefrontal cortex activity, and increases connectivity between the amygdala and dorsomedial prefrontal cortex (304). However, the influence of ALLO on neural circuits implicated in depression has not been studied in women with PMDD, who, based on the ALLO findings presented earlier, may show the opposite pattern of results. Nonetheless, the existing research on reproductive steroid and neurosteroid regulation of mood provides important clues for understanding the role of neural networks in PMDD.

Neuroimaging in PMDD—Brain imaging (e.g., EEG, fMRI, or PET) has been employed to detect abnormalities that distinguish women with PMDD from healthy, regularly menstruating control women. Using EEG, Baehr et al. (10) demonstrated that women with PMDD had greater cerebral asymmetry during the luteal phase compared with the follicular phase, a pattern that was absent in control women. As described earlier, this result is consistent with prior EEG research linking cortical asymmetry, left frontal hypoactivity, behavioral approach deficits, and MDD (61, 325) and is also consistent with the temporal pattern of mood symptoms in PMDD, which are confined to the luteal phase and distinguish PMDD from MDD. In two independent fMRI studies, women with PMDD showed increased amygdala responses to negative stimuli when compared with healthy control women (109, 243), implicating the frontolimbic “emotion processing” circuitry in PMDD. Other studies have demonstrated that PMDD is characterized by decreased responsiveness to behavioral inhibition in the medial orbitofrontal cortex during the premenstrual phase (243), increased right cerebellar blood flow during the luteal phase compared with the follicular phase (247), and decreased activity of the left insula during the follicular phase (both compared with controls and with the luteal phase) (13). To directly assess whether reproductive steroids influence brain function in PMDD, Baller et al. (11) (Fig. 5) examined brain responsivity to a working memory task using fMRI and PET under conditions of experimentally induced hypogonadism, estradiol add-back, and progesterone add-back in women with and without PMDD. Across all hormone conditions, women with PMDD showed greater activation of the dorsolateral prefrontal cortex, medial prefrontal gyrus, and cerebellum. Among the women with PMDD, dorsolateral prefrontal cortex activation was associated with lower global assessment of functioning, earlier age of onset, and greater preintervention menses-related changes in negative affect (11). Taken together, these findings suggest that PMDD is characterized by a combination of stable, trait-like functional abnormalities in the dorsolateral prefrontal cortex and amygdala, areas responsible for cognitive, emotional, and social functions, as well as menstrual phase-specific abnormalities that may result from changing reproductive steroid levels. The focus of imaging studies thus far have largely relied on whole-brain and region-of-interest analyses designed to examine activity of individual brain areas. The future demand, however, will be on a network neuroscience approach to understanding how the neural networks implicated in depression are regulated by neurosteroids and neuroactive steroids in those with and without PMDD.

Postpartum depression

Diagnosis—According to the DSM-5, PPD is defined as a MDE beginning either during pregnancy or within the first four weeks following delivery (6). Although PPD is only distinguished from MDE by the timing of onset (i.e., they share the diagnostic criteria of persistent sadness, anhedonia, sleep disturbance, appetite change, psychomotor agitation/retardation, lethargy, impaired cognition, feelings of worthlessness or guilt, and suicidal ideation) (6), psychomotor agitation and impaired concentration/decision-making have been shown to be prominent symptoms of PPD, whereas sadness, suicidal ideation, and anhedonia are prominent symptoms of non-perinatal MDD (24). PPD also is characterized by mood fluctuations and preoccupation with infant health. In addition, the majority of women with PPD have a comorbid anxiety disorder, and symptoms commonly associated with PPD include generalized anxiety symptoms, panic attacks, and rumination (353). Approximately 20% of women experience a clinically significant depressive episode (i.e., either a minor depressive episode or a MDE) and 7% meet full diagnostic criteria for a MDE within three months postpartum (105). Although nearly every study conducted to date suggests that PPD is not more common than nonpregnancy-related MDD (220), one large epidemiological study demonstrated that the postpartum period is associated with an increased risk of depression (334).

The effect of perinatal changes in gonadal steroids on mood in PPD—Many have hypothesized that reproductive steroids play an etiological role in PPD (221) because the precipitous drop in hormone concentrations that occur at childbirth are temporally associated with the reported onset of depressive symptoms in the majority of women with PPD (268, 309). Progesterone initially is produced by the corpus luteum, until about the tenth week of gestation when the placenta becomes the primary source of progesterone. Circulating progesterone, derived from maternal cholesterol, increases progressively from 10 ng/mL in early pregnancy to 100 to 200 ng/mL at term. ALLO also increases about 10-fold during pregnancy. Estrogen hormones, first derived from maternal then from fetal androgens, are synthesized by the placenta during pregnancy. Estradiol and estrone increase 100-fold during pregnancy, while estriol increases about one thousand-fold. Estradiol drops to prepregnancy, follicular phase levels immediately following delivery. Despite the dramatic changes in reproductive steroids during and after pregnancy and substantial interindividual differences in absolute circulating steroid levels, there is no reliable evidence that women who develop PPD have blunted postpartum hormone levels or experience greater or more rapid reductions in reproductive hormone levels at delivery than women without PPD.

Treatment studies involving the administration of exogenous estradiol to women with active PPD symptoms or those at high risk for PPD have suggested a role for reproductive hormones in the pathogenesis of PPD. Sichel et al. (290) conducted a prevention study in which they treated 11 women a history of PPD with Premarin, a conjugated equine estrogen, starting just after delivery to prevent the precipitous drop in estradiol and the onset of MDD. Almost all (10 out of 11) of the women remained free of depression in the first year post-partum (290). A couple of small treatment studies have been conducted in women with current PPD. Gregoire et al. (118) showed that those randomly assigned to receive transdermal estradiol treatment ($n = 34$) improved significantly more than those who

received placebo (n = 27). However, it is worth noting that nearly half the participants received concurrent antidepressant treatment. Ahokas et al. (2) conducted a subsequent treatment study examining the effects of short-term (8 week) sublingual estradiol on depressive symptoms in 23 women with severe PPD. Many of the women in the study were considered treatment resistant and hypogonadal based on their serum estradiol concentrations. Depressive symptoms significantly decreased after the first week of treatment, and by the end of the eighth week, all of the participants had achieved remission based on their depressive symptom scores. Results of this study suggest that low or decreasing estradiol levels may contribute to or maintain depressive symptoms in susceptible women, while stable or increasing estradiol levels may ameliorate depressive symptoms. While these treatment studies support the notion that estradiol plays a role in PPD, they have low statistical power, lack control groups, and were conducted with a heterogeneous sample of women (i.e., those with and without exposure to antidepressant medication; those with depression onset before, during, or after pregnancy; those with and without "hypogonadism"). In addition, the stress, sleep deprivation, and homeostatic fluctuations that occur during pregnancy and parturition are important confounds that limit the ability to draw definitive conclusions about the role of estrogen in PPD based on these studies.

To isolate the effects of reproductive steroids on mood symptoms, Bloch et al. (34) mimicked the hormone profile of pregnancy and the postpartum in nonpregnant, asymptomatic women with a history of PPD and those without such a history by administering high-dose estradiol and progesterone during ovarian suppression followed by placebo only (to induce hormone withdrawal). Despite identical hormonal conditions, women with a history of PPD showed increased mood symptoms during estradiol and progesterone add-back and a further exacerbation of mood symptoms during hormone withdrawal, whereas those without a history of PPD showed no change in mood (Fig. 6). Similar to research in PMDD, the precise mechanism by which changing estradiol and progesterone trigger affective dysregulation is unclear.

Neurosteroid regulation of mood in PPD—The neurosteroid ALLO may play a role in PPD, albeit a paradoxical one. PPD most commonly begins during pregnancy (when ALLO levels are relatively high) (115), and anxiety and depressive symptoms during pregnancy are the strongest predictors of PPD (222). Epperson et al. (85) demonstrated that the postpartum period is associated with decreased cortical GABA and ALLO compared with the follicular phase, and this effect was seen in postpartum women regardless of whether they experienced mood disturbance. Treatment with progestin (norethisterone enanthate, also known as the "mini pill"), which is thought to increase circulating ALLO levels, has been shown to increase depressive symptoms in the post-natal period (168). However, compared with the untreated control group, circulating progesterone levels were lower in those administered norethisterone (168), and thus, ALLO levels would have been lower as well. Progesterone administered in combination with estradiol precipitates depressive symptoms in women with a history of PPD (34), suggesting that ALLO may have role in provoking symptoms, albeit an indirect one. Although these findings run counter to the literature demonstrating that ALLO is a potent anxiolytic and antidepressant, animal

models help explain the emergence of depressive symptoms in the context of reproductive steroid withdrawal.

As mentioned earlier, Maguire and Mody (181) demonstrated a $GABA_A$ receptor δ-subunit knockout mouse that displays no behavioral abnormalities until during and after pregnancy, at which point the dam exhibits depressive behavior and cannibalizes its offspring (181). Thus, in the context of a genetic susceptibility, hormonal states associated with reproduction may provoke affective dysregulation. Reproductive hormone changes that occur during pregnancy and parturition alter the $GABA_A$ receptor δ-subunit (179–181). As ALLO levels increase during pregnancy, $GABA_A$ receptor δ-subunit expression is downregulated, and as ALLO levels rapidly decrease after delivery, $GABA_A$ receptor δ-subunit is recovered (179). The knockout animal's inability to regulate the $GABA_A$ receptor δ-subunit during pregnancy and the postpartum results in behavioral abnormalities consistent with PPD (Fig. 7). Thus, similar to women with PPD, $GABA_A$ receptor δ-subunit knock-out mice exhibit no behavioral abnormalities before pregnancy, but they are insensitive to ALLO during pregnancy and show behavioral abnormalities consistent with anxiety and depression after pregnancy (181). This model demonstrates that changes in circulating ALLO levels are capable of triggering depression in the context of a genetic susceptibility.

Neuroimaging in PPD—PPD is associated with decreased resting state functional connectivity between the ACC, amygdala, hippocampus, and dorsolateral prefrontal cortex in the context of falling progesterone and ALLO levels in the postpartum period (65). Notably, PPD is characterized by functional abnormalities of the same brain areas seen in nonpuerperal MDD: the amygdala, insula, striatum, orbitofrontal cortex, and dorsomedial prefrontal cortex (210,211,291). PPD also is associated with decreased connectivity between the amygdala and prefrontal cortex, which suggests emotion processing (corticolimbic) network dysfunction is involved in the pathophysiology of PPD (211). The majority of neuroimaging studies of PPD have included women with histories of both PPD and nonpuerperal depression. As we make the case here, reproductive mood disorders like PPD may have neuroendocrine triggers that are distinct from the etiopathology of nonpuerperal depression. As such, results of prior imaging studies are difficult to interpret in the context of a hypothesized neuroendocrine trigger. As reviewed here, however, the human literature provides evidence of a hormone-sensitive PPD subtype that is characterized by behavioral (affective) and neural dysregulation present only during pregnancy and the postpartum period in the context of rapid changes in reproductive steroid concentrations. A future direction of this line of research is to examine the effects of reproductive steroid changes on the functional neural networks implicated in depression in women susceptible to PPD.

Perimenopausal depression

Diagnosis—Perimenopausal depression is not recognized formally in the diagnostic nomenclature. Our research team has defined perimenopausal depression as MDD with an onset temporally associated with menstrual cycle irregularity and elevated FSH in women age 45 or older. The risk of new onset depression increases twofold during the menopause transition (53, 98). Prior research suggests that women with a longer transition to menopause, vasomotor symptoms, stressful life events proximate to the menopause

transition, histories of depression (i.e., MDD, PPD, or PMDD), poor physical health, histories of smoking, disrupted sleep, reduced parity, and those who are unmarried are at increased risk of developing perimenopausal depression.

The effect of perimenopausal changes in gonadal steroids on mood—The Stages of Reproductive Aging Workshop (STRAW) criteria (130) are used to define 10 discrete stages of the menopause transition (Fig. 8). During the early stages of reproductive aging (sometimes called the “premenopause”), the menstrual cycle is regular and FSH levels remain normal. As women approach the menopausal transition, they enter the “late reproductive stage” (STRAW stage-3a), which is characterized by subtle changes in menstrual flow and the length of the menstrual cycle and variable FSH levels. The menopause transition (the “perimenopause”) includes both the early and late stages. The early menopause transition (STRAW stage-2) occurs when a woman experiences a change of 7 or more days in the length of consecutive menstrual cycles and FSH levels begin to rise. Prior research suggests that FSH levels begin to rise and estradiol levels begin to fall about 2 years before the final menstrual period (44, 84), but the length of early menopause transition is variable (130). The late menopause transition (STRAW stage-1) is characterized by amenorrhea of 60 days or longer accompanied by an FSH level greater than 25 IU/L and lasts between one and three years. Women often begin experiencing vasomotor symptoms (hot flashes, night sweats) during this time. Menopause is defined as the permanent end of menstruation for 12 months accompanied by the loss of ovarian activity. The postmenopause occurs after the final menstrual period and involves continuous decline of ovarian hormones but steady, elevated levels of FSH. Given the reproductive steroid variability and withdrawal in the transition to menopause, some have hypothesized a role for estrogen and progesterone in perimenopausal depression.

In a 5-year longitudinal study of 29 women, a 14-fold increase in MDD was observed in the 24 months surrounding menopause (273). In a larger cross sectional study ($N = 116$), depressive episodes were more likely during the late perimenopause compared with the pre-, early-, and postmenopause (306). Although estradiol levels are highly variable in regularly cycling women and during premenopause and early perimenopause, the average level of circulating estradiol declines dramatically during the transition from early to late perimenopause (44), which is accompanied by an increased incidence of depression (273, 306). In a large study of perimenopausal women, greater variability in estradiol concentrations, and not absolute estradiol concentrations per se, was associated with both elevated depression symptom severity as well as diagnosed MDD during the menopause transition (98). The role of estradiol in perimenopausal depression is further supported by hormone manipulation studies. Depressive symptoms decreased following 3 weeks of estradiol treatment in 34 women with perimenopausal depression compared with baseline and women taking placebo (275). Despite comparable ovarian hormone levels in women with perimenopausal depression and controls (273, 274), women with a history of perimenopausal depression (but not those lacking that history) rapidly experience depression recurrence when blindly withdrawn from estradiol (272). Thus, estradiol withdrawal appears to trigger perimenopausal depression in susceptible women, and estradiol treatment ameliorates these symptoms.

Neuroimaging of perimenopausal depression—Although several neuroimaging studies have attempted to identify hormonal mechanisms of cognitive dysfunction seen during the perimenopause (21,22,78,79), none has examined neural correlates of depression or the neural mechanisms of the antidepressant effects of estradiol. Existing imaging studies do, however, document abnormalities in neural networks responsible for cognition and memory in postmenopausal women, which are reversed by estrogen therapy (21,22,78,79, 149). Menopause is associated with reduced phonemic verbal fluency and increased activation of the bilateral inferior frontal cortex and left temporal pole (21). Short-term estrogen treatment of postmenopausal women is associated with increased prefrontal activation (78). Long-term estrogen treatment of postmenopausal women is associated with increased activation of the frontal and parietal cortices, insula, hippocampus, cingulate, putamen and raphe (22). In the context of an anti-cholinergic challenge, estrogen treatment buffered activation of the left medial frontal gyrus and increased activation of the precuneus (79). Thus, estradiol affects cholinergic system regulation of cognition-related brain activation in post-menopausal women. The effects of estrogen and progesterone on perimenopausal women have not been as well studied, and this represents an important area for future research given that the effects of estradiol are likely to be most beneficial when started during the menopause transition rather than in the postmenopause.

Conclusion

Reproductive steroids powerfully regulate a number of behaviors extending well beyond reproductive and maternal behavior to eating behavior, cognition, motor behavior, sleep, and impulse control. Reproductive steroid regulation of behavior is therefore essential to our survival as a species. Not surprisingly, then reproductive steroids are potent neuroregulators from the subcellular to cellular level to circuit to behavior. Reproductive steroid regulation of circuits and behaviors is relevant to mood disorders. In particular, mood disorders are characterized by affective, cognitive, behavioral, and neurovegetative symptoms, which suggests the presence of neural network dysfunction. The neural circuits and networks shown to be dysregulated in depression include the frontosubcortical regulatory network, central executive network, mesolimbic reward circuitry, and DMN. Activity in regions throughout these networks is modulated by estrogen and progesterone or their metabolites. Changes in reproductive steroid levels during specific reproductive states (i.e., the premenstrual phase of the menstrual cycle, pregnancy, parturition, and the menopause transition) have been shown to trigger affective dysregulation in susceptible women. In those with PMDD, fluctuations in estradiol and progesterone destabilize mood. Similarly, in PPD, both increases and decreases in estradiol and progesterone appear to trigger depressive symptoms in susceptible women. Finally, the twofold increase in depressive symptoms seen during the menopause transition is temporally coincident with the decrease in estradiol that occurs during the late perimenopause. Further, mood destabilization is associated with the degree of estradiol variability rather than absolute levels, suggesting once again that the change in hormone levels contributes to mood dysregulation in the context of an antecedent susceptibility. In addition, animal models suggest that ALLO may trigger mood symptoms as a function of $GABA_A$ receptor α4- and/or δ-subunit alterations that are heritable or consequent to ALLO withdrawal combined with stress (179–181, 286, 300). Thus, the

source of susceptibility to reproductive mood disorders may involve estradiol, progesterone (mediated by ALLO), or both. Understanding the source of individual susceptibility is critical to both preventing the onset of illness and developing novel, individualized treatments for reproductive-related affective dys-regulation. The capacity of changes in reproductive steroids to dysregulate affect suggests a potentially important role of these hormones and their metabolites in reproductive mood disorders.

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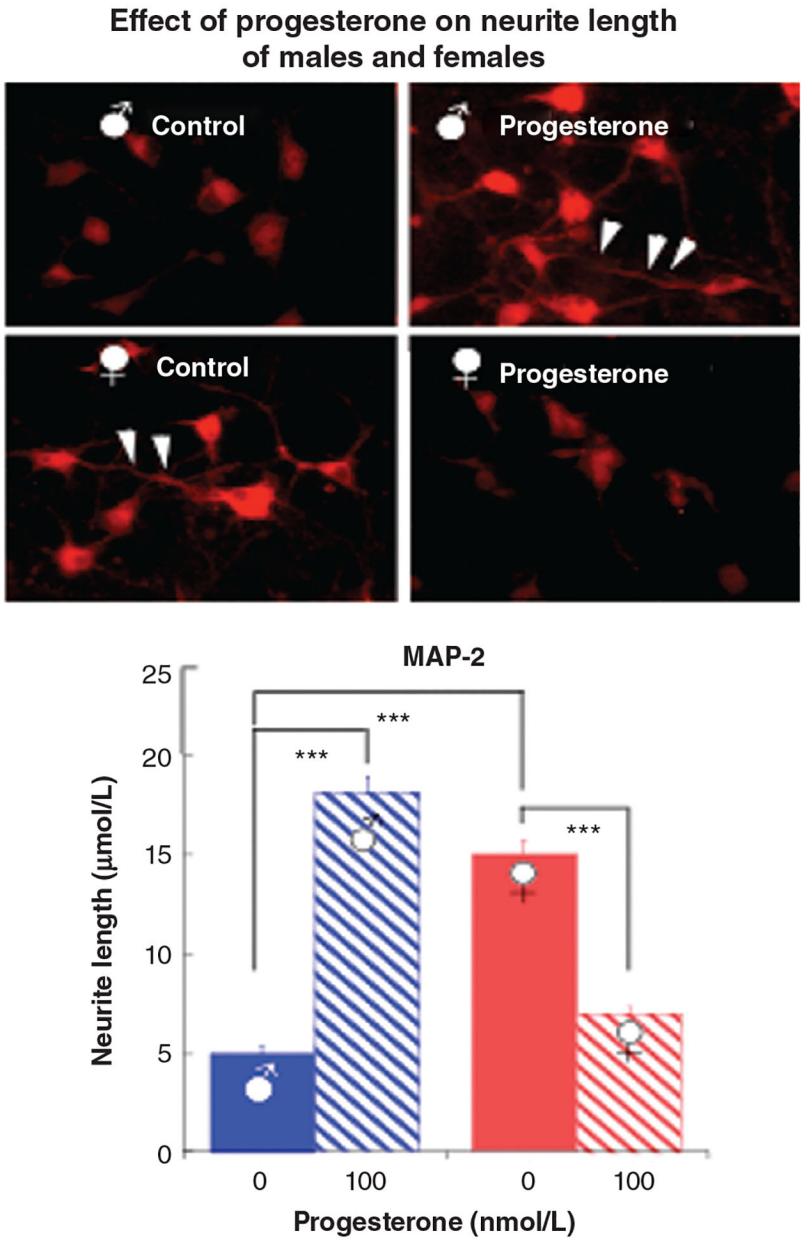


Figure 1.

Seventy-two hours of culture of rat cortical neurons with 100 nm progesterone has opposite effects on neurite length [assessed after staining with microtubule associated protein-2 (MAP2)] in neurons from male and female animals. The top panel shows cortical neurons stained with MAP2 in male (top) and female (bottom) untreated control rats (left) and those treated with progesterone (right). The bottom panel is a bar graph showing neurite length in male (blue) and female (red) untreated control rats (solid) and those treated with progesterone (striped). Neurite length is greater in female animals compared with males in the absence of progesterone, whereas the opposite is true following exposure to progesterone (L. Zhang et al., unpublished data). ***$P < 0.001$.

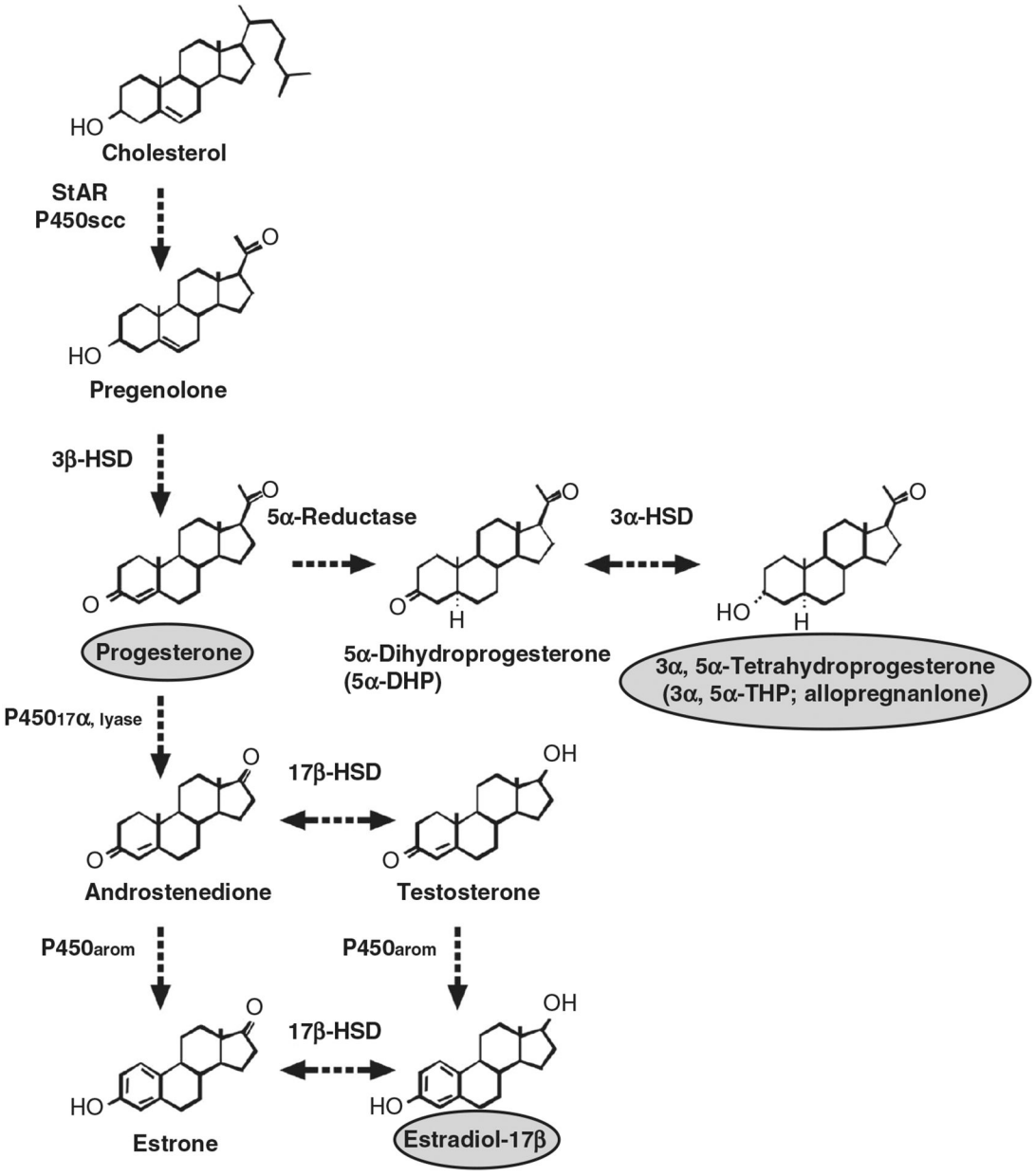


Figure 2.

Synthetic pathways for the steroid hormones progesterone, estradiol, and allopregnanolone, reproduced with permission from (328). Note that the same enzymes have multiple actions in the hormone cascade.

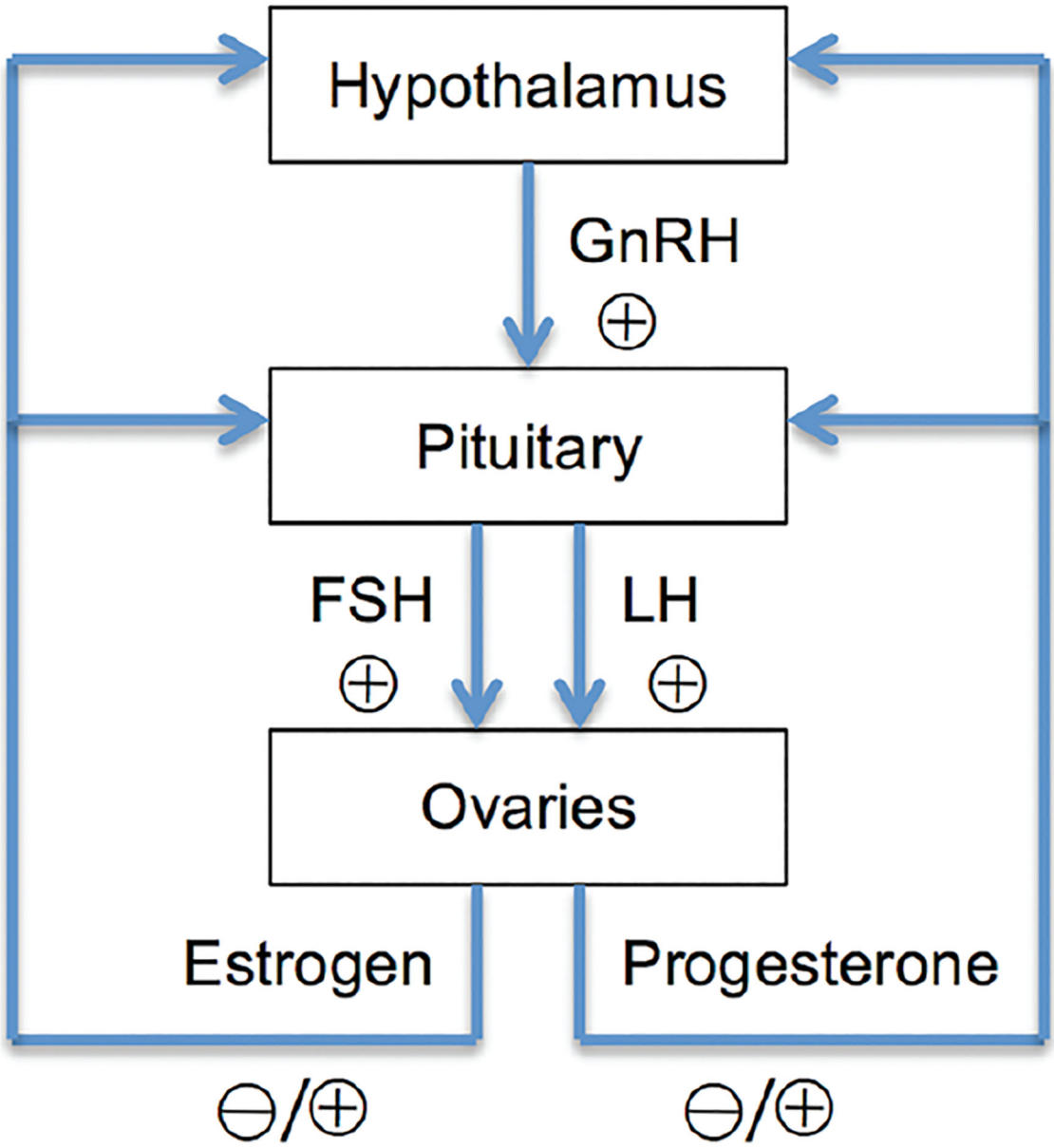


Figure 3.

The hypothalamic-pituitary-gonadal (HPG) axis. The hypothalamus secretes GnRH, which acts on the pituitary gland. In response, the pituitary gland releases the gonadotropins LH and FSH. LH and FSH stimulate the ovaries to produce estrogen and progesterone. Depending on the menstrual cycle phase, estrogen and progesterone provide either positive or negative feedback to the hypothalamus and pituitary.

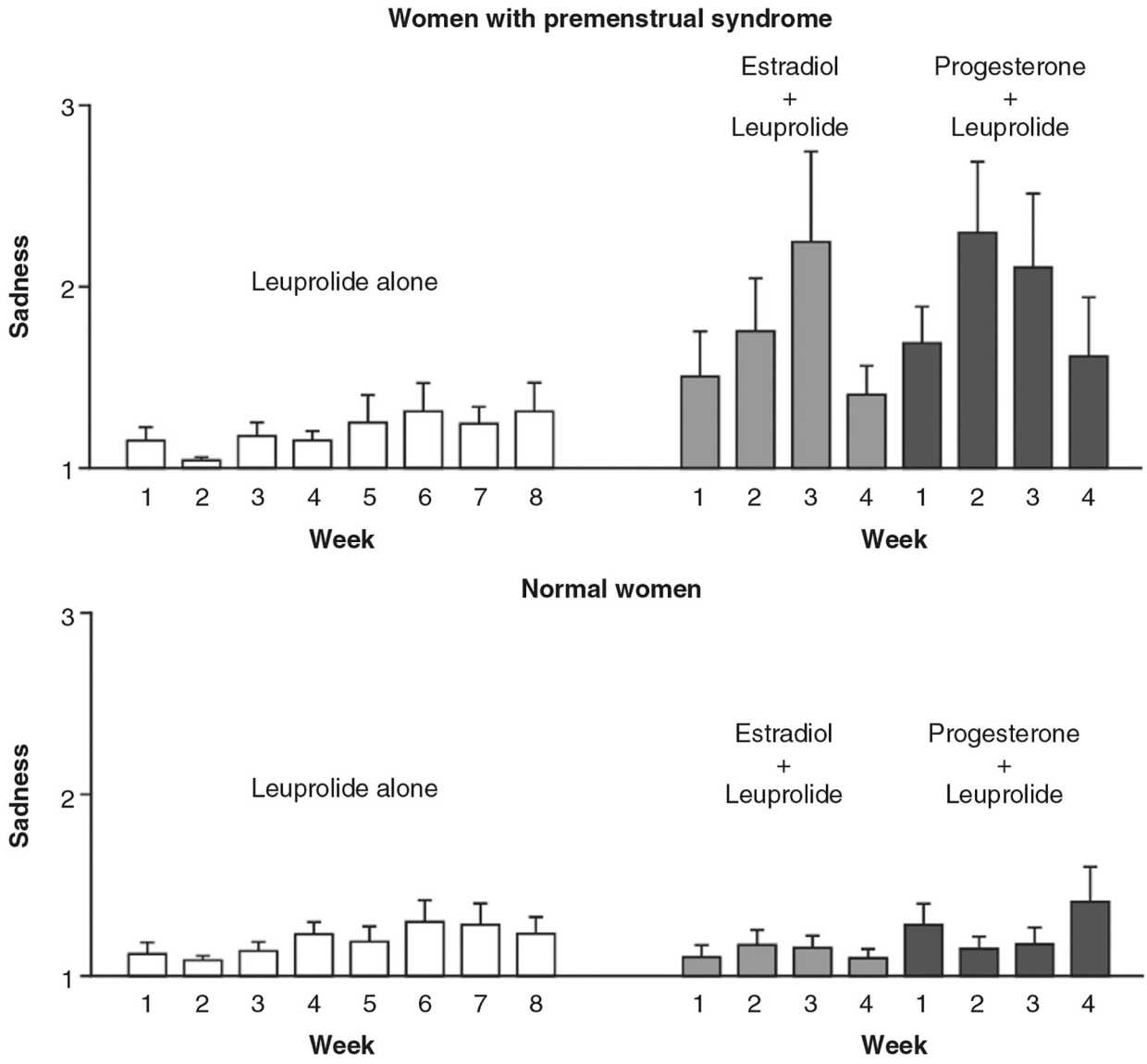


Figure 4.

Recurrence of sadness in women with premenstrual syndrome during estradiol or progesterone add-back in the context of GnRH agonist-induced ovarian suppression, reproduced with permission from (276). Ten women with premenstrual syndrome and 15 control women had minimal mood symptoms while receiving leuprolide acetate (a GnRH agonist). In contrast, the women with premenstrual syndrome but not the controls had a significant increase in sadness during the administration of either estradiol or progesterone. Values are the means (±SE) of the seven daily scores on the sadness scale of the Daily Rating Form (82, 125) for each of the 8 weeks preceding hormone replacement (leuprolide alone) and during the 4 weeks of estradiol (plus leuprolide) and progesterone (plus leuprolide) replacement. A score of 1 indicates that they symptom was not present, and a score of 6 indicates that it was present in the extreme. $P = 0.003$ for interaction of treatment condition, diagnostic group, and week.

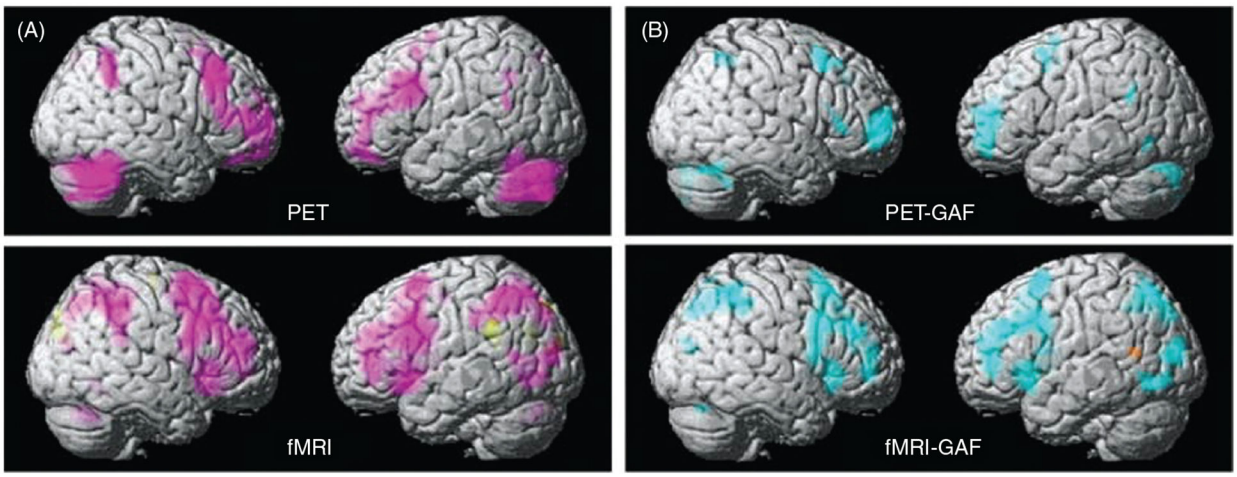


Figure 5.

PET and fMRI activation in a multimodal imaging study of women with PMDD and a comparison group of women, reproduced with permission from (11). Panel A shows the between-group differences in activation using PET and fMRI. Regions in which patients had greater activation than comparison subjects are shown in pink. Panel B shows the correlations between Global Assessment of Functioning Scale (GAF) scores and activation in patients using PET and fMRI. Regions in which these two measures were negatively correlated (the greater the overactivation, the more severe impairment indicated by GAF scores) are shown in blue.

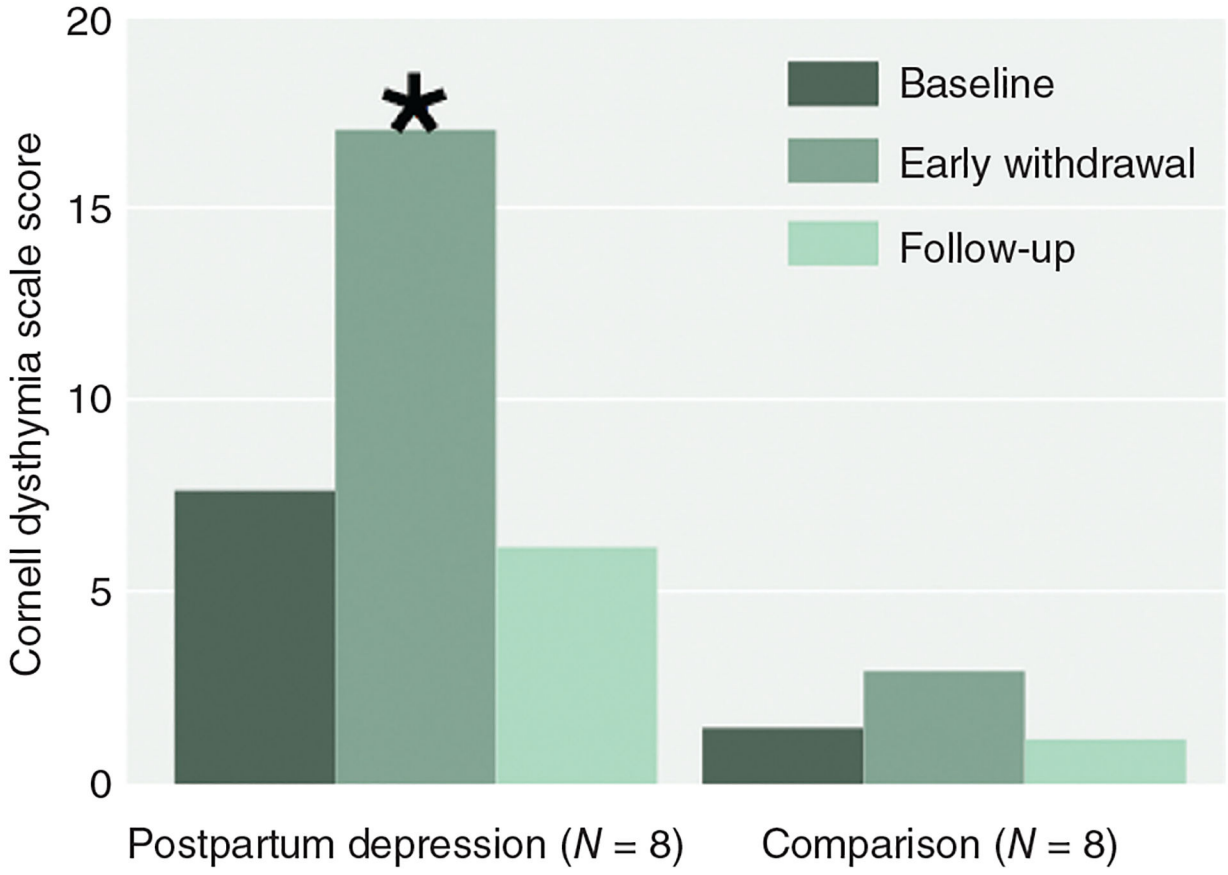


Figure 6.

Mean scores on the Cornell Dysthymia Scale before and after estrogen and progesterone replacement in eight women with a history of postpartum depression and eight healthy comparison women, reproduced with permission from (34). The significant difference between baseline and hormone withdrawal periods in the group with a history of postpartum depression ($P < 0.01$) is denoted by the symbol (∗).

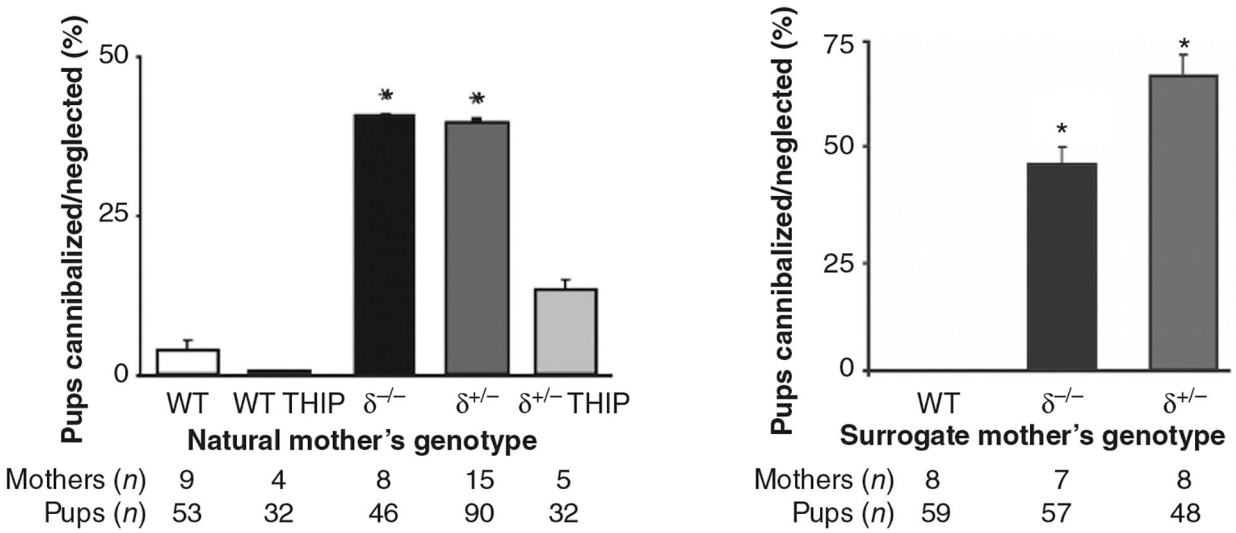
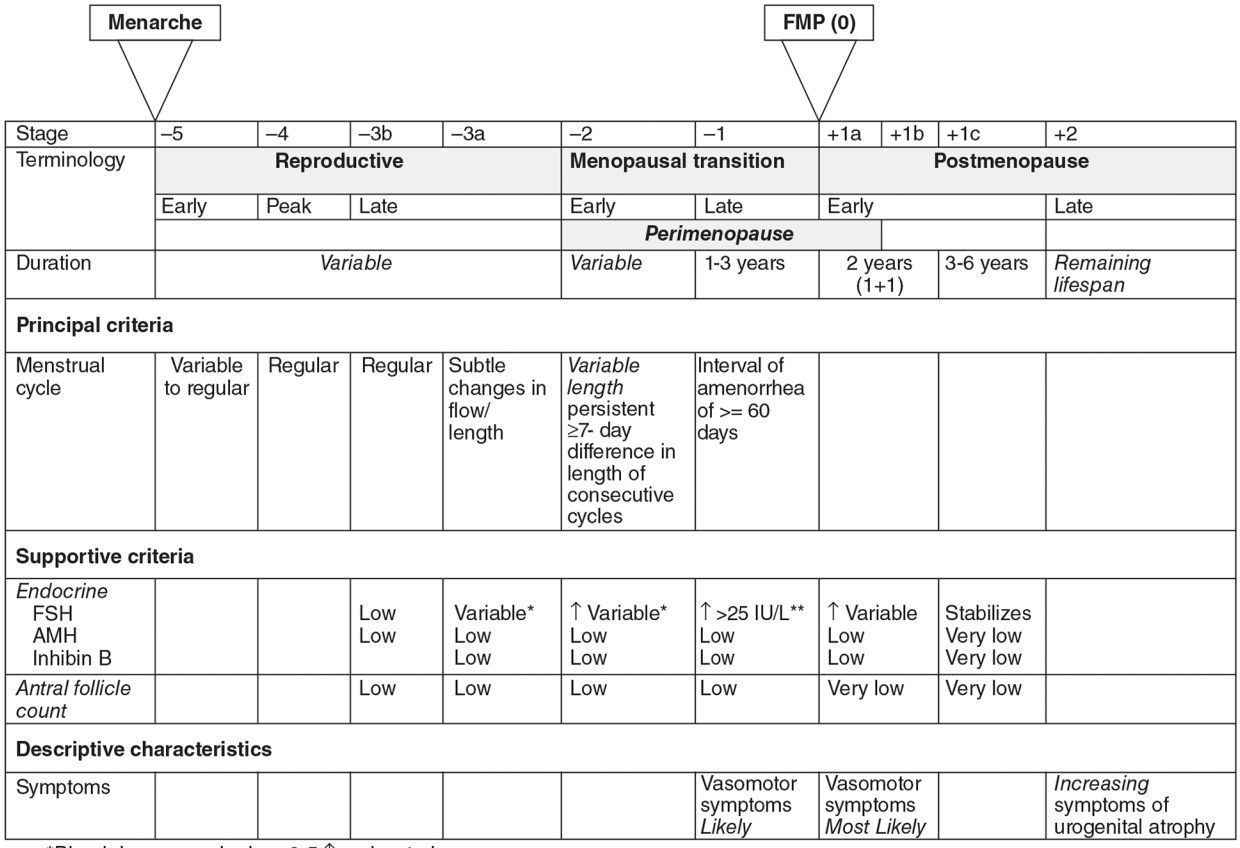


Figure 7.

Abnormal maternal behaviors in $GABA_A$ receptor δ-subunit-deficient mice, reproduced with permission from (181). Panel on right shows that decreased survival of pups born to $GABA_A$ receptor δ-subunit-deficient ($Gabrd^{+/-}$ and $Gabrd^{-/-}$) mice is reduced by including a $GABA_A$ receptor δ-subunit-selective agonist (THIP) in drinking water. Panel on left shows that pups born to $Gabrd^{+/-}$ and $Gabrd^{-/-}$ mice but reared by a surrogate wild-type mother immediately following birth had an increase in survival compared with wild-type pups reared by $Gabrd^{+/-}$ and $Gabrd^{-/-}$ surrogate mothers immediately following birth.



Stage	–5	–4	–3b	–3a	–2	–1	+1a	+1b	+1c	+2
Terminology	**Reproductive**				**Menopausal transition**		**Postmenopause**			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
Principal criteria										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ length	*Variable length* persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >= 60 days				
Supportive criteria										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low		Stabilizes Very low Very low	
Antral follicle count			Low	Low	Low	Low	Very low		Very low	
Descriptive characteristics										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

*Blood draw on cycle days 2-5 ↑ = elevated.
**Approximate expected level based on assays using current international pituitary standard.[67-69]

Figure 8.

The STRAW +10 staging system for reproductive aging in women, reproduced with permission from (130). FMP, final menstrual period.