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Estrogen, Stress, and Depression: Cognitive and Biological Interactions

Kimberly M. Albert[1], **Paul A. Newhouse**[1,2]

[1]Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, Tennessee 37212, USA

[2]Geriatric Research, Education, and Clinical Center, Tennessee Valley Veterans Affairs Medical Center, Nashville, Tennessee 37212, USA

Abstract

This article reviews the interactions of estrogen changes and psychosocial stress in contributing to vulnerability to major depressive disorder (MDD) in women. Estrogen modulates brain networks and processes related to changes in stress response, cognition, and emotional dysregulation that are core characteristics of MDD. Synergistic effects of estrogen on cognitive and emotional function, particularly during psychosocial stress, may underlie the association of ovarian hormone fluctuation and depression in women. We propose a model of estrogen effects on multiple brain systems that interface with stress-related emotional and cognitive processes implicated in MDD and discuss possible mechanisms through which reproductive events and changes in estrogen may contribute to MDD risk in women with other concurrent risk factors.

Keywords

depression; estrogen; stress; steroids; attention; emotion regulation

INTRODUCTION

Increased vulnerability to depression in women begins with puberty and declines after menopause. While the rate of new onset mood disorders may decline after menopause, women still suffer disproportionately from mood, anxiety, and stress-related disorders into old age. Studies have shown that the perimenopause produces increased vulnerability to both depressive symptoms and new onset depression even among women with no prior history of affective disorders. While the reasons for vulnerability to such disorders in women remain to be fully understood, the strongest candidate is the influence of cycling levels of gonadal steroids on neurotransmitter systems and mood regulatory systems interacting with biological vulnerability and life stress. Alterations in how the brain conducts emotional processing and encodes and retrieves emotional information may be critical to sex and

paul.newhouse@vanderbilt.edu .

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age differences in the incidence, prevalence, and appropriate treatment of emotional and cognitive disorders. The effects of the gonadal steroid estradiol (the predominant circulating estrogen) on emotions are complex and vary according to reproductive life stage.

The stress-exposure model of depression suggests that depression is the result of a biological vulnerability combined with the trigger of stressful life events. Altered functions of the brain regions important to the stress response have been consistently found in individuals with depression, and they resemble an unregulated stress response, including hypothalamic–pituitary–adrenal (HPA) axis hyperactivity and insensitivity to negative feedback of the stress hormone cortisol. The cortisol response to stress shows sex differences, and it decreases during the high estradiol phases of the menstrual cycle. Women remain more sensitive than men to lower levels of cortisol following repeated stressors, and, thus, women may be more sensitive to mood dysregulation following psychosocial stress than men because of changing ovarian hormone effects on the HPA axis and brain circuits important for the stress response.

Major depressive disorder (MDD) is complex, impacts multiple systems in the brain and periphery, and alters emotional and cognitive processes that are integral to healthy daily functioning and quality of life. The incidence and prevalence of MDD in women are two to three times higher than in men (Kessler et al. 2005). In men, new onset rates and 12-month prevalence of MDD remain fairly constant from puberty to old age, but increase in women at puberty and remain higher than in men until menopause (Kessler 2003). Depression risk for women changes across the life span, with higher risk corresponding to life stages in which ovarian hormones fluctuate across the monthly menstrual cycle and to reproductive events, such as parturition and menopause. Ovarian hormones have varied effects in the brain, including modulation of emotional perception, mood regulation, and the stress response, as well as effects on cognition. The concurrence of increased depression risk with the reproductive life phase indicates that ovarian hormone fluctuations may contribute to mood disruption in women. Naturally occurring periods of low estrogen (premenstrually and during late perimenopause) may introduce windows of increased vulnerability to depression through the withdrawal of beneficial modulation of emotional processing and mood regulation.

MAJOR DEPRESSIVE DISORDER: DIAGNOSIS AND EPIDEMIOLOGY

MDD is the largest contributor to disability due to mental and behavioral disorders, accounting in the United States for 3.7% of disability-adjusted life years and 8.3% of years lived with disability (Murray et al. 2013). Although mood and anxiety disorders are the most prevalent psychiatric disorders in the United States, current strategies for treating MDD fail to induce lasting remission or prevent recurrence in a significant portion of sufferers. Better understanding of the role of ovarian hormones in MDD in women may provide novel targets or better focus prevention strategies.

Depressive episodes may leave a scar, such as a cognitive bias for negative information, that results in maladaptive behavior and dependent stressful events (De Raedt & Koster 2010). Thus, with each depressive episode the association between negative cognitive patterns

and negative mood may be reinforced and make the individual more vulnerable to future depressive episodes (Dent & Teasdale 1988).

COGNITIVE MODELS OF MAJOR DEPRESSIVE DISORDER

Ventral and Dorsal Systems of Emotion Perception and Regulation

Theories of the neurobiology of MDD have evolved into complex network models that include mechanisms of cognitive and emotion regulation. One useful model that incorporates emotion processing and cognitive function is the division of stimuli evaluation and emotion regulation into ventral and dorsal brain systems (Phillips et al. 2008) (Figure 1). Structures in the ventral system include the amygdala and ventral and orbital prefrontal areas (Phillips et al. 2008). The dorsal division includes the hippocampus, dorsal anterior cingulate cortex, subgenual prefrontal cortex (subgenual PFC), and dorsal lateral prefrontal cortex (Phillips et al. 2008). The ventral system allows for the rapid appraisal of emotionally valenced stimuli, while the dorsal system provides the capacity to modulate the affective, physiological, and cognitive consequences of ventral output (Phillips et al. 2003).

The overlap in circuits for mood regulation and cognitive function in the ventral–dorsal model is indicative of an intimate connection between cognition and mood (Fink et al. 1996). The cognitive model of MDD posits that emotion processing circuits in the brain are altered in depression such that there is a bias toward negative information and attenuated processing of positive information (Disner et al. 2011).

Attention Bias

The focus of attention is determined by interactions between bottom-up (stimulus-driven) processes in the ventral system and top-down processes in the dorsal system (Egeth & Yantis 1997). Memory deficits and bias for negative information have commonly been found in MDD (Sears et al. 2011, Sheline 2000). It may be that altered memory in MDD is largely due to the effects of attention bias on the sensory processing of emotional information and the subsequent effects on memory encoding (De Raedt & Koster 2010). Emotionally valenced stimuli drive bottom-up attention more than emotionally neutral stimuli do. Vuilleumier and colleagues (Pourtois et al. 2013) propose a model of attention by which emotional information is amplified and preferentially processed. In this model, the amygdala has a significant role in generating emotional bias signals—that is, ventral system processes initiated by the amygdala direct attention to emotionally relevant stimuli and modulate sensory systems such that the processing of such stimuli is enhanced and maintained.

Ventral and dorsal mechanisms interact to guide attention; the ventral system facilitates the evaluation of stimuli and directs top-down processes toward emotionally relevant information (Chun & Turk-Browne 2007), while dorsal system processes maintain attention congruent with endogenous goals and motivational states (Mohanty & Sussman 2013). Studies demonstrating that acute stress and anxiety enhance both the amygdala response and subsequent sensory systems' activity to negative emotional stimuli (Bishop 2004, Cornwell et al. 2011, Shackman et al. 2011, van Marle et al. 2009, Vogel & Luck 2000) provide

evidence that negative mood states bias attention and sensory processes toward negative information.

Cognitive Bias in Depression

Mood-congruent cognitive bias is a common finding in currently depressed individuals (Gaddy & Ingram 2014). Negative cognitive bias not only affects the processing of emotional information but also appears to be related to emotional responding to psychosocial stress. Individuals with current MDD fixate longer and more frequently on sad faces than healthy controls do, and they also take longer to recover from negative mood following a laboratory stressor (Sanchez et al. 2013). Women with remitted MDD show greater attention bias for negative stimuli, despite being euthymic, than women with no history of MDD do (Albert et al. 2017). A causative link between cognitive bias and mood is also suggested by the finding that experimental methods that modulate attention bias also affect symptoms of anxiety and depression. Cognitive bias modification, an experimental technique in which attention is trained away from or toward negative stimuli, is effective in modulating depressive symptoms as well as attentional performance (Hallion & Ruscio 2011). The mood effects of cognitive bias modification training support the idea that cognitive bias may be a causative factor in mood disruption rather than a consequence (Hallion & Ruscio 2011).

Cognitive models of MDD accord with neural system dysregulation models in that cognitive bias is associated with altered activity in dorsal and ventral systems (De Raedt & Koster 2010). Greater activity in ventral system structures and less activity in dorsal structures to negative stimuli is a consistent finding in MDD (Drevets et al. 2008, Savitz & Drevets 2009). Enhanced amygdala activity in currently depressed, remitted, and at-risk individuals (Albert et al. 2017, Arnone et al. 2012, Zhong et al. 2011) may indicate greater signal-driven automatic evaluation or reduced regulation by dorsal system structures, resulting in biased processing of negative information (Sears et al. 2011). Neuroimaging studies show that in MDD additional regions of the PFC are recruited during automatic control of emotional responses, suggesting that compensatory activity in dorsal regions may be activated to control enhanced bottom-up activity that is driven by amygdala hyperactivity in MDD (Phillips et al. 2003, Zhong et al. 2011).

Individuals with MDD appear to have diminished dorsal system capacity to regulate ventral-driven sensory and emotional processing of negatively valenced information. Strengthening dorsal system regulation of emotional processing may be an important component of successful MDD remission (Erk et al. 2010, Gotlib & Joormann 2010). However, even during remission, automatic ventral system processes may be prioritized when cognitive resources need to be allocated efficiently (such as during stress), resulting in negative mood and reinforcing negative cognitive bias. Cognitive bias in remitted MDD may reflect continued dysregulation in emotional processes and a neurobiological basis for vulnerability to MDD recurrence, especially following stress.

STRESS AND MAJOR DEPRESSIVE DISORDER

The Stress-Response System

The stress-response system normally serves to coordinate optimal neuroendocrine, immune, and autonomic responses to stress (for a review, see Stokes 1995). During stress, cortisol acts throughout the body to increase the energy available to manage the demands of the stressor and maintain homeostasis. The endocrine response to stress is regulated through the negative feedback mechanisms of glucocorticoids at the pituitary, hypothalamic, hippocampal, and limbic regions (Gillies & McArthur 2010) (Figure 2).

The optimal HPA axis response to stress is dynamic, both quickly releasing cortisol and rapidly stopping its action, thus preventing peripheral and central nervous system damage due to prolonged cortisol exposure (Lupien et al. 2005). Inefficient regulation of the HPA axis and chronic exposure to high levels of cortisol are associated with increased blood pressure, increased risk for diabetes, hypertension, arterial diseases, impaired growth and tissue repair, and suppressed immune function (Derijk & Sternberg 1994, Lupien et al. 2009, Moulton et al. 2015, Munck & Guyre 1991). Thus, HPA dysregulation is a common factor in comorbid diseases such as depression and cardiovascular disease (Carney & Freedland 2003, Chen et al. 2007, Jiang et al. 2002, Joynt et al. 2003, Miller et al. 2002, Nikkheslat et al. 2015). Chronic cortisol dysregulation may negatively impact a variety of body systems and may present a general vulnerability factor that contributes to the risk for a number of diseases, including MDD.

Ventral and Dorsal Systems in the Stress Response

The hypothesis that stress system dysfunction is integral to the etiology of MDD is consistent with neuroanatomical models of MDD that posit mood dysregulation as a result of an imbalance in functional activity in the ventral and dorsal systems, which are sensitive to cortisol and show reciprocal activity changes during stress responding (Drevets et al. 2008, Mayberg 1997, Phillips et al. 2008).

During the healthy stress response, activity in the brain shifts from dorsal system mood regulation to ventral system threat evaluation and management as cognitive resources are preferentially allocated to automatic processes for responding to threat (Arnsten 2009). Enhanced ventral activity results in acute dysphoria, which is a normal and necessary component of the stress response, as negative mood motivates the managing of stressors (Gold 2015). There are two regulatory components of the dorsal system: Hippocampal activity is automatically enhanced in response to amygdala activity, while frontal activity is recruited through later-stage or voluntary processes (Phillips et al. 2008). In the unstressed state, the subgenual PFC inhibits amygdala activity and, consequently, attenuates amygdala-driven attention (Gold 2015). During stress, dorsal system function is downregulated in favor of automatic, rapid emotional responses in the ventral system. Once dorsal activity is decreased through automatic or voluntary processes, the amygdala is released from inhibition (Drevets et al. 1997, Simpson et al. 2001).

The amygdala has a central role in both the mood and cognitive response to stress—through reciprocal projections with dorsal system structures—and in orchestrating endocrine and

autonomic responses—through projections to the hypothalamus and central autonomic centers (Gold 2015). The release of amygdala inhibition promotes negative mood and cognitive responses to stress, and it both directly and indirectly (through downregulation of dorsal region activity) drives HPA axis and autonomic responses. In a recent review, Gold (2015) posits that an unregulated feedforward system, decreased dorsal system activity, and increased amygdala activation cause a prolonged dysphoric state and bias cognitive processes toward negatively valenced emotional information.

Stress and Cognition

The changes in ventral and dorsal activity that occur during the normal stress response result in altered cognitive processing of emotional information, including memory (McGaugh 2004), and attention bias for threatening or negatively valenced stimuli (Arnsten 2009). Normally, short-term cognitive bias toward negative information serves to efficiently process and manage stressors; however, in a dysregulated stress system, persistent cognitive bias may become established and contribute to cognitive vulnerability for sustained depression or depressive illness.

These findings in healthy adults, as well as memory impairment and hippocampal volume loss in patients with Cushing's disease or on cortisol treatment, support the glucocorticoid cascade hypothesis, which posits a direct effect of chronic high cortisol on hippocampal integrity (impaired function and decreased volume) (Sapolsky et al. 1986).

The hippocampus is an important negative feedback site for cortisol and a regulator of HPA axis activity (Herman & Cullinan 1997, Jankord & Herman 2008). The occupation of glucocorticoid receptors results in increased hippocampal activity and inhibits HPA axis function; however, this regulatory loop is suppressed during acute stress to maintain the endocrine response (Feldman & Weidenfeld 1999). Mild acute stress promotes neurogenesis in the dentate gyrus of the hippocampus and appears to support adaptive responding to stress and the efficient return to basal HPA axis activity and cortisol levels (Duman & Li 2012,Ming & Song 2011). In mice, blocking hippocampal neurogenesis during acute stress produces depression-like behavior (Snyder et al. 2011), suggesting that hippocampal adaptation may be an integral component of the healthy stress response that prevents depressive responding. Additionally, animal studies suggest a beneficial effect of acute glucocorticoids on hippocampal function: Removing corticosterone impairs hippocampally mediated memory, and replacing corticosterone rescues performance (Lupien et al. 2005). However, in rodent models of chronic stress, hippocampal volume and plasticity are reduced (Magariños & McEwen 1995, Watanabe et al. 1992), suggesting that chronically elevated glucocorticoid levels negatively impact the hippocampus. These alterations in hippocampal structure and function may result in stress system dysregulation as the ability of the hippocampus to regulate stress responding and modify its activity in response to acute stress is reduced.

Prolonged HPA dysregulation may alter the dynamics of glucocorticoid receptor activity and modify the cognitive effects of acute stress. Lupien et al.'s (2005) longitudinal studies in older adults provide evidence that chronically high cortisol similarly alters the cognitive effects of stress in humans. Older adults with normal, moderate basal cortisol show a

beneficial effect of acute cortisol increase on memory; however, in older adults with high basal cortisol, acutely increased cortisol impairs memory performance, suggesting that in humans chronically high cortisol levels alter the effect of acute cortisol changes.

The acute stress response in the brain is characterized by a shift toward ventral system activity and away from dorsal system activity. This shift may result in dysphoric mood, which motivates behavioral responses to stress and cognitive bias in attention and memory that focus cognitive resources on managing the stressor. In healthy systems, these responses last only as long as necessary to cope with the stressor. However, dysregulation of the stress response may result in a prolonged dysphoric state and a cognitive bias for negative information followed by depression. Cognitive and stress-exposure models of MDD are complementary, as the altered cognitive processing of negative emotional information may result from and be maintained by stress system dysregulation.

Stress System Dysregulation in Major Depressive Disorder

Altered HPA axis function is common in MDD (Burke et al. 2005, Lupien et al. 2009), and the onset of depressive episodes is often attributed to stressful life events (Jessen et al. 2014, Kendler et al. 2000). The association of stress with MDD supports a stress-exposure model of MDD in which depressive episodes are triggered by stressful events and maladaptive responding (Hankin et al. 2007, Liu & Alloy 2010). Individuals with MDD show chronically elevated cortisol; however, cortisol feedback at the pituitary appears to be intact, indicating that HPA axis dysregulation originates from blunted feedback at the hypothalamus or in higher-level brain systems that regulate HPA axis activity (Holsboer et al. 1984). Evidence that frontal dorsal system regions may be less sensitive to HPA axis negative feedback in depression is provided by reduced densities of cortisol-releasing hormone receptors in frontal regions in postmortem studies following suicide (Nemeroff et al. 1988). Cortisol-releasing hormone levels are elevated in depressed patients and decrease with successful treatment (Nemeroff et al. 1984, Widerlöv et al. 1988), again suggesting that MDD is characterized by HPA axis dysregulation, and remission is associated with restored regulation. Chronically altered sensitivity for cortisol-releasing hormone and cortisol may have long-term effects on brain regions that respond to these hormones.

The alterations in brain structure and function that are found under chronic stress parallel changes in MDD; patients with MDD show structural changes in brain regions that are integral to stress responding, including decreased subgenual PFC and hippocampal volumes and increased amygdala volume (McKinnon et al. 2009). Reductions in dorsal system volume are likely due to reduced neuronal size, the loss of glial cells, and diminished dendritic arborization (Drevets et al. 1997, 2008; Jaako-Movits et al. 2006), while in the amygdala, dendritic arborization and spine density are increased (Drevets 2000). These changes suggest that plasticity is reduced in dorsal regions and increased in the amygdala, which accords with disrupted dorsal system–amygdala interactions as a mechanism in MDD etiology (Gold 2015).

Cognitive alterations in MDD also parallel shifts in cognitive resource allocation during stress responding (Gotlib & Joormann 2010, Isaac et al. 2014), indicating that dysregulated stress system function may contribute to behavioral changes in MDD. In addition to the

effects of amygdala hyperactivity, altered HPA axis function and reduced negative feedback by glucocorticoids may contribute to the hippocampal atrophy seen in MDD.MDD is associated with bilateral hippocampal atrophy (8–19%) that appears to have functional significance, as individuals with past MDD who are currently in remission continue to show deficits in hippocampally mediated tasks (such as declarative and verbal memory) (Sheline 2000).

The origin of HPA axis dysregulation in MDD remains unclear; however, the organization of peripheral and brain stress systems makes these systems vulnerable to dysregulation (Gold 2015). MDD may result from an initial alteration in stress system function (perhaps through genetic traits or environmental factors) that is maintained and amplified through the numerous feedback loops and reciprocal interactions that constitute the stress-response system. In a recent review, Gold (2015, p. 45) defines MDD as a disease that contributes to “multiple systemic pathologies.” The organization of the stress system, with its multiple feedforward loops to assure the successful management of stressors, and the mood and cognitive effects of even acute, well-managed stress create a system that is vulnerable to dysregulation. The symptoms that characterize MDD resemble prolonged, unregulated stress responses; once the stress system becomes dysregulated, feedforward mechanisms sustain hypercortisolism and enhanced amygdala function, reinforcing the mood and cognitive consequences of stress system activity (Gold 2015). Successful MDD treatment likely requires approaches that target multiple mechanisms that are impacted by stress system activity, including those that promote neuroplasticity and cognitive strategies to support adaptive cognitive processes.

Altered HPA function may be especially important in the etiology of MDD in women. The cortisol response to stress does show sex differences (Young & Korszun 2010), and it is altered by the menstrual cycle (Kirschbaum et al. 1999, Kudielka et al. 2004) and pregnancy (Altemus 2006). During the low estrogen phases of the menstrual cycle, women show greater negative mood response and less hippocampal activity during acute psychosocial stress than they do during the high estrogen phases (Albert et al. 2015). Also, women appear to remain more sensitive than men to lower levels of cortisol following repeated stressors (Wang et al. 2007). These findings suggest that ovarian hormone levels may modulate stress system functioning in women. Estrogen may support efficient and dynamic stress responding and prevent disrupted ventral–dorsal system interactions through supporting neuroplasticity in prefrontal areas and the hippocampus. Maintaining function in dorsal system structures preserves regulatory control over ventral activity (particularly over the amygdala) and allows for the efficient return to a baseline state. Loss of dorsal system function may predispose the brain to relying on ventral system processes that bias attention and memory toward negative information and aberrantly prolong emotional, endocrine, and autonomic stress responding. Periods of increased stress sensitivity, contributed to by ovarian hormone changes, may present windows of vulnerability to mood dysregulation in women who are at risk for MDD.

THE HYPOTHALAMIC–PITUITARY–GONADAL AXIS

The hypothalamic–pituitary–gonadal axis is a multilevel hormonal system that regulates the secretion of ovarian hormones in females (estrogen and progesterone) through multiple feedback mechanisms at the ovary, pituitary, and brain. Gonadotropin-releasing hormone from the hypothalamus induces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH and FSH modulate the ovarian cycle, with FSH stimulating follicle maturation and the release of estrogen during the follicular phase and LH triggering ovulation as well as progesterone release from the corpus luteum (ruptured follicle) during the luteal phase. Estrogen (primarily estradiol in humans) feedback to the pituitary and hypothalamus controls the release of gonadotropin-releasing hormone, FSH, and LH, and this system of feedforward and feedback mechanisms orchestrates activity within the hypothalamic–pituitary–gonadal system that establishes the menstrual cycle (Figure 3).

Women experience dramatic changes in cyclic ovarian hormones across the life span. During reproductive life, estrogen and progesterone levels fluctuate throughout the monthly menstrual cycle. During the early follicular phase and menstruation, both estradiol (the principal circulating estrogen in nonpregnant reproductive-age women) and progesterone levels are low. Estradiol increases in the mid-to-late follicular phase prior to ovulation. Estradiol levels decrease immediately following ovulation, and both estradiol and progesterone levels increase during the luteal phase until menstruation. Outside of the periovulatory phase, progesterone fluctuations parallel those of estradiol; thus, it is difficult to ascertain the separate effects of progesterone in studies of endogenous ovarian hormones. Progesterone generally appears to antagonize the effect of estradiol on mood; however, the effects of progesterone have been much less studied.

The reproductive life phase is preceded and followed by hypogonadal states both prior to puberty and during menopause. The menopause transition is characterized by irregular ovarian hormone fluctuations; both estradiol and progesterone levels can vary dramatically during the early transition period (which may last years) and generally settle into a stable, low estradiol state proximal to the final menstrual period. This variability in ovarian hormones during the reproductive years and menopausal transition creates a dynamic environment for the functioning of the mood regulatory and cognitive systems that are influenced by these hormones.

Depressive symptoms and depressive episodes in women appear to be linked to ovarian hormone changes. Women with a history of depression are more likely to experience increased depressive symptoms during periods of ovarian hormone fluctuation than at other times (Young & Korszun 2010). Also, a history of MDD increases a woman’s risk for mood disorders that are directly associated with ovarian hormone changes, including premenstrual mood disorder (Halbreich et al. 1995a) and postpartum and perimenopausal depression (Freeman et al. 2014). Even in healthy women, low estrogen phases of the menstrual cycle are associated with increased symptoms of negative mood (Gonda et al. 2008). Women with MDD and reproductive phase–related mood disorders generally have normal ovarian hormone levels (Schmidt & Rubinow 2009), indicating that these disorders are not directly

attributable to abnormally low levels of circulating estradiol (Young et al. 2000). While most women do not develop mood disorders as a result of ovarian hormone changes, the increased risk for first onset depression as estrogen declines during the late perimenopause (Schmidt & Rubinow 2009) and the relation of premenstrual dysphoric disorder to the low estradiol phase of the menstrual cycle suggest that some women may be susceptible to mood dysregulation as a result of changing estradiol levels. It may be that the role of estrogen in MDD is characterized by an altered brain response to normal fluctuations rather than to differences in estradiol levels.

ESTROGEN IN THE BRAIN

Estradiol has a variety of effects at the cellular level, including genomic actions, interactions with second messenger and G protein systems, effects on calcium signaling, and neuroprotection (McEwen et al. 2012). Classical nuclear receptors (ERα and ERβ) are nuclear transcription factors that regulate genes by binding to sequences of DNA nucleotides that contain specific regulatory elements, and this results in cascades of intracellular reactions that alter protein synthesis. These actions are relatively slow but result in long-lasting changes at the synapse or in neural function (Luine 2014). ERβ appears to predominate in areas of the human brain that are important for cognition, including the hippocampus, entorhinal cortex, and thalamus. In addition, membrane-associated G protein–coupled receptors, such as the G protein–coupled estrogen receptor GPER (GPR30), are also expressed in the hippocampus, hypothalamus, and midbrain. Membrane-bound estrogen receptors may activate signaling pathways, and they have rapid effects, on the order of seconds and minutes (Kelly & Levin 2001). These membrane-bound receptors are found in the PFC and hippocampus, and they may be responsible for the acute effects of estrogen on cognition (Luine 2014).

Estradiol modulation of the overlapping and interacting systems for stress responding and the emotional and cognitive processing of information provides a number of pathways through which estradiol fluctuations may contribute to MDD risk. In women with MDD vulnerability, estrogen may support the healthy functioning of these systems, while having little or opposite effects for women in whom these systems are already functioning optimally. Periods of low estradiol may represent windows of risk for depressive episodes in women with vulnerability to MDD because of the differential effects of estrogen on mood regulation, stress, and cognitive systems (Newhouse & Albert 2015). Understanding the interactions of vulnerability to MDD, stress, and estrogen will be important for developing more effective prevention and treatment strategies for women with MDD.

Estrogen and Emotion Processing

Sex differences in evaluating and responding to emotional information provide a basis for understanding the effects of ovarian hormones on emotion processing in women. It is important to note that androgens are aromatized to estradiol in the brain, so men generally experience constant high estrogen activity in the brain, while women experience fluctuations, including periods of low estradiol. Thus, emotion processing in men may represent the effects of stable estradiol levels (although interactions with organizational

sex differences must be considered). Accordingly, sex differences in emotion processing are most apparent when men are compared with women during periods of low estradiol. Neuroimaging studies of emotion detection or recognition show sex differences in the brain regions active during these tasks, with women showing greater limbic, inferior frontal, and temporal activity, and men showing greater prefrontal and parietal activity (Whittle et al. 2011). It has been suggested that this difference in activation patterns during emotion recognition may indicate that men and women perceive emotion at different levels of visual processing (Hall et al. 2004). Greater limbic activity in women suggests that emotion perception occurs at a primary level, while emotion perception in men occurs at a secondary level, involving the prefrontal areas. This sex difference in emotion perception may contribute to the speed and accuracy advantage in women (especially for identifying negative emotions such as fear and anger) (Thompson & Voyer 2014), as emotion recognition occurs early in visual processing, while in men, emotion detection requires additional information about the learned significance of emotional facial expressions (Whittle et al. 2011).

Earlier recognition of negative emotional information in women may influence women's ability to regulate emotional responses to such stimuli. Enhanced emotion detection at lower levels of processing may represent greater signal-driven automatic activity in the ventral system in women that requires greater top-down modulation to maintain adaptive mood responses. Earlier detection of emotion information and greater amygdala activity to negative information in women suggest that emotion evaluative processes in women are more strongly influenced by ventral system activity. Regulation of ventral system activity in women may be particularly important for healthy mood and supported by estrogen's action in the dorsal system, while the loss of estrogen may predispose women toward emotion responding through the ventral system.

Generally, studies of passive viewing of emotional images or words have found that women are more reactive to emotional stimuli whether measured through self-report, behavioral response, physiological response, or neuroimaging (Kret & De Gelder 2012, Whittle et al. 2011). The sex difference appears to be specific for negative emotional information, with consistent findings in women of greater amygdala activity during negative images or words (Whittle et al. 2011). Sex differences in activation patterns during encoding and recalling emotional information indicate there is greater overlap in activity in the brain areas that are involved in processing current emotional experiences and encoding emotional information into memory in women, including in the limbic, insular, and prefrontal regions (Piefke et al. 2005). In women, this overlap in activity correlates with subsequent successful memory recall (Canli et al. 2002), suggesting that differences in memory encoding for emotional information may contribute to better memory for emotional experiences in women than men. More integrated brain circuits for emotional and cognitive processes may enhance attention to and memory for emotional information and contribute to a cognitive vulnerability for depression in women.

Sex differences in emotion processing and responding are modulated by ovarian hormone fluctuations, indicating that these processes and vulnerability to mood dysregulation may be influenced by circulating ovarian hormones. Sex differences in emotion recognition

(Hampson et al. 2006) are reduced during periods of high estrogen levels in women (Derntl et al. 2008), suggesting that estrogen enhances emotion processing through higher-level association pathways and may support healthy mood responding to emotional information. Fluctuating ovarian hormones in women alter the perception of emotionally valenced information and the mood and cognitive responses to such information. In healthy women, these changes may be experienced as the normal mood changes that accompany periods of low estrogen; however, in a subset of vulnerable women they may contribute to increased depression risk. Although studies demonstrate that estrogen attenuates emotion processing and supports mood regulation in healthy women, the effects of estrogen in women with current or remitted MDD, in whom ventral–dorsal interactions are likely altered, remain less well understood.

Estrogen and Cognition

In addition to estrogen having indirect effects through emotion processing, it may also directly modulate cognitive processes that are altered in MDD (Halbreich et al. 1995a). Cognitive alterations in a number of domains after menopause, including attention and processing speed, are greater than would be expected from the effects of age alone (Halbreich et al. 1995b), indicating that estrogen supports cognition and such support diminishes as estradiol declines during and after menopause. Consistent findings of cognitive decline and increased risk for dementia in women who undergo early menopause, and thus experience a longer period of life with low ovarian hormone levels, further support a negative impact of estrogen loss beyond the effects of age in older women (Rocca et al. 2007). In meta-analyses, estrogen replacement generally benefits cognition in young postmenopausal women (Hogervorst & Bandelow 2010, Maki et al. 2007) and following oophorectomy (Bove et al. 2014, Rocca et al. 2014), indicating that estrogen withdrawal at menopause is a significant factor in cognitive decline with age in women (Maki & Dumas 2009, Newhouse & Dumas 2015).

Studies examining the effects of estrogen fluctuation across the menstrual cycle indicate that performance on tasks that rely on the hippocampus and PFC are enhanced during high estradiol phases of the menstrual cycle, including cognitive control and verbal and spatial memory (Poromaa & Gingnell 2014). Suppression of estradiol in young women causes reductions in blood flow and metabolism to frontal regions, and these are restored with estradiol administration, demonstrating that even acute and short-term changes in estrogen may impact dorsal region functions (Craig & Murphy 2007).

Estrogen’s effects at the amygdala and hippocampus may alter processing and subsequent memory for emotionally valenced information. Memory for emotional information is enhanced during menstrual phases when estradiol is low and progesterone is high (Ertman et al. 2012). Of note, memory is not only enhanced for the emotional content but also for peripheral information (Nielsen et al. 2013), indicating that low estradiol may enhance attentional vigilance for emotional information and more strongly associate previously neutral information with emotional information. This linking of neutral and emotional information in memory may underlie the spontaneous, intrusive recollections in posttraumatic stress disorder or rumination in depression. Intrusive recollections are

more common for traumatic events that occur during the low estradiol–high progesterone phases of the menstrual cycle (Bryant et al. 2011, Ferree et al. 2011), suggesting that ovarian hormone effects on memory may contribute to maladaptive cognitive processes following psychosocial stress. Further evidence that estradiol levels and menstrual phase impact memory processes for emotional information is provided by a series of studies by Milad and colleagues (Zeidan et al. 2011) that demonstrated the extinction of fear conditioning is greater during high estradiol phases of the menstrual cycle and even after acute administration of exogenous estradiol. Whereas low estrogen or high progesterone levels appear to enhance emotional processing and memory for negative information, high estradiol levels support top-down modulation of cognitive processes and may restrain ventral participation in attention and memory.

POTENTIAL MECHANISMS OF ESTROGEN'S ROLE IN MAJOR DEPRESSIVE DISORDER

Acting at nuclear and membrane-associated receptors allows estradiol to have both rapid and long-term effects on neuronal function as well as varied modes of action in brain regions that are important for emotional and cognitive processes. There are a number of mechanisms through which ovarian hormones may affect brain function, including modulating neurotransmitter system functions and neurotrophic effects that promote neuronal plasticity (Schmidt & Rubinow 2009). Estradiol interactions with and modulation of serotoninergic and cholinergic neurotransmitter systems have particular relevance as these are putative mechanisms that intersect with estrogen support of dorsal regulatory system function.

Neurotransmitter Systems

Commonly used antidepressant medications alter synaptic levels of the monoamines serotonin and norepinephrine or alter receptors for these neurotransmitters. The effectiveness of these treatments accords with the monoamine hypothesis of MDD that altered levels of serotonin or norepinephrine are involved in the etiology of depression. Norepinephrine from the locus ceruleus has projections to frontal and limbic regions and appears to participate in a number of stress system feedback loops, with effects on arousal and sympathetic activity (Gold 2015). There is some evidence that estradiol increases central norepinephrine levels and that the reduction of hot flashes following hormone replacement in menopausal women may be due to estradiol's effect on norepinephrine (Archer et al. 2011). However, estrogen–norepinephrine interactions and the role of these effects in depression have been little studied. The effects of estradiol on the serotonergic system has been more extensively examined and is one of the strongest candidate mechanisms by which estrogen influences depression.

Studies using tryptophan depletion (which decreases central serotonin) demonstrate that lower serotonin levels are more likely to precipitate depressive symptoms in women than in men (Booij et al. 2002); however, this sex difference is not seen following norepinephrine depletion (Moreno et al. 2006), suggesting that serotonin dysfunction may be of particular importance to MDD in women. Estradiol augments the antidepressant effects of selective

serotonin reuptake inhibitors in women, and estradiol may have beneficial mood effects through its action on the serotonergic system (Halbreich et al. 1995b). In animal models, ovariectomy reduces and estradiol add-back increases serotonin receptors in the dorsal raphe nucleus, and in the anterior frontal and cingulate regions. This experimental finding is paralleled by an increased density of serotonin receptors in the forebrains of female rats during natural proestrus when endogenous estrogen levels are high (Fink et al. 1996). Further evidence that the presence of estrogen alters serotonin function in the brain arises from studies of androgens in male animals. Testosterone, but not nonaromatizable androgens, in male animals increases serotonin receptor density (Fink et al. 1996), suggesting that the effects of testosterone on serotonin function are mediated through the aromatization of testosterone to estradiol.

In women, serotonin responsivity is reduced after menopause and restored following estradiol treatment (Halbreich et al. 1995a). While studies of estradiol alone as an antidepressant agent in peri- and postmenopausal depression have had inconsistent findings, estrogen–serotonin interactions may impact depressive symptoms or vulnerability to MDD through the cognitive and mood regulatory functions of the serotonergic system. Tryptophan depletion impairs the consolidation of episodic memory, reduces activity in brain areas important to the encoding of memory, and induces negative memory and attentional bias and difficulty with autobiographical memory (Roiser et al. 2008). These cognitive changes under reduced serotonin support the hypothesis that diminished serotonin function may contribute to cognitive mechanisms of depression, such as preferential processing of and memory for negative information. Epperson and colleagues (2013) have shown that estradiol treatment reduces the effects of tryptophan depletion on brain activity during both verbal working memory and emotion recognition tasks, suggesting that estradiol supports serotonergic-related cognitive functioning.

Tryptophan depletion generally has little mood effect in healthy individuals; however, mood effects are common in individuals with remitted MDD or family histories of MDD (Neumeister 2003). Increased risk for mood dysregulation during periods of low estrogen may be due to the loss of estrogen support of the serotonergic system (Halbreich et al. 1995b) or indirect effects on shared pathways (Schmidt & Rubinow 2009).

Estrogen’s procognitive effects may be mediated though interactions with the cholinergic system, which is critical for primary processes such as attention and memory that underlie higher-order cognition. Loss of cholinergic function appears to be one of the primary mechanisms of cognitive change in pathological aging, particularly the memory detriments seen in Alzheimer’s disease. Cholinergic function modulates both bottom-up and top-down attentional processes, and, thus, it is involved in cognitive processes that require the differentiation of relevant and irrelevant information and the efficient allocation of attentional resources (Newhouse & Dumas 2015).

In animal models, ovariectomy produces impaired performance on learning and memory tasks that is paralleled by a decline in cholinergic activity and in choline acetyltransferase levels in several brain regions, including the basal forebrain neurons projecting to the hippocampus. Treatment with estradiol replacement restores these markers (Gibbs 2010).

Estrogen replacement in ovariectomized animals counteracts the negative effects of cholinergic antagonists on spatial learning and memory. Studies in postmenopausal women similarly demonstrate that estrogen replacement protects against impaired verbal working memory, episodic memory, learning, and attention following cholinergic antagonism (Dumas et al. 2012, Maki & Dumas 2009, Newhouse & Dumas 2015). However, the beneficial effect of estrogen is seen only in animals with relatively intact cholinergic systems, suggesting that estrogen modulates cholinergic function rather than acts through a separate parallel mechanism. Estrogen's support of cholinergic function may essentially increase cognitive resources and maintain adequate dorsal regulation of emotional cognition.

Estrogen Effects in the Dorsal Regulatory System

Alterations in how changing estradiol levels regulate the neural response to adverse or stressful life events and emotional cognitive functioning may contribute to depression vulnerability. The similarity between changes in cognitive emotional processing in depression and following acute stressors may reflect shared brain networks for mood regulation, emotional processing, and stress responding

The amygdala has reciprocal interactions with the PFC and hippocampus such that amygdala activity suppresses activity in dorsal regions. During the healthy stress response, these reciprocal interactions allow for quick evaluation of and response to stressors; however, these feedforward systems may become dysregulated. Reduced dorsal activity releases amygdala inhibition and may have long-term negative effects on dorsal region structure and function (Gold 2015). Loss of estrogen support for dorsal system functioning may contribute to this dysregulation and, thus, increase depression risk in vulnerable women.

The hippocampus is uniquely situated at the intersection of cognitive, emotional, and endocrine circuits, and, thus, it may have a particularly central role in vulnerability to MDD. Hippocampal structure appears to be sensitive to depression history; a meta-analysis of imaging studies in depression found that reduced hippocampal volume is a consistent finding in individuals with MDD (Videbech & Ravnkilde 2004). Furthermore, hippocampal volume reduction is associated with depression recurrence, with smaller volumes seen in individuals with more past episodes and longer illness duration (Sheline 2000). It remains unclear whether smaller hippocampal volume is the result of depression or a marker of vulnerability due to developmental differences; however, the association between depression history and hippocampal structure accords with the hippocampus as a central component of overlapping networks for endocrine regulation, emotion, and cognitive processes that are integral to MDD etiology.

Estrogen may support adaptive mood regulation through its effects on hippocampal functioning and neuronal plasticity. Estradiol has been shown to increase the density of dendritic spines on CA1 pyramidal neurons (especially following neuronal damage or estradiol loss), and estrogen receptor antagonists block this effect (McEwen 2002). Estrogen receptor localization to the plasma membrane in dendritic shafts and spines (McEwen 2002) suggests that estrogen may have local effects on plasticity in the hippocampus. The presence of estradiol appears to prime the neuron for new synapse creation through an increase

in dendritic spines; however, these new spines are maintained only following synapse activation (McEwen 2002). Estradiol does not globally increase hippocampal synapses, but it supports the production and maintenance of active synapses. Additionally, estradiol treatment protects hippocampal synapses from the detrimental effects of acute cortisol increases (Ooishi et al. 2012). Paralleling these structural changes, estradiol replacement in animal models improves performance on cognitive tasks that are hippocampally mediated (Gibbs 2010). Similarly, changes in cognitive performance across the menstrual cycle and with estrogen replacement in postmenopausal women suggest that ovarian hormones have specific effects on cognitive tasks that rely on hippocampal function (Dumas et al. 2012).

Estrogen receptor density in the hippocampus responds dynamically to ovarian hormone changes, increasing dendritic spines during low estrogen phases of the estrous cycle and decreasing them during high estrogen phases (McEwen et al. 2012). These changes in estrogen receptor density may be part of a mechanism that maintains stable hippocampal function across estrogen fluctuations. A deficit in this dynamic response to estrogen changes may be associated with increased vulnerability to mood and anxiety disorders in some women.

Estrogen has similar effects on cholinergic and serotonergic functioning, and these may converge in the dorsal system. In postmenopausal women, estradiol treatment prevents anticholinergic impairment in memory and attention, indicating that estrogen's support of cholinergic function benefits prefrontal and hippocampal function (Dumas et al. 2012). Similarly, estrogen replacement in postmenopausal women increases serotonin tone in the PFC and anterior cingulate cortex, which is paralleled by improvements in tasks of executive function and verbal memory (Kugaya et al. 2003). Estrogen effects in the PFC may modulate executive function, thus having global implications for cognition and emotional response regulation. Neuroimaging studies examining the effects of estradiol replacement in postmenopausal women show that estradiol replacement enhances hippocampal and prefrontal activity during tasks in which estradiol treatment improves performance (episodic memory and working memory) (Lethaby et al. 2008). Additionally, ovarian hormone suppression in young women impairs executive function and cognitive flexibility and decreases metabolism in the prefrontal, temporal, and parietal regions (Berman et al. 1997). Enhanced function in these dorsal system regions may support cognitive resources and decrease automatic emotional processing or provide better top-down regulation of emotional responses.

Although the sex difference in the prevalence of MDD and the concurrence of ovarian hormone fluctuations with increased risk for mood disorders in women suggest that estrogen may have a significant role in MDD, it is not clear how estrogen influences depression vulnerability. Perhaps estrogen's role in MDD can be best understood through examining estrogen's role in the emotional and cognitive processes that are integral to healthy mood. MDD is characterized by dysfunction in mood regulation and endocrine responses to stress and negative emotional information. These core symptoms are indicative of altered function in proposed systems for emotion evaluation and response (the ventral system) and regulation of emotion and cognitive processes (the dorsal system).

The ventral and dorsal systems are interconnected and work to manage acute responses to environmental stimuli and coordinate long-term cognitive consequences through attention and memory. Dysphoric mood is a natural and healthy response to stress; however, the ability to efficiently return to normal ventral–dorsal system dynamics and euthymic mood confers resilience (Gold 2015). Healthy stress responses acutely bias stimuli processing toward automatic ventral evaluation and response pathways. Consistent findings of endocrine dysregulation in the HPA axis and the relation of stressful life events to depressive episodes indicate that in MDD stress system function is dysregulated, with possible consequences for the cognitive processing of emotional information. When information must be evaluated quickly, such as during stress, altered brain networks in MDD may be prone to ventral activity, resulting in enhanced attention to and cognitive processing of negative information along with dysphoric mood. According to cognitive models of MDD, these alterations remain during remission and contribute to continued recurrence risk, especially following psychosocial stress.

Evidence of estrogen's positive effects on both cognitive and emotional processes indicates that estrogen supports healthy functioning in dorsal regions (particularly the hippocampus and PFC). Estrogen's effect of enhancing dorsal system function may attenuate ventral system activity or allow dorsal system regions to regain regulatory function more efficiently. Conversely, low estradiol reproductive phases in women and the loss of estrogen support of dorsal systems may predispose brain activity to ventral system automatic processing. Sex differences in emotion recognition suggest that women recognize and respond to emotional information at earlier stages in visual processing, that is, before modulation by the dorsal system and integration with associative information. The loss of estrogen support for dorsal systems may bias emotional processing toward these lower-level automatic systems in which amygdala activity predominates and may enhance the salience of negative emotional information, thus increasing depression risk in vulnerable women.

SUMMARY

A neuroanatomical model of depression posits that mood dysregulation is a result of an imbalance in functional activity in the dorsal and ventral divisions of the limbic system and PFC (Phillips et al. 2003). The ventral system is particularly important for identifying the emotional significance of a stimulus and producing an affective state in response to the stimulus. This allows for the rapid appraisal of emotionally valenced stimuli, while the dorsal system provides the capacity to modulate the affective and physiological consequences of ventral output. Greater activity in ventral system structures and less activity in dorsal structures to negative stimuli have been a consistent finding in depression. The dorsal and ventral systems also have roles in the response to psychosocial stress (Pruessner et al. 2010) and emotional cognitive tasks. The HPA axis response to psychosocial stress is associated with increased activity in ventral system structures that is paired with decreased activity in the dorsal system. Alterations in the activity of these structures following stressful events and changes in sex hormone levels may contribute to cognitive bias toward negative information in women with depression and may enhance the perception that negative events are more salient than neutral or positive events.

Fluctuations in estradiol across the menstrual cycle and during the menopause transition may modulate the activity of brain circuits integral to these emotional processes. Gonadal steroid levels during the normal menstrual cycle and exogenously administered compounds have been shown to alter brain activation patterns during cognitive tasks and emotional stimuli. Functional neuroimaging studies in premenopausal women have demonstrated significant differences in cortical activation in response to negative emotional stimuli during high versus low estradiol phases, suggesting estradiol enhancement of top-down modulation of limbic activity with the accompanying suppression of sensory evaluative function (Goldstein 2005). By contrast, a study of emotional conflict resolution in peri- and postmenopausal women showed greater dorsal lateral PFC activation and lower amygdala activation than are typically seen in younger participants and supports a menopause transition for emotional regulation circuitry at this stage (Frey et al. 2010).

A model has been proposed (Kim & Diamond 2002) in which stress, by acting indirectly through elevations in cortisol levels and directly through excess amygdala input to the hippocampus, impairs hippocampal plasticity and, subsequently, cognitive functioning. While amygdala involvement is essential to emotional learning, excess amygdala activation or activation combined with stress appears to impair hippocampal functioning. Estradiol may modulate this process and protect hippocampal activity to reduce the psychological effects of stress and reduce a negative bias in emotional memory. Memory for negative emotional information appears to be directly linked to the degree of amygdala activation during encoding and the interaction between the amygdala and medial temporal lobe memory systems. In addition, psychosocial stress may impair learning by suppressing the activity of these structures. Psychological and psychosocial stress may interact with altered hormone levels during the menopause transition to suppress hippocampal activity and alter memory, particularly for emotional information that requires amygdala input. We have recently shown that periovulatory estradiol levels reduce brain and behavioral aspects of psychosocial stress during the normal menstrual cycle (Albert et al. 2015), with high estradiol levels enhancing the activity of the hippocampus in response to experimental stress. However, high estradiol levels appear to exaggerate the behavioral and cognitive effects of experimental psychosocial stress after menopause (Newhouse et al. 2008), perhaps suggesting why estradiol alone is not a successful antidepressant strategy for most postmenopausal depression.

The amygdala can modulate both the encoding and storage of hippocampus-dependent emotional memories, and bidirectionally the hippocampus, by forming episodic representations of emotional significance, can influence the amygdala response when emotional stimuli are encountered. Estrogen receptor expression in the hippocampus changes across reproductive cycles (McEwen et al. 2012), and this dynamic fluctuation may be part of a mechanism that maintains stable hippocampal function across estradiol fluctuations: increasing estrogen receptors during low estradiol phases and decreasing them during high estradiol phases. A deficit in this receptor response to estradiol changes may be associated with increased vulnerability to mood and anxiety disorders in some women.

In summary, changing levels of estradiol may directly modify the activity of dorsal and ventral emotional regulation nodes and circuits, modifying the cognitive consequences of

life stress (Newhouse & Albert 2015) (Figure 4). When estradiol levels are low, for example during low estradiol phases of the menstrual cycle or during the perimenopause, there is evidence for alterations in the activity of structures involved in affective regulation, and women may experience altered reactivity to stressful life events and negative emotional information. This may lead to enhanced processing and memory for negative emotional information. By contrast, during high estradiol phases, the activity of higher-level structures is enhanced, leading to better stress modulation and less cognitive bias toward negative information. Changes in estrogen levels during the menstrual cycle and during the menopause transition may also alter the amygdala–hippocampus activity relationship in response to negative information. These systems are sensitive to estradiol effects in healthy women, and that relationship may be altered through the menopause transition, thus exposing vulnerable women to mood disruption. Changing levels of estradiol may alter emotional reactivity and the cognitive processing of negative information, but the impact of this effect may be determined by the preexisting emotional state and the presence or absence of concurrent psychosocial stress. Data suggest that varying estradiol levels may have a significant impact on depression in vulnerable women, emotional reactivity, and associated cognitive mechanisms. The brain regions that have been identified in recent neuroimaging studies of depression and psychosocial stress are important targets for investigating vulnerability and are responsive to estradiol manipulation. The clinical implications of these findings suggest that estrogen status may be important for the maintenance of normal mood in genetically vulnerable women and that estrogen treatment or replacement may be appropriate during the perimenopause or postmenopause. While not all women will benefit from the maintenance of hormonal status for the treatment of depression, individuals with early-life depression or those who have clear links to stressful life events may be more vulnerable and may benefit from such adjunctive treatment.

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SUMMARY POINTS

1. The concurrence of a greater prevalence of mood disorders, including major depressive disorder (MDD), in women with reproductive life phases in which estrogen fluctuates suggests a role for estrogen changes in MDD vulnerability in women.
2. MDD is characterized by complex interactions among dysregulated stress system function, emotional regulation, and cognitive processes. The brain systems important for stress response and emotional and cognitive processes show functional alterations in MDD and interact to contribute to MDD symptoms and risk.
3. The brain systems that are affected in MDD are also sensitive to estrogen, and previous research supports that estrogen affects stress response, emotional processes, and cognitive function.
4. In healthy women, estrogen may support brain functioning that optimizes the stress response, emotional processing, and cognitive function, thus preventing cycles of hypothalamic–pituitary–adrenal system dysregulation and emotional dysregulation from leading to depression.
5. In women with other vulnerability factors for MDD, periods of estrogen fluctuation or reduction may present windows of increased risk for the effects of psychosocial stressors or other triggering events on depression occurrence.

FUTURE ISSUES

1. The effect of estrogen on both brain function and emotional response to psychosocial stress should be more carefully examined using methods that focus on altered emotional cognition following stress.
2. The effect of estrogen on stress responding and mood should be specifically examined in women who are currently depressed or at increased risk for MDD.
3. A potential role for estrogen in MDD recurrence should be examined, including assessing the predictive benefit of estrogen effects on stress response and emotional cognition.

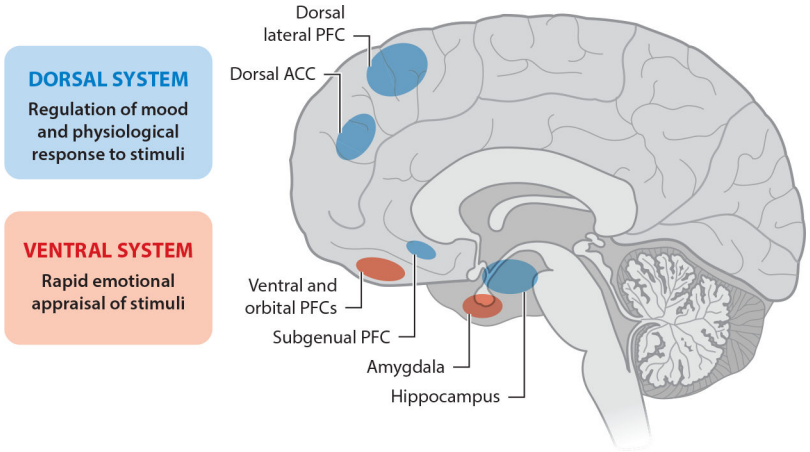

Figure 1.

Ventral and dorsal brain systems for emotion appraisal and regulation. Abbreviations: ACC, anterior cingulate cortex; PFC, prefrontal cortex.

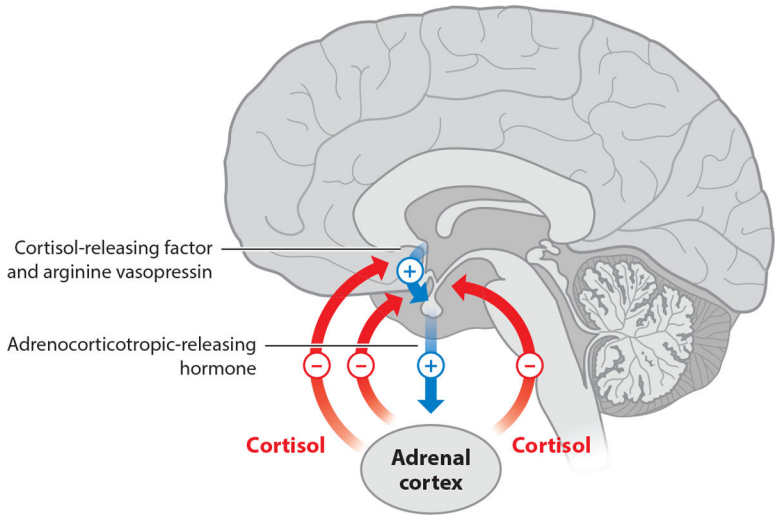

Figure 2.
Hypothalamic–pituitary–adrenal axis.

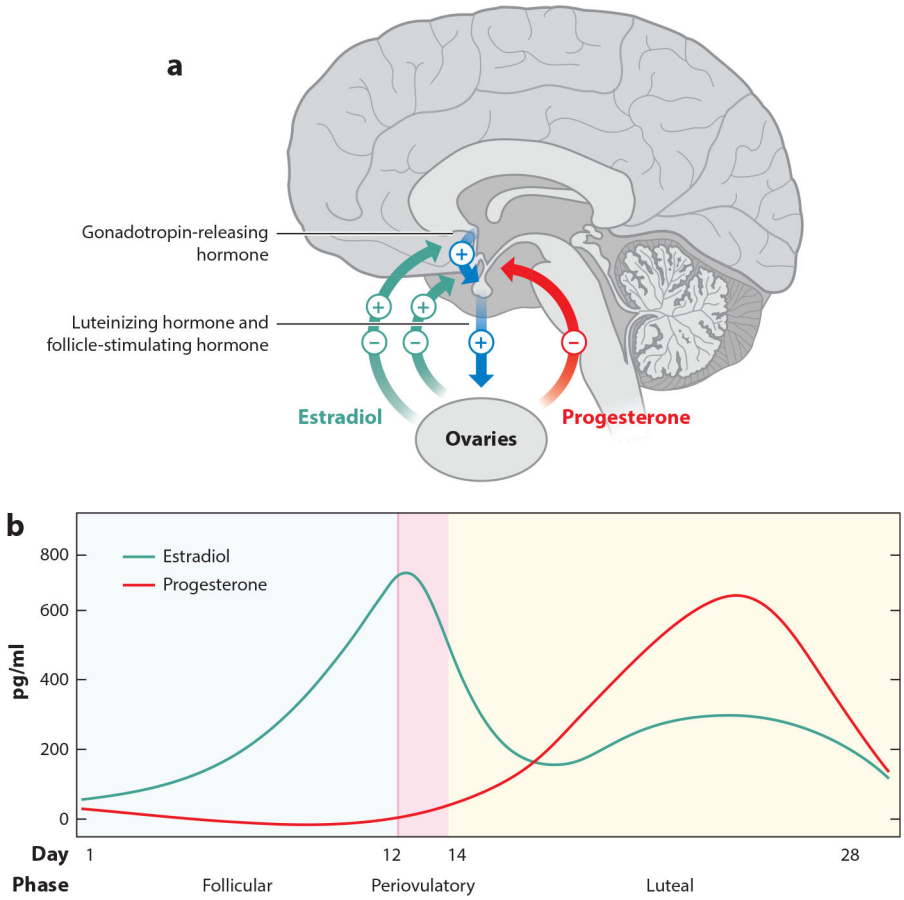

Figure 3.

Ovarian hormones. (*a*) The hypothalamic–pituitary–gonadal axis in women. (*b*) Ovarian hormones during the menstrual cycle.

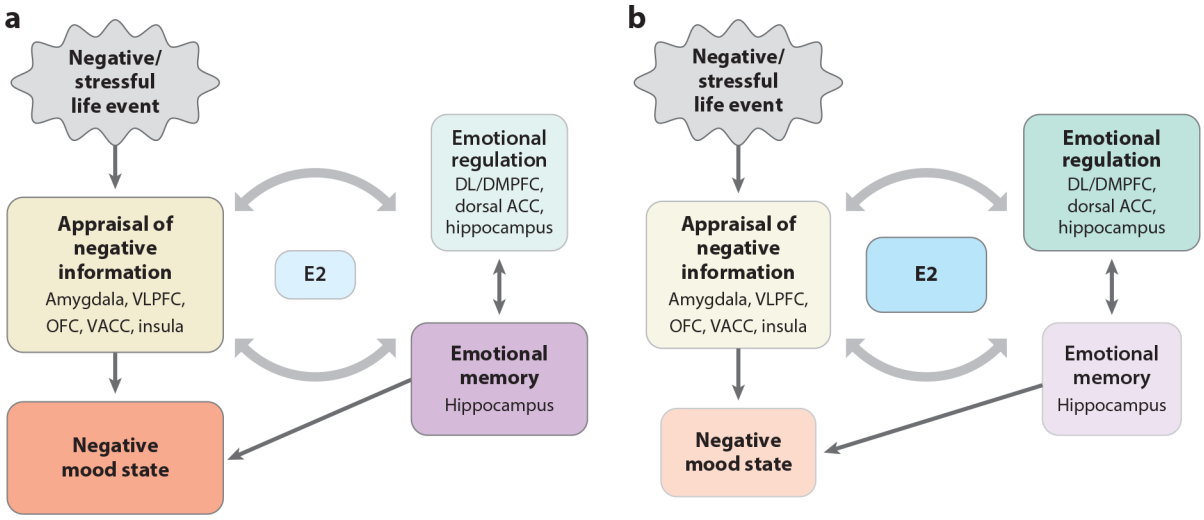

Figure 4.

Proposed effect of differing estradiol levels during the menstrual cycle on dorsal and ventral emotion systems and interactions with stressful life events (e.g., trauma). (*a*) Low estradiol levels during the early follicular phase. (*b*) High estradiol levels during the periovulatory phase. The relative size of shapes indicates increased or reduced effects. High-estradiol-level phases during the menstrual cycle enhance the activity of dorsal regulatory structures during or following stressful events and lead to reduced activity of structures associated with negative emotions and better reappraisal, less negative emotional memory, and reduced negative affective state. This relationship changes during low estradiol phases. Abbreviations: ACC, anterior cingulate cortex; DL, dorsal lateral; DM, dorsal medial; OFC, orbital frontal cortex; PFC, prefrontal cortex; V, ventral; VL, ventral lateral. Figure adapted from Newhouse & Albert (2015).