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Opinion

Hormonal Cycles, Brain Network Connectivity, and Windows of Vulnerability to Affective Disorder

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The rate of affective disorder is substantially higher in women than in men, and considerable evidence points to the actions of ovarian hormones in mediating this disparity. In this Opinion, we discuss the hypothesis that cyclic changes in ovarian hormone levels produce cyclic alterations in connectivity between the intrinsic networks of the brain. These alterations produce specific temporal windows within the menstrual cycle when internetwork connectivity is increased, associated with increased stress reactivity and better memory for unpleasant, arousing events, leading to increased negative mood and susceptibility to affective disorder. Our windows of vulnerability model offers insights for both treatment of affective disorder and research on sex differences in the brain.

Sex Differences in Affective Disorder

It is well established that disorders of affect are substantially more common in women than in men [1]. Women are about twice as likely as men to suffer from depression and anxiety disorders [1,2] and twice as likely to experience post-traumatic stress after a traumatic experience [3,4], even when exposed to equivalent types of trauma [5]. The source of this disparity is not fully understood, but converging evidence points to a relationship between cycling ovarian hormone levels and symptoms of affective disorder in women [6]. These findings suggest that the sex difference in susceptibility to affective disorder is not static, but may be heightened during specific time periods within the hormonal cycle, as well as during specific periods during the lifespan when ovarian hormones are particularly elevated or variable, such as in adolescence.

In this Opinion, we propose a model of how the neural, physiological, and cognitive effects of ovarian hormones may combine to create temporal windows of increased vulnerability to affective disorder. We suggest that high levels of ovarian hormones, particularly progesterone, released during the luteal phase of the menstrual cycle, serve to transiently alter communication within and between the intrinsic networks of the brain, which in turn leads to enhanced stress reactivity, enhanced memory for negative experiences, and ultimately, increased risk of affective disorder.

We first review evidence for the role of ovarian hormones in sex differences in affective disorder, and then present our model. Next, we summarize links between affective disorder and network connectivity, stress reactivity, and memory for evocative events. We then examine the effects of ovarian hormones in each of these domains, to illustrate similarities between alterations observed in affective disorder and cyclic changes in brain, body, and memory. Finally, we consider the implications of hormone fluctuations, for both clinical treatment and basic research on sex differences in neural activation and connectivity.

Highlights

Prevalence of affective disorder points at a prominent sex-specific component. Specifically, women are diagnosed with affective disorder approximately twice as frequently as men are.

Women experience more frequent affective symptoms during the luteal phase of the menstrual cycle, when progesterone levels are high.

During the luteal phase, connectivity between the default mode and salience networks of the brain, endocrine stress responses, and memory for affective experience all increase. Similar increases in these areas are observed in comparisons between individuals with affective disorder and healthy controls.

We propose that sex differences in affective disorder can be explained by a midluteal window of vulnerability in women, in which increased connectivity, stress reactivity, and affective memory make negative experiences more potent and memorable, promoting negative affect.

We argue that examining sexually dimorphic aspects of brain structure and function at singular time points can be misleading, and that such differences should be conceptualized as part of a dynamic process unfolding over time. This may help explain discrepancies in studies of sex differences in brain function.

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Role of Ovarian Hormones in Women's Increased Rates of Affective Disorder

It has been frequently suggested that women may suffer from affective disorder at rates greater than men, in part, because of the mediating actions of ovarian hormones [6,7] (see Box 1 for a discussion of sex vs gender differences). This hypothesis is based primarily on two distinct temporal patterns of affective symptomology in women. First, sex differences in affective disorder are not constant over the lifespan but emerge at adolescence [8] and decline postmenopause [9,10], such that the higher rate of affective disorder in women becomes more pronounced during the reproductive years, when ovarian hormone levels are at their highest levels. Periods of maximal change in ovarian hormone levels, such as during and after pregnancy [11], and during menopausal transition [12], are also associated with more frequent affective symptoms. Second, affective symptoms vary over the course of the menstrual cycle, with more intense and frequent symptoms occurring in the luteal phase when progesterone levels are at peak and estrogen levels are moderate, and fewer occurring postmenses in the early follicular phase, when levels of both hormones are low [13] (for a schematic of hormone levels throughout the menstrual cycle, see Figure 1A, Key Figure; and see Box 2 for a discussion of menstrual phase terminology). Women suffering from depression [14,15] as well as panic and anxiety disorders [16,17] report more frequent symptoms in the mid-to-late luteal period, when ovarian hormones begin a rapid decline from the midluteal peak.

The hypothesis that ovarian hormones are linked to affective symptoms is supported by observing hormone changes in women suffering from depression. Some studies have reported elevated luteal levels of progesterone and reduced estrogen in depressed women compared to controls, suggesting that larger hormonal contrasts, particularly in the luteal phase, may promote depressed mood [18,19]. The hormone hypothesis is also supported by studies that have observed the effects of exogenous application of ovarian hormones. Exogenous progesterone increases neural responses to negative stimuli and alters the communication of brain networks involved in emotion regulation, leading some to suggest that activational effects of ovarian hormones underlie sex differences in affective disorder [7]. Furthermore, two recent large epidemiological surveys have indicated that the use of oral contraceptives (which acutely bind estradiol and progesterone receptors with synthetic hormones, but reduce endogenous hormone levels over time [109]) is associated with significantly increased risk of depression [20] and suicide attempts [21], particularly among adolescents. Notably, the use of progesterone-only contraception is associated with greater risk when compared to combined estrogen/progesterone treatments [20,21]. Thus, it seems that alterations of ovarian hormone levels, particularly involving the greater progesterone levels of the midluteal phase, promote intense, unpleasant moods associated with affective disorder.

Box 1. A Note on Sex and Gender

In our discussion of vulnerability to affective disorder, we focus exclusively on differences pertaining to a person's sex chromosomes, sex hormone levels, and reproductive phenotype, colloquially referred to as a person's biological sex. We refrain from any discussion of gender, which is a social construct including various aesthetic and normative notions often related to sex, which is determined by an individual's self-identification, rather than any measurable biological factor. While many of the relevant studies report their findings as gender differences, in many of these cases the term gender is used (imprecisely, in our view) as synonymous with sex.

It must be acknowledged that gender roles and the various societal institutions that shape them likely play some role in sex differences in affective disturbances. This is particularly relevant in cases in which biological sex and self-identified sex or gender differ. For the purpose of this article, we limited the discussion to sex-related effects, which can be mapped to biological factors such as the actions of ovarian hormones in a more straightforward way.

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Key Figure

Windows of Vulnerability Model

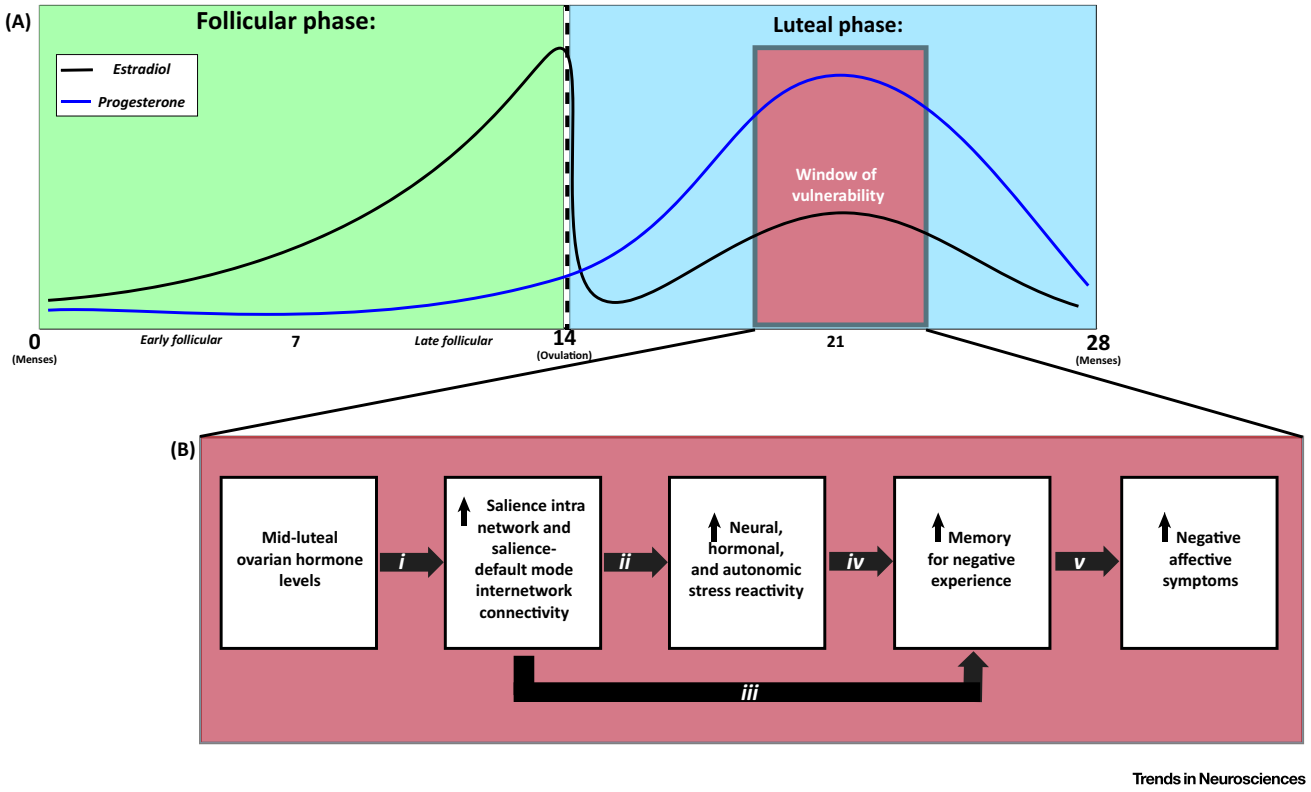

Figure 1. (A) Schematic of the midluteal window of vulnerability in the context of hormone levels across the menstrual cycle. Increased risk of affective disorder occurs midway between ovulation and next menstruation, when progesterone levels are at peak, and estradiol levels are moderate. (B) Effects of ovarian hormones on brain, body, and memory, leading to increased affective vulnerability. (i) Elevated ovarian hormone levels in the midluteal phase alter connectivity between the salience network and default mode network. (ii) Increased internetwork connectivity promotes greater neural, hormonal, and autonomic stress responses. (iii) Increased internetwork connectivity also promotes encoding, consolidation and retrieval of negative experiences. (iv) Enhanced stress responses cause negative experiences to be experienced as more arousing, further promoting affective memory enhancement. (v) Enhanced encoding, consolidation, and retrieval of negative events produce distortions of memory, which promote experiences of intense negative affect.

A Luteal Window of Vulnerability to Mood-Related Symptoms

We hypothesize that the greater frequency of affective symptoms at luteal hormone levels can be explained by the enhancing effects of ovarian hormones on connectivity between brain networks, physiological stress responses, and affective memory. Our luteal window of vulnerability model is shown in Figure 1. We propose that high levels of ovarian hormones present during the midluteal phase of a woman's menstrual cycle produce changes in brain, body, and memory, which make negative life events more potent and memorable, promoting affective disturbances. Midluteal levels of estrogen, progesterone, and their metabolites are associated with increased connectivity within and between brain networks involved in affective and memory processing, promoting greater communication between these networks (Figure 1B, path *i*). This has the effect of both

Box 2. Differences in Menstrual Phase Terminology

The terminology used to describe differing phases of the menstrual cycle varies in the research literature. Some studies defined menstrual phases in terms of their position relative to the ovulatory luteinizing hormone surge (i.e., midluteal = 4–10 days postovulation, as in [22]). Others count from the onset of menstruation (i.e., midluteal = days 18–24 postmenstruation). We define menstrual cycle phases relative to the timing of ovulation, because they are more likely to capture meaningful hormonal contrasts, and therefore better able to account for individual variability in cycle length (see [23,24] for discussion). The majority of studies discussed in this opinion article did not measure ovulation, however; therefore we use terminology relative to menstruation throughout this Opinion for ease of comparison. We describe all studies using the following definitions: early follicular = days 2–7 postmenstruation; late follicular = days 8–13; early luteal = days 15–17; midluteal = days 18–24; and late luteal = days 25–28. These windows are intentionally broad so that studies with varying phase definitions can be described using a common vocabulary. These may not always be the terms used in the papers we discuss, but using these definitions we aimed to accurately reflect the number of days since menstruation reported in the original text.

facilitating the neural, hormonal, and autonomic responses to stress (path *ii*), and increasing the influence of arousal on memory (path *iii*). Additionally, facilitated stress responses enhance the consolidation of memory for negatively arousing events (path *iv*). This results in a bias in encoding and retrieval favoring high-arousal, unpleasant experiences. Together, increased reactivity to and memory for negative events promotes the experience of intense negative affect (path *v*), increasing the prevalence of affective symptoms through the end of the luteal phase, when ovarian hormones return to low levels.

Evidence from clinical research points to increased internetwork brain connectivity, stress reactivity, and negative memory bias in affective disorder, consistent with the notion that these changes in brain, body, and memory promote an affectively vulnerable state. We review this evidence in the following section to illustrate similarities to changes observed during the midluteal window of vulnerability.

Network Connectivity, Stress Reactivity, and Memory in Affective Disorder

Intrinsic Brain Network Connectivity in Affective Disorder

A common feature of nearly all psychiatric disorders is a loss of coherence in the intrinsic networks of the brain [25]; networks that are typically dissociable at rest (i.e., when a person is not exposed to an extrinsic stimulus) show increased connectivity and communication. Two of these networks, conventionally named the default mode network and salience network, have been implicated both in affective experience [26,27] and in disorders of affect [28]. The default mode network is a collection of brain regions including precuneus/posterior cingulate cortex, medial prefrontal cortex, hippocampus, and lateral parietal cortex (Figure 2A) and whose increase in activity has been associated with a wide range of psychological phenomena including the encoding and retrieval of memory [29,30] and affective processing [26,31]. The salience network is a collection of brain regions including the anterior sector of the midcingulate cortex (also called dorsal anterior cingulate cortex [32]) and the dorsal anterior insula (Figure 2A), and is similarly associated with a wide variety of psychological phenomena [36], including anxiety [33], stress [34], affect [27,35], and memory [36]. Default mode and salience networks overlap in various brain regions, which may serve as one of many points of communication between them, including amygdala and several rich club hubs [37] that are important for synchronizing activity across brain networks [38].

Alterations of connectivity both within and between these networks have been reported in affective disorder. Individuals suffering from depression exhibit increased connectivity within the default mode network, particularly between medial prefrontal cortex and its other nodes [39], as well as decreased connectivity of the anterior insula to the salience network [40], which

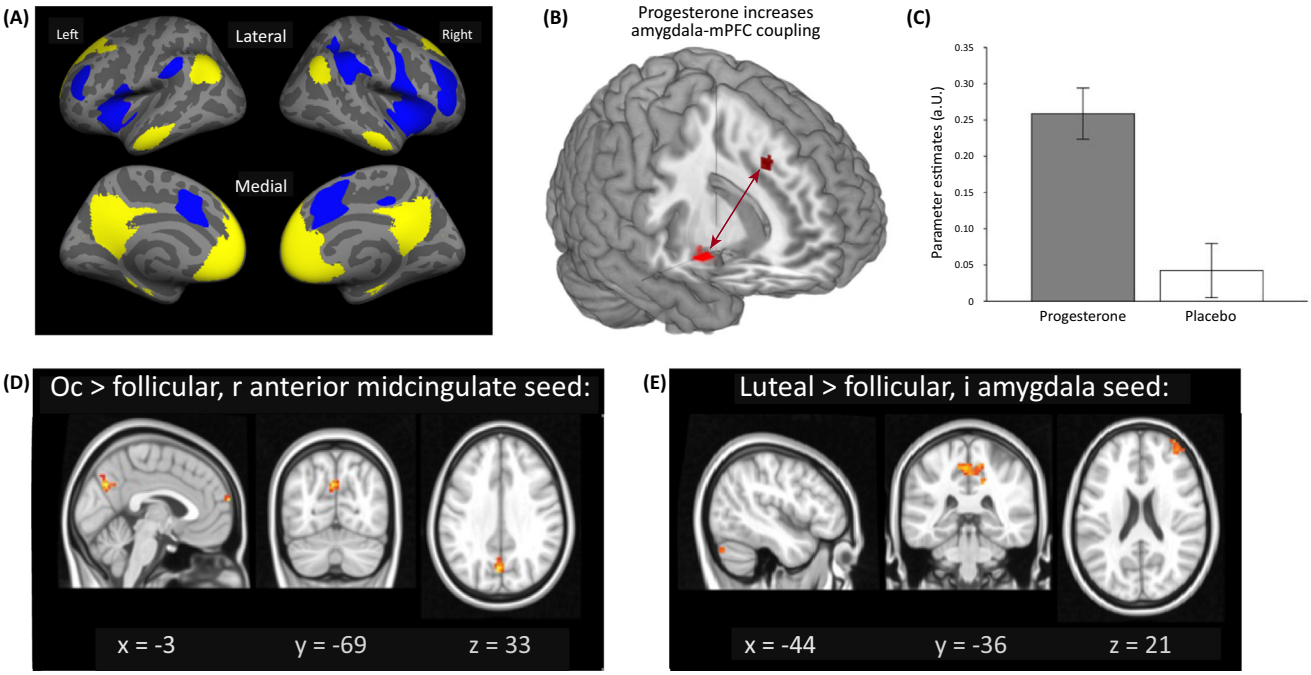

Figure 2. Ovarian Hormones Influence Salience Network Connectivity. (A) Default mode (yellow) and salience (blue) networks [122]. (B) Exogenous progesterone increases connectivity between amygdala and medial prefrontal cortex [75]. (C) Exogenous progesterone increases connectivity between amygdala and anterior midcingulate [75]. (D) Treatment with oral contraceptives increases connectivity of anterior midcingulate to precuneus [73]. (E) Regions of greater connectivity to left amygdala in luteal versus follicular phase, including cerebellum, precuneus (center), and lateral prefrontal cortex [73].

predicts symptom severity [41]. In post-traumatic stress disorder (PTSD), default mode connectivity is reduced, and connectivity between salience nodes, notably amygdala and insula, increases [42]. The default mode network has been associated with internally directed attention and self-referential processing, leading some to suggest that greater default mode coherence in depression represents excessive bias towards the internal versus external world, leading to decreased motivation towards external goals [39]. Increased connectivity between salience nodes in PTSD is believed to represent hypervigilance and increased sensitivity to threat [42].

Multiple forms of affective disorder are associated with altered connectivity between the salience and default mode networks, such that salience connectivity to the anterior portion of the default mode network decreases, while connectivity to the posterior nodes increase. Studies of internetwork connectivity suggest, for example, that depression is associated with differing patterns of connectivity between the salience network and anterior versus posterior regions within the default mode network. A recent meta-analysis observed reduced connectivity between medial prefrontal cortex (an anterior node in the default mode network) and multiple salience nodes in depressed individuals [39]. In contrast, both lateral [41,43] and medial posterior regions of the default mode network, such as the posterior cingulate cortex/precuneus area show increased connectivity to nodes within the salience network during depression [39,41,44]. Similarly, both social anxiety and PTSD are associated with decreased amygdala–medial prefrontal cortex connectivity [40,42,45], and increased connectivity

between salience network and posterior cingulate/precuneus [40,42,46]. Consistent with these findings, greater internetwork connectivity predicts PTSD symptom severity [47].

One possibility is that differences in internetwork connectivity between anterior and posterior components of the default mode network represent distinct deficits associated with affective disorder. Decreased connectivity between medial prefrontal cortex and salience nodes has been suggested to represent a reduced capacity for emotion regulation [39]. Hyperconnectivity between salience nodes and posterior cingulate/precuneus may represent increased self-relevance in negative affect, and has been associated with enhanced memory for negative experiences [40]. Consistent with this view, salience connectivity with medial posterior default mode network is associated with increased depressive rumination [48].

Stress Responsiveness in Affective Disorder

Individuals suffering from affective disorder also show altered neural and physiological responses to stress. During the viewing of unpleasant stimuli such as faces depicting scowls and frowns [49] and negatively arousing scenes [50], individuals diagnosed with major depressive disorder show significantly larger amygdala responses when compared to healthy controls, suggestive of greater negative arousal [35]. Consistent with this observation, both depression and PTSD [51] are also associated with significantly reduced heart rate variability; a measure that is influenced by both the sympathetic and parasympathetic divisions of the autonomic nervous system, and can thus serve as an indicator of the balance of activity between them, where greater sympathetic activity promotes larger stress responses. Reduced variability suggests a withdrawal of parasympathetic control of the heart, and increased control by the sympathetic nervous system. Additionally, depression is characterized by alteration of cortisol metabolism; depressed individuals exhibit both augmented [52,53] and prolonged [54] cortisol responses to psychosocial stress, as well as inhibited negative feedback of cortisol release [55]. Similarly augmented responses [56] and feedback inhibition [57] have been observed in PTSD.

Memory and Affective Disorder

Many mood disorders are accompanied by the distortion of memory. Depression has been consistently associated with a negative memory bias, such that negative experiences are better remembered than positive ones [58]. Similarly, words signaling threat are better remembered in anxiety disorder than neutral words are [59]. Persistent and intrusive memories of trauma are the hallmark of PTSD [60], which is also associated with disruptions of neutral memory function [61].

Effects of Ovarian Hormone on Network Connectivity

In our window of vulnerability model, we propose that the chain of events leading to increased affective vulnerability begins with midluteal hormone levels promoting increased internetwork brain connectivity (Figure 1B, path *i*). In this section, we discuss evidence supporting the hypothesis that ovarian hormones transiently alter connectivity between the default mode and salience networks during the menstrual cycle, setting the stage for effects on stress reactivity and memory (for evidence of neural effects of ovarian hormones in animal models, see Box 3).

Ovarian hormones may influence connectivity in the brain both directly and indirectly. Estrogen and progesterone receptors are expressed throughout the brain, including in multiple nodes of the default mode and salience networks [62,63]. Notably, estrogen receptors are robustly expressed in the hippocampus, and the amygdala shows the densest expression of progesterone receptors in the brain outside of the hypothalamus [62,63]. Additionally, progesterone

Box 3. Neural, Endocrine, and Behavioral Effects of Ovarian Hormones in Animal Models

Many of the behavioral, hormonal, and neural findings described for humans have also been reported in studies of non-human animals, particularly in rodent models. Rodent studies have shown that high levels of ovarian hormones promote the growth of new synapses, thereby altering brain connectivity. This leads to a cyclicity of synaptogenesis in the hippocampus and other brain regions, with the highest levels occurring during the high-hormone proestrus (analogous to late follicular) phase [106].

Estrus cycle effects on stress responsiveness have also been demonstrated, with greater cortisol responses observed in the proestrus phase, when estrogen and progesterone levels are high, compared to the low-hormone estrus phase (analogous to menstrual/early follicular in humans) [107].

Cyclic effects of stress on memory in rodent models have also been observed. Associations with threat learned in the postovulatory metestrus phase (analogous to luteal) are significantly more resistant to extinction than those learned in the preovulatory proestrus phase (analogous to follicular), suggesting that affective memories are better encoded or consolidated when ovarian hormone levels are high. Additionally, high ovarian hormone levels predict higher levels of anxiety behavior in rodents [108].

Thus, each of the core predictions of the windows of vulnerability model on connectivity, stress reactivity, memory, and mood has been observed in animal studies.

effects may be mediated by the actions of the progesterone metabolite allopregnanolone, a positive modulator of the GABA-A receptor [64]. Cyclic variation in allopregnanolone levels matches the pattern of progesterone, with a midluteal peak. Allopregnanolone can influence connectivity both within and between salience and default mode networks [65,66], and is also associated with increased amygdala activity and negative affect [64].

Studies of ovarian hormones on connectivity show diverse influences on multiple intrinsic brain networks, including default mode, salience, and frontoparietal control networks [40]. The majority of these studies indicate that cyclic changes in ovarian hormones can alter the communication of the intrinsic networks of the brain. Some, however, have not detected phase-related effects on connectivity [67,68]. Among studies that do show ovarian influences, effects vary by the menstrual phase at time of study and the network of interest (Table 1). Additionally, in studies that compare multiple menstrual phases, both the choice of phases compared and the specific definition of those phases seem to influence outcomes.

Additionally, individual hormones may influence network connectivity in various ways, depending upon other elements of the hormonal milieu during a particular menstrual phase. Multiple studies of the default mode network indicate that increasing levels of estradiol prior to ovulation predict greater connectivity between nodes of the default mode network compared to the early follicular phase [22,69,70]. However, estradiol only predicts greater default mode network connectivity prior to ovulation. It does not enhance connectivity in the luteal phase [66], and comparisons of default connectivity between the early follicular phase and the higher-estrogen luteal phase have shown both increased [22] and decreased [71] luteal connectivity. In the luteal phase (but not during the follicular phase), greater connectivity between nodes of the default mode network is instead associated with increased levels of the progesterone metabolite allopregnanolone [66].

Recent studies of cyclic effects on the salience network have also pointed to increased intra- and internetwork salience connectivity during the luteal phase. Both the anterior midcingulate cortex and the amygdala show broad increases in connectivity relative to the (low-hormone) follicular phase; most notably to other regions within the salience network, such as the ventral striatum [72] and to the posterior hubs of the default mode network such as the precuneus [73]

Table 1. Studies of Ovarian Influences on Network Connectivity

Authors	Study population	Finding
Pletzer *et al.*, 2016 [22]	18 NC F	Diverse hormone effects in DMN, FPN, sensory and limbic
Syan *et al.*, 2017 [66]	25 NC F	No Fo vs L effect: numerous connectivity/hormone correlations
De Bondt *et al.*, 2015 [67]	18 NC F, 18 OC F	No difference in DMN or ECN, Fo vs L
Hjelmervik *et al.*, 2014 [68]	16 NC F, 15 M	No cyclic effect on connectivity in frontoparietal regions
Lisofsky *et al.*, 2015 [69]	25 NC F	↑ hippocampal volume, DMN connectivity in LF vs EF
Weis *et al.*, 2011 [70][a]	14 F 15 M	↑ DMN connectivity in Fo vs Me
Petersen *et al.*, 2014 [71]	45 NC F, 46 OC F	↑ DMN connectivity, ↑ ACC-ECN connectivity in EF vs ML
Wetherill *et al.*, 2016 [72]	38 F	↑ dACC connectivity to frontal cluster including sgACC in L
Engman *et al.*, 2018 [73]	35 NC F	↑ SN and SN-DMN connectivity in L and OC users vs Fo
Thimm *et al.*, 2014 [74][a]	21 NC F	↑ L asymmetry in SAN in menstrual vs Fo or L
van Wingen *et al.*, 2008 [75][a]	18 NC F	Exogenous P increases amygdala–ACC, amygdala mPFC connectivity
Ottowitz *et al.*, 2008 [77]	11 F	Exogenous E increases hippocampus–MFG connectivity

ACC, anterior cingulate cortex; DMN, default mode network; E, estradiol; ECN, executive control network; EF, early follicular; F, female; Fo, follicular; FPN, frontoparietal; L, luteal; LF, late follicular; M, male; Me, menstrual; MFG, middle frontal gyrus; ML, midluteal; mPFC, medial prefrontal cortex; NC, naturally cycling; OC, oral contraceptive; SAN, selective attention network; sg ACC, subgenual anterior cingulate cortex; SN, salience network.
[a]Task-related connectivity.

(Figure 2E). Additionally, elevated levels of the progesterone metabolite allopregnanolone, which reaches peak levels in the midluteal phase, predict greater communication between the anterior midcingulate cortex, a key salience node, and temporal nodes of the default mode network [66]. Other studies, however, have reported reduced connectivity between some network nodes in the luteal phase [22] or no luteal-phase-related effects on connectivity [67,68].

These divergent findings may be explained by differences in network definitions. For example, Hjelmervik and colleagues [68] have reported no phase-related effects on intrinsic connectivity, whereas other studies have observed cyclic differences [72,73], but they have restricted their search to frontoparietal regions and excluded connectivity to subcortical regions such as the amygdala, hippocampus, and striatum.

Divergent findings may also result from differences among studies in the choice of which specific menstrual phases to compare. Studies reporting greater internetwork [73] and intrasalience network connectivity [72,73] in the luteal phase have contrasted luteal connectivity with the early follicular phase, when both estradiol and progesterone levels are low. In contrast, studies reporting no effect have focused on the later part of the follicular phase (days 7–11) [68], and the midfollicular phase (days 5–10) [66], during which the preovulatory estradiol surge may have already begun in some participants. Thus, midluteal levels of hormones may produce greater connectivity relative to low hormone levels, but elevated estradiol seems to attenuate this effect.

Additionally, inconsistencies in cycle measurement may also explain some conflicting results. Many studies comparing network connectivity between cycle phases have relied exclusively on self-report; a measure that is frequently inaccurate [24]. Others have produced more reliable estimates by supplementing self-report with measurements of gonadal hormone levels or

tracking of the preovulatory luteinizing hormone surge [23]. Variability in cycle length could further complicate matters. While a mean cycle length of ~28 days is consistent across studies, few women actually report cycles of exactly 28 days [24]. However, few of the studies surveyed here report adjustment for individual differences in cycle length in assignment of cycle phase [68,70,74]. Without this adjustment, phase assignment may be unreliable or imprecise.

Studies of exogenous application of ovarian hormones have the advantage of avoiding difficulties with cycle measurement and definition, although they present the additional challenge of observing hormone function in the context of a varying hormonal milieu. Even so, findings from these studies have consistently indicated ovarian effects on brain work connectivity. Treatment with exogenous progesterone during the otherwise low-hormone early follicular phase increases connectivity between a lateral region of the amygdala and multiple nodes of the salience and default mode networks, including the midcingulate and medial prefrontal cortices [75] (Figure 2B,C). The progesterone-mediated increase in amygdala–medial prefrontal cortex connectivity has been hypothesized to promote greater rumination on negative events [7], and indeed greater connectivity between these regions has been associated with perseverative negative thoughts [76]. Exogenous estradiol infusion also increases connectivity between the amygdala and medial prefrontal cortex [77], suggesting that estrogens also play a role in midluteal increases in internetwork connectivity. Consistent with this view, the use of combined oral contraceptives (which include both exogenous estradiol and progesterone) increases connectivity between the anterior midcingulate, a major salience network node, and precuneus, a key node of the default mode network [73] (Figure 2D).

Thus, while more precise research is needed to standardize cycle measurement and definition, the available evidence indicates that the intra- and internetwork connectivity of the salience network is elevated in the midluteal phase compared to the low hormone early follicular/menstrual phase. Exogenous doses of both hormones released in the midluteal phase similarly promote greater salience-default mode internetwork connectivity; a brain state observed in multiple studies of affective disorder.

Effects of Ovarian Hormones on Endocrine, Physiological, and Neural Responses During Stress

A key hypothesis of our windows of vulnerability model is that increased intrasalience network connectivity, as well as increased internetwork connectivity of salience and default mode network nodes lead to increased neural, physiological, and endocrine responses during stressful events (Figure 1B, path *ii*). Consistent with this hypothesis, several studies have indicated that measures of both physiological and endocrine stress reactivity are positively correlated with the connectivity among various salience and default mode nodes. On the physiological level, connectivity of both the amygdala and anterior midcingulate to the brainstem, thalamic, and prefrontal regions positively predicts heart rate variability, which is a marker of autonomic nervous system function [78,79]. On the hormonal level, connectivity within the salience network [80], as well as between the amygdala and hippocampus, is associated with the magnitude of cortisol responses [78,81]. Thus, cyclic changes in brain network connectivity described previously (Table 1) could lead to cyclic changes in stress reactivity, as our hypothesis predicts.

Ovarian Hormone Effects on Neural Responses to Negative Stimuli

High levels of ovarian hormones, particularly progesterone, produce augmented amygdala responsiveness to negative stimuli, representing an increase in stress reactivity similar to that

observed in affective disorder. During the luteal phase, when progesterone levels are elevated, the amygdala is generally more reactive to stress [82], producing greater responses to both negative faces [83] and scenes [84] (Figure 3A) as compared to the follicular phase when progesterone levels are lower. A similar increase in amygdala responsiveness is produced by the exogenous application of the hormone at midluteal levels [75]. Gray matter volume of the dorsal amygdala increases in the late luteal phase relative to the late follicular estrogen surge, and this increase predicts stress sensitivity, suggesting that cyclic effects on stress responsiveness are related to anatomical changes [85].

Rising estrogen in the late follicular period is associated with a decreased response in the amygdala and other affective regions relative to the low-hormone early follicular period [86,87], suggesting that estrogen opposes the effects of progesterone, reducing stress reactivity.

Ovarian Hormone Effects on Physiological and Endocrine Stress Responses

Midluteal levels of ovarian hormones also produce a state of facilitated physiological reactivity, producing a pattern of findings that parallels many of those seen with neural stress reactivity. During the luteal phase, multiple markers of sympathetic nervous system activity, including heart rate, [88] low frequency heart rate variability [89], and muscle sympathetic nerve activity [90] are all increased relative to the follicular phase, indicating a greater physiological reaction during stress. Similarly, high frequency heart rate variability is reduced in the luteal phase [88,89], suggesting a reduction in calming parasympathetic activity, as observed in previous studies of depression [91].

Further supporting our hypothesis of greater luteal stress reactivity, endocrine stress responses are also facilitated in the midluteal phase. Both noradrenergic [92] (Figure 3D) and cortisol responses during social [93] and physical stress [94] (Figure 3B) are facilitated in the luteal relative to follicular phase. These physiological and endocrine changes are accompanied by increased subjective anxiety and depression during stress in the midluteal phase [81].

Taken together, these findings indicate that luteal levels of ovarian hormones augment neural, physiological, and hormonal responses during stress, producing alterations in stress responsiveness similar to those found in affective disorder, possibly through ovarian influences on network connectivity.

Ovarian Hormone Effects on Memory for Negative Material and Events

Our model predicts that both increases in internetwork connectivity and augmented physiological stress responses serve to facilitate memory for unpleasant or stressful events (Figure 1B, paths *iii* and *iv*). Consistent with these hypotheses, multiple studies indicate that women have better memory for negative, unpleasant material during the midluteal phase, when progesterone levels are at peak. Women exhibit a greater enhancement of memory for negative versus neutral material during the luteal compared to follicular phase [95–97], as well as a positive relationship between memory for negative material and progesterone levels at encoding [95,98]. This enhancement of memory extends beyond intentional retrieval, as negative material encoded during the luteal phase (vs follicular) is also significantly more likely to produce spontaneous intrusive recollections [99,100]. Enhanced memory for negative material in the luteal phase may be a result of cyclic changes in the effects of hormones released during stress on memory; cortisol levels at encoding positively predict memory only during the midluteal phase, with negative and nonsignificant relationships in the early and late follicular phases [94].

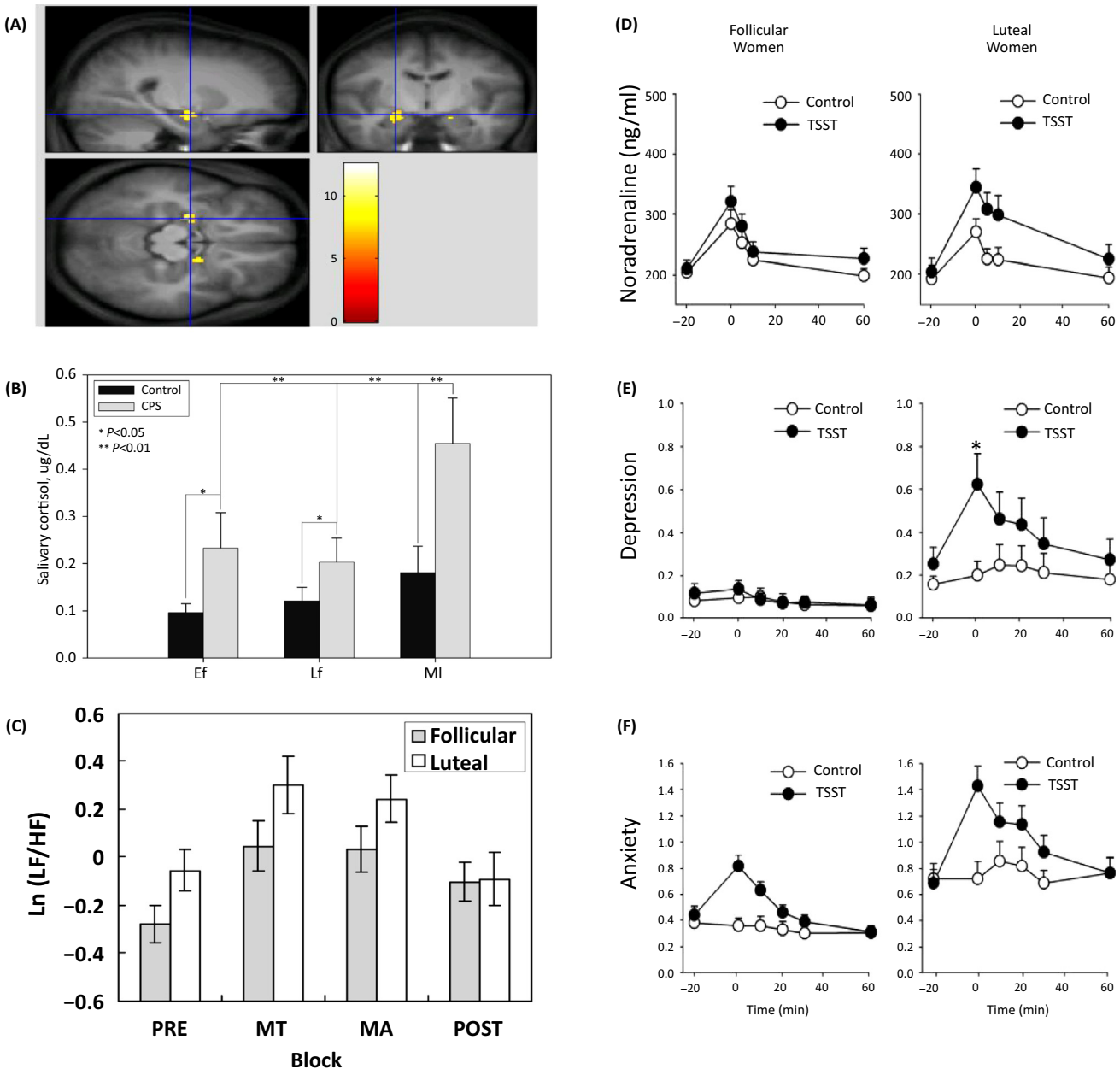

Figure 3. Ovarian Hormones Influence Stress Reactivity. (A) Enhanced amygdala signal to negative images in luteal versus follicular phase [84]. (B) Cortisol response to cold pressor stress in early follicular (EF), late follicular (LF), and midluteal (ML) phases. Cortisol response is significantly elevated in ML [94]. (C) Ratio of high frequency to low frequency heart rate variability before and after mirror-tracing (MT) and mental arithmetic (MA) tasks in follicular and luteal phases. LF/HF ratio is significantly greater in luteal phase [89]. (D–F) Comparison of follicular and luteal women's response during cold pressor stress in terms of (D) noradrenaline response, (E) subjective depression, and (F) subjective anxiety. TSST, Trier Social Stress Test [92].

As hypothesized in our model (Figure 1B, path *iii*) these cyclic changes in memory for negative material could be mediated by cyclic changes in network connectivity and stress reactivity. Communication between nodes of the salience and default mode networks has been associated with improved memory for evocative stimuli [101–103]. They could also result from facilitated hormonal responses during stress (Figure 1B, path *iv*), as increased levels of both cortisol [104] and epinephrine [105] postencoding are associated with enhanced memory, particularly for evocative material.

Concluding Remarks

In this paper, we have outlined evidence to support the hypothesis that, during the midluteal phase of the menstrual cycle, women may experience a window of vulnerability to negative events, such that these events are experienced more intensely, produce larger effects on the body, and are easier to encode and retrieve. Evidence from brain imaging research indicates that two intrinsic brain networks involved in affective and memory processing, the salience – and default mode networks – become better connected when ovarian hormones are at midluteal levels. At the same time, neural, endocrine, and physiological responses to stress are increased. Both increased internetwork connectivity and stress response lead to enhanced memory for unpleasant material, making negative life events easier to recall, promoting negative affective experience, and potentially leaving women vulnerable to developing a longer lasting mood disturbance. These changes in connectivity, stress reactivity and memory resemble changes observed in studies of affective disorder.

Substantial research is still needed to clarify the causal links proposed in Figure 1 (see Outstanding Questions). Nonetheless, the windows of vulnerability model may offer new options for prevention and treatment, as well as new interpretations for research on sex differences in the brain, and neuroimaging more generally.

Implications for Prevention and Treatment

The findings reviewed here indicate that both acute administration of exogenous ovarian hormones and use of oral contraceptives over a period of one cycle produce effects on brain network connectivity and reactivity similar to those observed in disorders of affect [73,75]. This suggests an elevated risk of affective symptoms in women beginning the use of hormonal contraception. However, it is not clear how longer-term use of contraceptive drugs might influence brain network connectivity, stress reactivity, and memory, as no study (to our knowledge) has directly compared short-term and long-term effects. The use of synthetic hormones tends to substantially reduce endogenous hormone secretion [109], which could perhaps attenuate vulnerability stemming from endogenous mechanisms, but exogenous hormone exposure, such as taking synthetic hormones, also typically increases risk of affective disorder [20,21], so the overall effect is difficult to predict in the absence of direct observational studies. Differences in types of oral contraception may complicate the picture further, as androgenic contraceptives seem to promote patterns of connectivity associated with depression, while nonandrogenics do not have this effect [22]. Further research is crucially needed to assess the long-term effects of contraceptive use on intrinsic network connectivity.

Even with these unanswered questions, the available evidence indicates that acute elevations in ovarian hormone levels tend to promote states of brain and body associated with memory and mood symptoms that are similar to those observed in affective disorder. Thus, the initiation or cessation of oral contraceptive use should be considered with caution for women suffering from or at risk for affective disorder. We would argue that this issue is of particular concern for

Outstanding Questions

Do cyclic changes in intra- and internetwork connectivity directly predict phase effects on affective learning and memory? To what extent do cyclic effects on stress reactivity mediate this relationship?

What is the contribution of the progesterone metabolite allopregnanolone to cyclic effects on network connectivity?

What influence does hormonal contraception have on stress reactivity, memory, and network connectivity?

Do the acute and long-term effects of oral contraception differ? How can we reconcile evidence of increased risk of depression with evidence of reduced endogenous ovarian hormone levels following long-term use of contraceptives?

To what extent do ovarian hormone effects on vascular function directly influence BOLD responses in functional neuroimaging?

Do relationships between brain network connectivity, stress reactivity, and memory differ between healthy controls and women with affective disorder?

How do windows of affective vulnerability over the cycle relate to periods of increased vulnerability to mood disorder over the lifespan? Do increased cyclic mood symptoms relate to risk of postpartum or perimenopausal depression?

Does the circadian rhythm of testosterone secretion produce analogous effects on connectivity in men, on a shorter timescale?

adolescent girls, whose shifting hormonal status may make them especially affectively vulnerable, considering recent evidence that depression rates may approach one in four for this demographic group [110].

Additionally, in women with affective disorder or at risk for it, the use of drugs that may affect hormonal cycle should be considered with caution. Antidepressants can alter cycle length and potentially influence the age at onset of menopause [111,112], suggesting that it is possible that some variation in treatment outcomes might be explained by antidepressant effects on ovarian function.

More broadly, pharmacological interventions for treating depression may benefit from consideration of the menstrual cycle, as the brain states these drugs address may fluctuate over the course of the cycle. Thus, for naturally cycling women, dosage and treatment plans tailored to women's individual hormonal status could be beneficial.

Implications for Research on Sex Differences in the Brain

The windows of vulnerability model suggests that there are dynamic, temporally varying structural and functional brain changes in women that have implications for understanding previous research on sex differences in the brain and their relationship to affective disorder. Sex differences in the neural response during presentation of negative stimuli [87], as well as in brain network connectivity, particularly between regions involved in affective processing [113] have been frequently cited as potential explanations for the greater rates of affective disorder in women [6]. Yet, there have been conflicting results [68,114–117]. Cyclic changes in network structure and function over the course of the menstrual cycle could provide an explanation for these disparate findings. It is conceivable that in one phase of women's menstrual cycle, certain aspects of network structure and function differ, compared to men, in a certain direction, whereas in another phase the difference is in the opposite direction (or becomes insignificant) [73]. The results of sex difference comparison, therefore, may depend on the hormonal status of the women studied. Furthermore, some studies may be more influenced by transient sex differences present in specific phases of the cycle than others due to sampling a greater number of women in that phase; this would be particularly true when studies use small samples.

More generally, we would argue that attempts to assess differences between the male brain and female brain at a single time point may be conceptually misguided. With respect to network connectivity and function, there is no prototypical female brain. Rather, neural sexual dimorphisms in women must be understood as temporally dynamic. Such time-dependent changes may also be present in men considering neural effects of testosterone [118], albeit on a shorter and less predictable timeframe (see Outstanding Questions). Thus, future studies of sex differences in the brain should consider time and ovarian status in women, ideally through separate comparisons of men to women at hormonally distinct menstrual phases.

General Implications for Brain Imaging Research on Affect, Stress, and Memory

More generally, hormone-driven cyclic changes in brain network connectivity and activity represent a potential source of uncontrolled variance across research in brain and behavior. Just as cyclic variability may bias analyses of sex differences in brain structure and function, it could also represent a potential source of noise in any study including women of reproductive age, particularly in studies with smaller sample sizes. Cyclic effects on memory in low arousal situations have also been reported [119,120], suggesting that memory studies that do not

consider menstrual position may also reflect uncontrolled hormonal influences. Similarly, while this discussion has focused primarily on salience and default mode networks, other nodes throughout the brain are sensitive to ovarian hormones and show cyclic, hormonal effects on brain connectivity [22,66]. Indeed, even in networks believed not to respond to ovarian hormones, cyclic effects might influence neuroimaging studies through vasodilatory effects of estrogen that could alter BOLD (blood oxygen level dependent) responses throughout the brain [121] (see Outstanding Questions). Attending to the hormonal status of female research participants could therefore enhance precision in multiple areas of research, improving the robustness and replicability of scientific findings.

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