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

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Abstract

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 brain's intrinsic networks. These alterations produce specific temporal windows within the menstrual cycle when inter-network 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.

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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 brain's intrinsic networks, 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.

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

It has been frequently suggested that the 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 symptomatology in women. First, sex differences in affective disorder are not constant over the lifespan but emerge at adolescence [8] and decline post-menopause [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 highest levels. Periods of maximal change in ovarian hormone levels, such as during and after pregnancy [11], and during the menopausal transition [12], are also associated with more frequent affective symptoms. Secondly, 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 relatively few occurring post-menses 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; 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-late luteal period, when ovarian hormones begin a rapid decline from the mid-luteal 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 observe the effects of exogenously applying 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-scale 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 was 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 mid-luteal phase, promote intense, unpleasant moods associated with affective disorder.

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 mid-luteal 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. Mid-luteal levels of estrogen, progesterone, and its 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 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 further 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 inter-network 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 brain's intrinsic networks [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 (see 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] [26].

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 (see 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 predicts symptom severity [41]. In post-traumatic stress disorder, 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 vs. external world, leading to decreased motivation towards external goals [39]. Increased connectivity between salience nodes in post-traumatic stress disorder (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 inter-network connectivity suggest, for example, that depression is associated with differing patterns of connectivity between the salience network and anterior vs. 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 inter-network connectivity predicts PTSD symptom severity [47].

One possibility is that differences in inter-network connectivity between anterior and posterior components of 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]. Hyper-connectivity 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 which 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 an 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 [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 mid-luteal 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 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 mid-luteal 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, frontoparietal control networks [40]. The majority of these studies indicate that cyclic changes in ovarian hormones can alter the communication of the brain's intrinsic networks. 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 (see 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. Interestingly, in the luteal phase (but not during follicular), 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 inter-network 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 ventral striatum [72] and to the posterior hubs of the default mode network such as precuneus [73], (see Figure 2e). Additionally, elevated levels of the progesterone metabolite allopregnanolone, which reaches peak levels in the mid-luteal 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] report no phase-related effects on intrinsic connectivity where other studies have observed cyclic differences [72, 73], but restrict their search to frontoparietal regions and exclude connectivity to subcortical regions such as amygdala, hippocampus, and striatum.

Divergent findings may also result from differences between studies in the choice of which specific menstrual phases to compare. Studies reporting greater inter-network [73] and intrasaliency 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 ‘mid-follicular’ phase (days 5–10) [66], during which the pre-ovulatory estradiol surge may have already begun in some participants. Thus, mid-luteal 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 which is frequently inaccurate [24]. Others supplement self-report with measurements of gonadal hormone levels or tracking of the pre-ovulatory luteinizing hormone surge to produce more reliable estimates [23]. Variability in cycle length could further complicate matters. While a mean cycle length of approximately 28 days is quite consistent across studies, relatively few women actually report cycles of exactly 28 days [24]. However, relatively few of the studies surveyed here report adjusting for individual differences in cycle length in assigning 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 a hormone’s 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 mid-cingulate 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 amygdala and medial prefrontal cortex [77], suggesting that estrogens may also play a role in mid-luteal increases in inter-network connectivity. Consistent with this view, the use of combined oral contraceptives (which include both exogenous estradiol and progesterone) increases connectivity between the anterior mid cingulate, 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 inter-network connectivity of the salience network is elevated in the mid-luteal phase compared to the low hormone early follicular/menstrual phase. Exogenous doses of both hormones released in the mid-luteal phase similarly promote greater salience-default mode inter-network 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 intra-salience network connectivity, as well as increased inter-network connectivity of salience and default mode network nodes lead to increased neural, physiological, and endocrine responses during stressful events (see Figure 1B, path *ii*). Consistent with this hypothesis, multiple studies indicate that measures of both physiological and endocrine stress reactivity are positively correlated with the connectivity among and between various salience and default mode nodes. On the physiological level, connectivity of both amygdala and anterior mid-cingulate to brainstem, thalamic, and prefrontal regions positively predicts heart rate variability, 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 has been associated with the magnitude of cortisol responses [78, 81]. Thus, cyclic changes in brain network connectivity described previously (see 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] (see Figure 3, a) 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 mid-luteal levels [75]. Interestingly, gray matter volume of the dorsal amygdala actually 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 may be related to anatomical changes [85].

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

Ovarian Hormone Effects on Physiological and Endocrine Stress Responses

Mid-luteal 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 3, d), and cortisol responses during social [93] and physical stress [94] (Figure 3, b) are facilitated in the luteal phase relative to follicular. These physiological and endocrine changes are accompanied by increased subjective anxiety and depression during stress in the mid-luteal 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 inter-network 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 mid-luteal phase, when progesterone levels are at peak. Women exhibit a greater enhancement of memory for negative vs. neutral material during the luteal phase compared to follicular [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 mid-luteal phase, with negative and non-significant relationships in the early and late follicular phases [94].

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] post-encoding have been associated with enhanced memory, particularly for evocative material.

Concluding Remarks

In this paper, we have outlined evidence to support the hypothesis that, during the mid-luteal 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 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 mid-luteal levels. At the same time, neural, endocrine, and physiological responses to stress are increased. Both increased inter-network connectivity and stress responding 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 on the other hand, 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 even further, as androgenic contraceptives seem to promote patterns of connectivity associated with depression, while non-androgenics 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 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 differences comparisons, 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 portion 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 timepoint may be conceptually misguided. With respect to network connectivity and function, there is no prototypical 'female brain'. Rather, neural sexual dimorphisms in females 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 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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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.
- Women experience more frequent affective symptoms during the luteal phase of the menstrual cycle, when progesterone levels are high.
- Affective disorder is associated with increased connectivity between the brain's default mode and salience networks, as well as increased endocrine responses to stress and negative memory bias.
- Connectivity between these networks is increased by high levels of progesterone in the midluteal phase.
- Stress reactivity and memory for affective experience are also enhanced in the mid-luteal phase
- We propose that sex differences in affective disorder can be explained by a mid-luteal 'window of vulnerability' in women, in which increased connectivity, stress reactivity, and affective memory make negative experiences more potent and memorable, promoting negative affect.
- More generally, 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.

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*, 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 where 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.

BOX 2 –**Differences in Menstrual Phase Terminology:**

The terminology used to describe differing phases of the menstrual cycle varies somewhat in the research literature. Some studies define menstrual phases in terms of their position relative to the ovulatory luteinizing hormone surge (i.e., mid-luteal = 4–10 days post-ovulation, as in [22]). Others count from the onset of menstruation (i.e., mid-luteal = days 18–24 post-menstruation). 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 the studies discussed in this paper did not measure ovulation, however, and 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 post menstruation; late follicular = days 8–13; early luteal = days 15–17; mid-luteal = days 18–24; 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.

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 further showed 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 to threat learned in the postovulatory metestrus phase (analogous to luteal) are significantly more resistant to extinction than that when 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 have been observed in animal studies.

OUTSTANDING QUESTIONS:

- Do cyclic changes in intra and inter-network 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 post-partum or perimenopausal depression?
- Does the circadian rhythm of testosterone secretion produce analogous effects on connectivity in men, on a shorter timescale?

Figure 1, Key Figure: Windows of Vulnerability Model:

Panel A: Schematic of the mid-luteal 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. Panel B: Effects of ovarian hormones on brain, body and memory, leading to increased affective vulnerability. (a) Elevated ovarian hormone levels in the midluteal phase alter connectivity between the salience network and default mode network. (b) Increased inter-network connectivity promotes greater neural, hormonal, and autonomic stress responses. (c) Increased inter-network connectivity also promotes encoding, consolidation and retrieval of negative experiences. (d) Enhanced stress responses cause negative experiences to be experienced as more arousing, further promoting affective memory enhancement. (e) Enhanced encoding, consolidation and retrieval of negative events produce distortions of memory, which promote experiences of intense negative affect.

Figure 2: Ovarian Hormone 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 mid-cingulate [75]. d) Treatment with oral contraceptives increases connectivity of anterior mid-cingulate to precuneus [73]. e) Regions of greater connectivity to left amygdala in luteal vs. follicular phase, including cerebellum, precuneus (center) and lateral prefrontal cortex [73].

Figure 3: Ovarian Hormones Influence Stress Reactivity:

a) Enhanced amygdala signal to negative images in luteal vs. follicular phase [84]. b) Cortisol response to cold pressor stress in early follicular (EF), late follicular (LF) and mid-luteal (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 f) subjective anxiety [92]

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 fronto-parietal regions
Lisofsky et al., 2015 [69]	25 NC F	↑ hippocampal volume, DMN connectivity in LF vs. EF
Weis et al., 2011[70] *	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] *	21 NC F	↑ L asymmetry in SAN in menstrual vs. Fo or L
van Wingen et al., 2008 [75] *	18 NC F	exogenous P increases amygdala-ACC, amygdala mPFC connectivity
Ottowitz et al., 2008 [77]	11 F	exogenous E increases hippocampus-MFG connectivity

Fo = follicular, EF = early follicular, LF = late follicular, L = luteal, ML = mid-luteal, Me = menstrual, F = female, M = male, NC = naturally cycling

OC = oral contraceptive, DMN = default mode network, ECN = executive control network, SAN = selective attention network, FPN = frontoparietal

SN = salience network, ACC = anterior cingulate cortex, sg ACC = subgenual anterior cingulate cortex, MFG = middle frontal gyrus

* = task related connectivity