Endocrine Modulation of Cognition: Cortisol Variability and Working Memory Across Menstrual Phases

Mei-Mei Hu

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Article Synopsis

This paper examines how hormonal changes during the menstrual cycle interact with the body's stress system to affect thinking and memory. Estrogen and progesterone shift across the cycle, and these changes influence cortisol, the main stress hormone. Research shows that when cortisol levels rise—especially in the luteal phase—working memory, or the ability to hold and use information in the moment, often becomes less efficient. By connecting hormone patterns with known effects of cortisol on the brain, the paper provides a biological explanation for why many women notice changes in focus or mental clarity at certain times of the month. It also highlights the need for long-term studies that track hormones more carefully.

Graphic by Tara Pratapa

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Mei-Mei Hu

Duke University
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Introduction

Cognitive fluctuations throughout the menstrual cycle are a recurring experience for countless women, with many reporting difficulties in their focus, memory, and mental clarity throughout certain phases of the cycle (Poromaa et al., 2014). These fluctuations–often ignored or dismissed as minor–can have significant effects on daily functioning, academic performance, and workplace productivity. As a result, understanding the mechanisms behind menstrual cycle-related cognitive fluctuations is essential for improving women's health, workplace equity, and overall wellbeing. However, despite being a common experience, the biological causes of these cognitive shifts remain poorly understood, perpetuating misconceptions about women's cognitive abilities and inadequate treatments.

The menstrual cycle is accompanied by complex hormonal changes, most notably in estrogen, progesterone, and cortisol–a primary stress hormone (Poromaa et al., 2014). These fluctuations interact with the hypothalamic-pituitary-adrenal (HPA) axis, which in turn influences cognitive processes such as attention, working memory, and emotional regulation. While multiple hormonal systems and environmental conditions influence cognition, growing evidence points to the HPA axis as a key factor driving these cognitive fluctuations, making it a critical area of study for understanding cognitive fluctuations (Leistner et al., 2020). Existing research has examined estrogen and progesterone's influence on cognition; however, cortisol, the primary stress hormone of the HPA axis, has received less attention, despite its well-established effects on memory in other populations (Boucher et al., 2019).

Understanding the relationship between cortisol variation and memory across the menstrual cycle is crucial because without this understanding, clinicians and educators lack the ability to confidently distinguish between stress-related cognitive changes and other neurological or psychiatric conditions. This review therefore centers on how cortisol fluctuations across the menstrual cycle influence working memory performance. Specifically, by investigating and linking cortisol's influence on working memory, cortisol regulation during the menstrual cycle, and working memory throughout the menstrual cycle, it argues that interactions between ovarian hormone shifts and the HPA axis lead to impairments in working memory performance, particularly in the luteal phase.

Cortisol and Working Memory

Determining how cortisol fluctuations during the menstrual cycle affect working memory requires first understanding the neurobiological mechanisms behind cortisol itself. As Leistner et al. (2020) explains, the process begins with the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is the primary neuroendocrine system that regulates the body's response to stress. When exposed to internal physiological stress, the hypothalamus, which helps manage body functions including temperature, hunger, mood, and sleep, increases production of corticotropin-releasing hormone (CRH), which then stimulates a rise in adrenocorticotropin hormone (ACTH) production and release from the pituitary cells. The ACTH then acts on the adrenal cortex, releasing glucocorticoids including cortisol into the bloodstream. This well-documented process allows the body to rapidly mobilize energy and maintain

homeostasis when faced with challenges. However, prolonged or unregulated activations–such as through chronic sleep deprivation or caffeine overuse–can disrupt neural functioning, particularly in the prefrontal cortex (PFC), which is central to working memory (Leistner et al., 2020).

From a mechanics perspective, cortisol's cognitive effects are mediated by its binding to glucocorticoid and mineralocorticoid receptors in the brain, especially in the PFC, and have been shown to dampen working memory performance. Arnsten (2009) found that excessive glucocorticoid receptor activation in the PFC, such as due to high cortisol levels, impairs the network connectivity used to maintain and manipulate information and thus working memory. This finding is supported by animal models showing the retraction of dendrites in the PFC neurons when under chronic stress. However, despite these findings being widely accepted, it should still be noted that much of their evidence comes from rodent models, and thus, directly extrapolating these findings to humans may not be fully representative of all nuances.

Fortunately, human studies have corroborated these findings. For example, Schoofs et al. (2008) used the Trier Social Stress Test (TSST) to elevate cortisol levels in participants. They found that participants showed reduced accuracy and slower reaction times on the n back working memory task–which requires observers to judge whether the current stimulus in a sequence matches the one presented N stimuli ago–within 20 to 30 minutes of stress onset. Taken together, these two studies demonstrate that elevated cortisol levels negatively impact working memory.

However, other studies have provided further nuance in cortisol's influence on working memory. Specifically, Oei et al. (2006) found in a landmark study of 20 healthy male participants tested on simple item recognition assessments with varying levels of cortisol that cortisol follows an inverted-U relationship with cognitive performance: moderate levels of glucocorticoid receptor activation boosts working memory performance, but excessive activation disrupts it. Schoofs et al. (2013) corroborated these findings in a similar experiment conducted on 29 young healthy women, suggesting that cortisol's influence on working memory operates comparably in both men and women. As a result, it should be noted that cortisol's negative influence on working memory isn't as simple as a negative relationship; rather, spikes in cortisol levels (both below and above a stable amount) can have this negative influence, meaning that investigating fluctuations from steady concentrations of cortisol during the menstrual cycle and comparing them to reported lapses in working memory amongst women should be prioritized.

Overall, analyzing various studies on cortisol's influence on working memory suggests that cortisol's effects on working memory are dose-dependent. Sharp increases in cortisol are linked with a negative impact on working memory performance, while stable levels can actually improve it. Thus, investigating cortisol levels and fluctuations throughout the menstrual cycle is a probable step towards understanding the menstrual cycle's influence on working memory.

Menstrual Cycle Hormones and Cortisol Regulation

The menstrual cycle is divided into four primary phases: menstruation, follicular, ovulation, and luteal, each with their own distinct patterns of hormone secretion. In the early follicular phase, both estrogen and progesterone are relatively low. Estrogen begins to rise in the mid-follicular phase, peaking around ovulation, while progesterone remains low until the luteal phase, where it surges (Reed et al., 2018). These fluctuations all exert systemic influence, including modulation of the HPA axis and thus, cortisol secretion.

Estrogen in particular has been proposed as a buffer against stress-induced elevations in cortisol levels. Evidence from both human and animal studies supports the notion that higher estradiol levels (a type of estrogen released during the menstrual cycle) are associated with weakened cortisol responses to stress. For example, Kirschbaum et al. (1999) established in what would become one of the most influential

studies in the field that women in the high-estrogen, low-progesterone late follicular phase demonstrated lower cortisol reactivity during the Trier Social Stress Test compared to women in the luteal phase, marked by lower estrogen. This suggests that estradiol may lower HPA axis activation, potentially protecting the body against stress-related working memory disruptions. However, it should be noted that despite Kirschbaum's study carefully controlling for cycle phase through hormonal verification, the study utilized a relatively small sample size (n=38) and laboratory stressors, meaning the results may not be fully generalizable to real-world stress contexts. Still, the evidence aligns with the notion that menstrual phase-specific hormone levels significantly alter cortisol levels.

In contrast to estrogen, progesterone, which is dominant during the luteal phase, appears to amplify the cortisol response. This effect may be due to progesterone's metabolite allopregnanolone, which modulates GABA-A receptor activity and can influence HPA axis reactivity (Lovick, 2012). In this study, the researchers recruited healthy women with regular menstrual cycles and measured salivary cortisol at multiple points across the follicular and luteal phases, finding that cortisol levels rose sharply during the luteal phase, directly correlating to rises in progesterone levels.

In addition, cortisol levels have been found to exhibit fluctuations across the menstrual cycle even without the influence of acute stress. A meta-analysis by Hamidovic et al. (2020) synthesizing data from multiple studies that measures basal cortisol at different menstrual phases using salivary and plasma assays found that morning cortisol levels tend to be lowest during ovulation and highest in the mid-to-late luteal phase. This finding further reinforces the notion that hormonal interaction between estrogen and progesterone is largely responsible for the fluctuations in cortisol levels throughout the menstrual cycle, lowering the likelihood that extraneous factors or that stress itself was responsible for fluctuations in cortisol levels during the menstrual cycle.

Overall, the interaction between estrogen, progesterone, and cortisol is not linear, but rather, phase-dependent. High estrogen levels appear to dampen cortisol reactivity, while high progesterone tends to spike cortisol activity. Considering that excessive levels of or spikes in cortisol levels are linked to weakened performance on working memory tasks, the luteal phase–with elevated progesterone and thus cortisol reactivity–emerges as a likely period of vulnerability for cognitive performance. These findings also support the overarching idea that interactions between the HPA axis and ovarian hormone shifts lead to impairments in working memory performance, particularly in the luteal phase.

Working Memory and the Menstrual Cycle

Analyzing working memory performance across different phases of the menstrual cycle could elucidate and confirm the theory that fluctuations in cortisol–driven by hormonal changes–are a key factor driving observed shifts in cognitive performance. Thus far, the evidence linking menstrual cycle phases to working memory performance is mixed, but a growing number of studies point to the luteal phase as a period of cognitive vulnerability. This aligns with the findings on hormonal and cortisol levels described earlier: specifically, higher progesterone levels leading to higher cortisol. Griksiene and Ruksenas (2011) directly examined phase-specific working memory performance in healthy women with regular menstrual cycles, using both verbal and visuospatial n-back tasks–the same method as Schoofs et al. (2008). Participants were tested twice: once during the mid-luteal phase (characterized by high progesterone and cortisol) and once during the late follicular phase (high estrogen, low progesterone). Salivary hormone samples were used to confirm the cycle phase. Results showed significantly slower reaction times and reduced accuracy in the luteal phase, particularly for the 3-back condition, which requires the greatest working memory performance. This effect was also found the most significant for verbal n-back trials, suggesting that verbal working memory may be more sensitive to luteal-phase hormonal and cortisol changes. As with most studies examined throughout this paper, it should be noted that the study relied on lab-based computerized tasks, meaning generalizability to real-world cognitive performance may not be perfect.

However, not all studies uniformly confirmed consistent luteal-phase impairment in working memory. For example, Mordecai et al. (2008) tested working memory in women using the digit span and letter-number sequencing portions of the WAIS-III test–which involve subjects repeating a series of increasingly long digits–during the early follicular and luteal phases. Unlike Griksiene and Ruksenas, they found no significant differences between phases. This could be attributed to the nature of the tasks themselves, since the digit span and letter-number sequencing are shorter and less cognitively demanding than n-back trials, potentially making them less sensitive to subtle hormonal effects. Moreover, the study did not collect cortisol or progesterone data, meaning that potential neuroendocrine differences between testing sessions could not be directly linked to performance outcomes.

Other works argue that menstrual cycle effects are task-specific. Hampson and Morley (2013) found that verbal working memory tasks (such as letter-number sequencing) tended to show phase-related fluctuations, with peak performance during the mid-follicular phase and mild declines in the luteal phase, whereas spatial working memory performance was not significantly affected. They similarly proposed that luteal-phase progesterone may interfere with working memory efficiency, supporting the argument that hormonal fluctuations are linked with working memory performance.

When synthesizing these findings, it becomes clear that findings regarding working memory performance throughout the menstrual cycle are not as straightforward as findings regarding changes in cortisol levels due to hormonal fluctuations. However, on net, the findings suggest that working memory performance is stable during the follicular phase but impaired during the luteal phase.

Synthesis and Discussion

Across the reviewed studies, interactions between menstrual hormone shifts and the HPA axis have been shown to lead to impairments in working memory performance, particularly during the luteal phase. Cortisol, as a primary stress hormone, modulates activity in the PFC. Evidence from both behavioral and neuroendocrine studies indicates that when cortisol levels deviate from an optimal range or spike, working memory performance suffers.

During the menstrual cycle, hormonal changes–especially in estrogen and progesterone– interact with the HPA axis, producing changes in cortisol levels. These changes overlap with reported and experimentally documented lapses in cognitive performance, particularly working memory, suggesting that the root causes behind such drops in working memory performance can be attributed to cortisol level changes. Specifically, progesterone led spikes in cortisol levels during the luteal phase overlap with experimentally documented diminished performance in working memory. While individual differences in stress reactivity, menstrual cycle regularity, and baseline cortisol levels can moderate this effect, the overall pattern supports the idea that menstrual phase linked cortisol peaks contribute to working memory deficits.

Future research should employ longitudinal designs tracking hormonal profiles, cortisol levels, and cognitive performance across multiple menstrual cycles to better establish a causal relationship to confirm these effects. Incorporating neuroimaging could clarify the neural mechanisms underlying cortisol's impact on prefrontal function, while experimental manipulations of stress could isolate the specific contribution of cortisol from other menstrual-related factors. Understanding these causes is paramount for better directing resources to mitigate stress and promote well-being during the menstrual cycle for millions of women.

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