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SEX HORMONES AND EMOTIONAL MEMORY: A BETWEEN OR WITHIN PERSON EFFECT? (86 PP).

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Posttraumatic stress disorder (PTSD) is a debilitating disorder that disproportionately affects women. Given that PTSD is theoretically a disorder of memory processes, sex differences in emotional memory formation and retrieval may account for this sex disparity in PTSD rates. Differences in levels of sex hormones (e.g., estradiol, progesterone) have been posited to explain sex differences in both PTSD and emotional memory suggesting the potential for shared underlying mechanisms. Although laboratory-based studies have suggested a positive relationship between menstrual phases with higher hormone levels (e.g., luteal phase) during encoding and emotional memory performance (i.e., greater recall or recognition of emotional compared to neutral stimuli), methodologies and results have been inconsistent. Notably, most previous studies have used between-subjects designs which do not account for individual differences in hormone fluctuations during the menstrual cycle. Only one study (with notable limitations) used a within-subjects design to examine the extent to which change in menstrual cycle phase/hormone levels impact emotional memory performance, and results were the opposite of those found in between-subjects studies. Thus, it remains unclear whether observed trends of hormone-related changes in emotional memory performance represent a within- or between- person effect. The current study examined the influence of between- versus within-subjects study designs on emotional memory performance. A total of 41 naturally cycling

women were included in the between-subjects design, and 35 were included in the within-subjects design. Women were tested during the early follicular and midluteal phases of their menstrual cycle in a randomized order. During each phase, participants presented to the lab and completed questionnaires, viewed a set of neutral and negatively valenced photos, and provided a saliva sample for hormone assay. Participants then performed a free recall memory test of the photo content remotely two days later. While emotional memory was demonstrated across all analyses, no significant main or interactive effects of the hormonally distinct menstrual cycle phases were observed, and performance across phases was found to be significantly equivalent within-subjects. In a control group of 10 oral contraceptive users, we obtained similar findings. Furthermore, no significant relationships between salivary sex hormone levels (i.e., estradiol, progesterone) and memory emerged. Although present analyses were underpowered, there was no suggestion of a relationship between sex hormones and emotional memory. However, this may be because sex hormones exert their influence via interaction with stress hormones (e.g., cortisol) and thus a greater level of physiological arousal may be needed in order to see an effect. It could also be that the influence of sex hormones within individuals is more nuanced. Thus, future research should incorporate added stressor paradigms to within-subjects studies of emotional memory and investigate potential individual differences with more sophisticated statistical analysis.

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Introduction

Women are more than twice as likely as men to develop disorders associated with emotional memory such as posttraumatic stress disorder (PTSD; Kilpatrick et al., 2013; Tolin & Foa, 2006) perhaps because women tend to have greater memory for emotional events than men (Cahill et al., 2004; Canli et al., 2002). Multiple explanations have been posited for sex differences in emotional memory and related psychopathology (Christiansen & Berke, 2020); however, one that has received consistent interest is the impact of female sex hormones (i.e., estrogen and progesterone) on emotional memory formation and subsequent psychopathology. Evidence for this has come from multiple directions including research suggesting that sex differences in PTSD exist predominantly during reproductive years (Ditlevsen & Elklit, 2010; Garza & Jovanovic, 2017; Mendle et al., 2016) and clinical studies that suggest menstrual cycle phase and contraceptive use at the time of trauma are predictive of subsequent intrusive emotional memories, a key component of PTSD (Bryant et al., 2011; Ferree et al., 2012). If sex hormones are influential in emotional memory formation, then there should be differences in emotional memory performance (i.e., greater recall or recognition of emotional stimuli compared to neutral stimuli) based on menstrual cycle phase (e.g., luteal, follicular) and hormonal contraceptive use (which suppresses hormone production), at time of encoding and consolidation.

Fluctuations in sex hormones have previously been shown to impact broader episodic memory (Boss et al., 2014; Yonker et al., 2006), cognitive functioning (Andreano et al., 2008), and the neurocircuitry of the stress response (Andreano et al., 2008; Goldstein et al., 2005;

Kirschbaum et al., 1999) theorized to underlie PTSD via the overconsolidation of trauma memories (Pitman & Delahanty, 2005). Despite relatively consistent findings of positive associations, studies of the relationship between sex hormones and emotional memory have produced equivocal results and are limited by methodological heterogeneity (Bayer et al., 2014; Ertman et al., 2011; Felmingham, Fong, et al., 2012; Ferree et al., 2011; Nielsen, Ahmed, et al., 2013; Pompili et al., 2016; Wassell et al., 2015; Zoladz et al., 2015). Notably, studies have varied in terms of menstrual cycle phases used for group comparisons, and group heterogeneity may have reduced the ability to detect differences in emotional memory performance. Additionally, prior investigations of the relationship between sex hormones and emotional memory have primarily been between-subjects designs which do not account for individual differences. Given existing individual variation in cycle phases (Fehring et al., 2006) and magnitude of hormone changes across the cycle (Anckaert et al., 2021), a within-subjects design more appropriately models how natural fluctuations in hormones may impact an individual's emotional memory across the cycle (Schmalenberger et al., 2021). Only one limited study has used a within-subjects approach (Bayer et al., 2014). Therefore, investigating the influence of between- versus within-subjects designs (and accounting for the influence of individual differences) may inform future research methodology and aid in elucidating a potential risk factor for women's development of disorders related to emotional memory such as PTSD.

Sex Differences in PTSD

Following exposure to a traumatic event, individuals are at risk of developing PTSD, a debilitating disorder characterized by intrusive thoughts, negative alterations in cognitions or mood, increased arousal or reactivity, and avoidance (American Psychiatric Association, 2013). Although only a minority of trauma-exposed individuals (approximately 8%) will develop

persistent symptoms warranting a PTSD diagnosis, a substantial sex difference in prevalence exists where women (12.8%) are more than twice as likely as men (5.8%) to develop PTSD (Kilpatrick et al., 2013) and to have increased severity and length of illness (Breslau, 2002; Gogos et al., 2019; Tolin & Foa, 2006). Notably, these disparities cannot be attributed to differences in number or type of traumas experienced (Blanco et al., 2018; Tolin & Foa, 2006). Instead, other possible explanations for the observed sex differences include sociocultural influences, genetics, and biological factors (e.g., the impact of sex hormones on trauma memory encoding: see Christiansen & Berke, 2020 for review). Evidence for the impact of sex hormones on increased PTSD rates stems from findings that the sex disparity in prevalence rates becomes apparent during puberty and persists through reproductive years (Ditlevsen & Elklit, 2010; Garza & Jovanovic, 2017; Mendle et al., 2016). Therefore, female sex hormones have become a focus of research in this area.

Additional evidence supports the connection between fluctuations in female sex hormones (i.e., estradiol and progesterone) and symptomology. First, higher endogenous hormone levels at the time of a trauma have been found to predict later PTSD symptom development (Bryant et al., 2011; Ferree et al., 2012). Further, PTSD symptoms appear to fluctuate in accordance with the menstrual cycle; women have reported more flashbacks during the high hormone midluteal phase (Bryant et al., 2011) and higher levels of fear-related and avoidance symptoms during the low hormone early follicular phase (Nillni et al., 2015). Given the established sex differences in prevalence rates and symptomatology, investigation of sex differences, and the role of female sex hormones specifically, in mechanisms hypothesized to underlie PTSD is warranted.

Theories of PTSD development are commonly rooted in learning and memory processes. One prominent theory is that hyperarousal during the traumatic event leads to the overconsolidation of trauma memories (Pitman & Delahanty, 2005). Thus, the discrepancy in sex differences of memory-related psychopathology such as PTSD may be due to the influence of female sex hormones on memory of emotional events (Andreano et al., 2018).

Female Sex Hormones: Estrogen and Progesterone in Women of Reproductive Age

Estrogens and progestogens are neuroactive steroids that encompass the broader classes of circulating sex hormones that predominate in biological women. The most prominent subtypes are estradiol (also referred to as oestradiol) and progesterone (Gogos et al., 2019). While there is individual variability (Fehring et al., 2006), the average menstrual cycle is 28 days and is characterized by distinct, predictable fluctuations in estradiol and progesterone that are controlled by the hypothalamus-pituitary-gonadal axis via a release of other hormones (i.e., gonadotropin-releasing, luteinizing and follicle-stimulating hormones; Knudtson & McLaughlin, 2019). There are two broad phases of the cycle, the follicular and the luteal phases, that refer to before and after ovulation, respectively (Knudtson & McLaughlin, 2019). These phases can be further divided into substages indicative of more nuanced alterations in hormone levels; however, specific days counted in different phases often differ slightly across studies (Allen et al., 2016). The early follicular phase comprises the beginning of the cycle and is characterized by low levels of both estradiol and progesterone. Estradiol levels then quickly increase to their peak, while progesterone levels remain low, as women approach ovulation in the late follicular phase (Knudtson & McLaughlin, 2019). During ovulation, estradiol levels begin to decrease, and progesterone levels begin to increase, leading into the midluteal phase which is characterized by peak levels of progesterone and a simultaneous second, more moderate, increase in estradiol

(Knudtson & McLaughlin, 2019). Levels of both estradiol and progesterone then decrease in the late luteal phase leading up to menstruation, and the cycle begins again. Thus, the subphases of the early follicular and the midluteal phases make for very distinct comparison groups in naturally cycling women because levels of both estradiol and progesterone are low in the early follicular phase and elevated in the midluteal phase. However, findings in naturally cycling women do not inform a very large percentage of women: those using hormonal contraceptives.

Almost half (~46%) of the women in the United States currently use a form of hormonal birth control (Kavanaugh & Jerman, 2018). Hormonal contraceptives are designed to prevent pregnancy and operate by artificially lowering and stabilizing circulating levels of endogenous estradiol and progesterone via negative feedback to the hypothalamic-pituitary-gonadal axis (Fleischman et al., 2010; Frye, 2006). The various forms of hormonal contraceptives (e.g., pill, injection, implant, etc.) differ primarily in their method of delivery, but ultimately operate similarly (Shulman, 2011). The most common form of hormonal contraceptive is the oral contraceptive pill (Shulman, 2011).

Oral contraceptive pills typically create 28-day cycles comprised of three weeks of active pills and one week of inactive, or placebo, pills (Blumenthal & Edelman, 2008; Rivera et al., 1999). Although there is variation in formulations, the most common are combined formulas consisting of both an estrogen and progesterone substitute (Shulman, 2011). There are some differences in the concentrations and consistency of hormone levels throughout the active pill phase across formulations; however, many monthly pill packs are monophasic and hold hormones at stable levels across the entire active pill phase to prevent hormone spikes and suppress ovulation (Blumenthal & Edelman, 2008; Rivera et al., 1999). In addition to preventing pregnancy, hormonal contraceptives have many secondary effects including impacting the stress

response. For example, women on oral contraceptives have been shown to exhibit lower levels of norepinephrine (Otterstetter et al., 1999) and cortisol (Kirschbaum et al., 1999; Rohleder et al., 2003) in response to stress.

Given the predictable fluctuations in hormone levels throughout the menstrual cycle and suppression of hormone surges by oral contraceptives, menstrual cycle phases and hormonal contraceptive use provide a means to group women to investigate effects of differing levels of sex hormones on psychological phenomenon including emotional memory. Examination of the potential influence of sex hormones on emotional memory may subsequently improve the understanding of women's individual vulnerability to emotional memory-related disorders such as PTSD.

Emotional Memory: The Enhanced Memory of Emotional Stimuli

Episodic memory is a type of long-term, declarative memory that is specific to prior events and experiences (Dickerson & Eichenbaum, 2010). Events, stimuli and information that elicit emotional responses are typically better remembered than those that do not (Anderson et al., 2006; Cahill & McGaugh, 1995; Christianson, 1992; Kensinger, 2004, 2009; LaBar & Cabeza, 2006; Levine & Pizarro, 2004; McGaugh, 2004; Todd et al., 2012), and the enhancement is both in terms of accuracy (LaBar & Cabeza, 2006) and vividness (Todd et al., 2012). This phenomenon is commonly referred to as emotional memory (Levine & Pizarro, 2004).

Although the enhancement of memory for emotional stimuli has been observed in both naturalistic studies and laboratory paradigms (Kensinger, 2004), it is difficult to study memories for emotional events in naturalistic settings where information on accuracy of what happened during an event cannot always be determined. Therefore, many studies of emotional memory

have been conducted in laboratory settings where researchers control the stimuli (Kensinger, 2004). A few different types of stimuli have been used to model memory for emotional events, including lists of emotionally charged words, emotional photos with and without accompanying narratives, and emotional film clips (James et al., 2016). Emotional memory performance is then measured by either the number or percentage of emotional stimuli correctly retrieved from memory during recall (i.e., describe the stimuli from memory without a cue) or recognized (i.e., respond yes or no to having seen stimulus before) compared to neutral stimuli.

Research into emotional memory has focused largely on examining the extent to which levels of arousal or emotional valence impact memory (for review see Kensinger, 2004). Emotionally arousing information is hypothesized to be more likely to be encoded due to its greater likelihood to capture attention and be perceived (Dolan & Vuilleumier, 2003; Hamann, 2001). Further, arousing information is also more likely than non-arousing information to be processed even when attentional capacity is reduced, suggesting a preferential, automatic encoding (Dolan & Vuilleumier, 2003). The impact of emotional valence on memory retrieval is more equivocal, with researchers finding both an increased memory for positive emotional events in some cases and for negative emotional events in others (Talarico et al., 2004). Further, researchers have observed more specific patterns suggesting that negative valence leads to a narrowing effect, or better memory of the central story (Kensinger, 2009), while positive valence enhances memory of peripheral details (Talarico et al., 2009). Despite reported differences in memory of positively versus negatively valenced stimuli, the notion that stimuli or events of either valence led to greater memory compared to neutral stimuli or events appears consistent across studies (Talarico et al., 2004).

Although both biological men and women exhibit an increased memory for emotional events, the effect is stronger in women (Cahill, 2003; Canli et al., 2002; Felmingham, Tran, et al., 2012; Hamann, 2005). There is also a fundamental difference in the specific information remembered by the sexes. For example, during free recall of an emotional film clip, men exhibited a greater recall of central gist information while women demonstrated enhanced recall of peripheral details (Cahill et al., 2004; Cahill & van Stegeren, 2003). One factor that may underlie or help explain this difference in emotional memory is levels of sex hormones that may interact with known mechanisms underlying emotional memory formation.

Distinct Mechanisms Underlying Emotional Memory

The mechanisms underlying emotional memory appear to be distinct from those involved in other types of memory (Levine & Pizarro, 2004). The enhancement of emotional memory has been most consistently tied to activation of areas of the brain associated with emotion processes, namely the amygdala, and its interactions with the primary declarative memory structure, the hippocampus (Canli et al., 2000; LaBar & Cabeza, 2006; McGaugh, 2004; Phelps, 2004; Phelps & Sharot, 2008). The activation of the amygdala is associated with long-term emotional memory and is hypothesized to modulate consolidation processes specifically (McGaugh, 2013). Although the relationship between the amygdala and enhancement of emotional memory has been observed across both sexes, the enhancement is more specifically associated with activity in the left hemisphere of the amygdala in men and the right hemisphere in women (Cahill et al., 2001; Canli et al., 2002). Further, although the amygdala appears necessary for emotional memory, some have found that it is not solely responsible and propose that other components of stress-induced arousal are key for the enhancement of emotional memory (Anderson et al., 2006; McGaugh, 2004, 2013).

Arousal results from the hypothalamus's initiation of two pathways of stress hormone release in response to a stressor: a fast peripheral release of epinephrine/norepinephrine and a slower central release of glucocorticoids (i.e., cortisol; LaBar & Cabeza, 2006; McGaugh, 2004; Wolf, 2008). Both hormone cascades then activate the amygdala, either directly in the case of cortisol or indirectly via stimulation of the vagus nerve in the case of epinephrine/norepinephrine (LaBar & Cabeza, 2006; McGaugh, 2004; Wolf, 2008). In addition to the activation of the emotion processing amygdala, the interaction of the noradrenergic and glucocorticoid systems is hypothesized to underlie the enhancement of voluntary and involuntary recall of emotional stimuli (Cahill & McGaugh, 1995; Hall & Berntsen, 2008; LaBar & Cabeza, 2006; McGaugh, 2004, 2013; Tsigos & Chrousos, 2002). However, the effects of arousal on memory appear dependent on phase of the memory process (i.e., encoding, consolidation, retrieval). For example, stress prior to retrieval has been found to impair memory of emotional stimuli (Smeets, 2011; Smeets et al., 2008), whereas stress surrounding encoding of emotional stimuli has been shown to be enhancing (Cahill et al., 2003; Hall & Berntsen, 2008; Payne et al., 2006; Smeets et al., 2008). There is also evidence that post-encoding stress differentially impacts emotional memory in men and women such that stress enhances memory for negative images in women, but not in men (Felmingham, Tran, et al., 2012). One explanation for this difference may be that sex hormones modify the influence of stress and associated arousal on emotional memory.

Influence of Estrogen and Progesterone on Emotional Memory Processes

Sex hormones have been found to impact emotional memory processes and to influence many brain structures, including the hippocampus and amygdala where sex hormone receptors are present in high concentrations (McEwen & Milner, 2017). Broadly, estrogen has been positively linked to fear learning, particularly extinction recall, in laboratory studies (for reviews

see Garcia et al., 2018; Ravi et al., 2019). Further, naturalistic studies have revealed that levels of estrogen and progesterone positively predict involuntary, or intrusive, memories of traumatic events. For example, women who experienced trauma during the high hormone luteal phase had more intrusion symptoms compared to those in the low hormone follicular phase (Bryant et al., 2011). Further, artificially lowering endogenous hormone levels via contraceptive use (both via typical use prior to sexual assault and via emergency contraceptive use in the acute aftermath) was associated with fewer intrusive memories of the trauma (Ferree et al., 2012). Additionally, imaging studies suggest that sex hormones influence activity of brain regions involved in emotional memory. An fMRI study found that, compared to women in the early follicular phase, women in the higher hormone midluteal phase had greater activity in both the amygdala and hippocampus when viewing emotional photos (Andreano & Cahill, 2010). In contrast, lower levels of endogenous hormones due to oral contraceptive use resulted in decreased amygdala reactivity (Petersen & Cahill, 2015). Further, amygdala reactivity to emotional stimuli was increased following a single dose of progesterone during the low hormone follicular phase, showcasing a specific mechanism of progesterone's influence on emotional memory processes (van Wingen et al., 2008).

In addition to impacting underlying brain structures, sex hormones may also exert influence on emotional memory via interaction with stress hormones during arousal (Felmingham, Tran, et al., 2012), and imaging studies suggest that the menstrual cycle impacts the neurocircuitry of the stress response (Goldstein et al., 2005). Also, there are sex differences in cortisol responses to stress, and some of these differences have been tied to levels of sex hormones (Andreano et al., 2008; Kirschbaum et al., 1999). For example, during the luteal phase of the cycle, when ovarian hormones are high, women had a higher cortisol response to a

psychosocial stressor compared to those in the low hormone follicular phase (Kirschbaum et al., 1999). Further, cortisol was higher during the high hormone midluteal phase and positively associated with long-term recall, but not associated with recall in other phases (Andreano et al., 2008).

The observed influence of sex hormones on mechanisms underlying emotional memory may explain sex differences in emotional memory performance. If sex hormones are influential, then memory of emotional stimuli should change in accordance with the hormone fluctuations of the typical menstrual cycle and with contraceptive use.

Sex Hormones and Emotional Memory

Research examining the relationship between sex hormone levels during initial stimuli encoding and emotional memory performance has varied substantially in terms of methodology. Studies differ in the type of stimuli used, valence investigated (i.e., negative, neutral, positive), type of memory test employed (i.e., recall, recognition), and length of memory test delay. Additionally, studies have varied in terms of menstrual cycle phases used for group comparison. More specifically, there are inconsistencies in definitions (i.e., day count) of cycle phases and which specific phases are compared to each other. Perhaps because of these inconsistencies, results of these studies have been mixed, particularly regarding the recollection of negative stimuli (Bayer et al., 2014; Ertman et al., 2011; Felmingham, Fong, et al., 2012; Ferree et al., 2011; Gamsakhurdashvili et al., 2021a, 2021b; Nielsen, Ahmed, et al., 2013; Pompili et al., 2016; Wassell et al., 2015; Zoladz et al., 2015). For example, while women in the high hormone luteal phase recalled more negatively valenced stimuli compared to those in the low hormone follicular phase in one study (Ertman et al., 2011), another found the opposite—women had better recognition memory for negative stimuli in the low hormone early follicular phase than in

the higher hormone luteal phase (Bayer et al., 2014). Another study found that emotional memory recall was not impacted by cycle phase (Wassell et al., 2015). Further, direct exploration of the relationship between hormone levels at stimuli encoding and emotional memory performance revealed no associations between estrogen levels and emotional memory performance (Bayer et al., 2014; Ertman et al., 2011; Ferree et al., 2011) whereas one study suggested a positive relationship between progesterone levels and memory of negative stimuli (Ertman et al., 2011). More research is needed to elucidate the relationship between sex hormones and emotional memory.

Because oral contraceptives artificially lower levels of endogenous estrogen and progesterone, researchers have attempted to compare the emotional memory performance of women using contraceptives to naturally cycling women. Multiple studies comparing these groups have failed to find differences in the number of emotional compared to neutral stimuli recalled (Nielsen et al., 2011; Nielsen, Segal, et al., 2013; Person & Oinonen, 2020). However, these studies neglected to control for phase or hormone levels of the naturally cycling group and potentially did not have enough variance in hormone levels between groups (Nielsen et al., 2011; Nielsen, Segal, et al., 2013; Person & Oinonen, 2020). Additional research within contraceptive users has not detected an effect of pill phase (i.e., active versus inactive/placebo) at encoding on emotional memory performance despite hormone levels being significantly higher during the inactive phase (Mordecai et al., 2017). Given that women on contraceptives maintain relatively stable hormone levels compared to fluctuations of hormone levels during the natural cycle (Wright et al., 2020), the inability to find differences in emotional memory during different pill phases (Mordecai et al., 2017) suggests that changes in emotional memory performance may require a greater magnitude of change in hormone levels.

Given the complicated influence of stress hormones on the relationship between sex hormones at encoding and emotional memory performance, some researchers added stress paradigms (e.g., cold pressor) to increase arousal via the stress response beyond the evocative nature of valenced stimuli. A slight majority of these studies revealed significant, or trending, interactions between sex hormones, stress near encoding, and valence of stimuli (Felmingham, Fong, et al., 2012; Nielsen et al., 2014, 2015; Nielsen, Segal, et al., 2013; Zoladz et al., 2015); however, as in studies without added stress induction, the directionality was mixed. Compared to a control no-stress condition, both high and low hormone groups exposed to stress had better recall of negative images while only the high hormone group also had better recall of positive images (Nielsen et al., 2015). In contrast, two studies including naturally cycling women found that those in the high hormone luteal phase exhibited greater recall for emotional stimuli following a post-encoding stressor compared to women with naturally (Felmingham, Fong, et al., 2012) or artificially (Nielsen et al., 2014) lower hormones. Further, another study found that post-encoding stress led to better recall, but not recognition, of non-arousing words in the luteal phase and for arousing words in the follicular phase (Zoladz et al., 2015). Thus, results remain equivocal when emphasizing the role of stress, and while it appears that stress paradigms may amplify the detection of effects, they do not appear to fully explain the effects.

Despite substantial differences across multiple design elements between studies (e.g., testing recall vs. recognition, inclusion of a stressor vs. not) and mixed findings in terms of presence and direction of effects, patterns have begun to emerge in recent systematic reviews and meta-analyses examining the impact of menstrual cycle/sex hormones on emotional memory. First, recall memory appears more sensitive than recognition memory and better able to capture the influence of sex hormones on emotional memory (Hsu et al., 2021). Systematic reviews and

meta-analyses suggest a moderate effect of sex hormones such that higher levels during encoding are associated with greater recall memory of negatively valenced stimuli, particularly with added stress induction (Gamsakhurdashvili et al., 2021a; Hsu et al., 2021). While meta-analytic effects of cycle phase on memory of both positive and negative valence were not significant in studies that did not employ an added stressor (Hsu et al., 2021), this is likely due to significant methodological differences and potentially smaller effects and not necessarily due to a lack of overall effect. In fact, a meta-analysis revealed that progesterone specifically was associated with changes in emotional memory in studies that did and did not incorporate an additional stressor but that the relationship was stronger in those that did incorporate a stressor (Hsu et al., 2021). Although there were mixed findings, the emergence of an effect across multiple studies with differing designs suggests a relatively robust impact of sex hormones. However, again, these findings were based largely on studies using between-subjects designs.

Between vs. Within-Subjects Design in Studies of Sex Hormones and Emotional Memory

Only one study (Bayer et al., 2014) has used a within-subjects approach to examine the relationship between menstrual cycle phase/sex hormone levels at encoding and emotional memory, and results of this study were notably inconsistent with emerging patterns from between-subjects findings of higher hormones equating to greater emotional memory (Gamsakhurdashvili et al., 2021a; Hsu et al., 2021). This study found that recognition accuracy did not vary by menstrual cycle phase, but recollection memory for negative stimuli was higher during the low hormone early follicular phase compared to high hormone luteal phase (Bayer et al., 2014). However, this was a small (likely underpowered) study of 22 participants that included an image categorization task and an additional unrelated task within each encoding trial (see Taylor et al., 2003 for a demonstration of how rating stimuli impacts neural activity and

reduces induction of emotion from viewing evocative stimuli), and measured one's confidence in their recognition memory (recently shown to have poor test-retest reliability in emotional memory paradigms according to Schümann et al., 2020; Bayer et al., 2014) rather than simple yes or no recognition or recall.

While inconsistent study design may explain some of the equivocal findings across studies, given the individual variation in menstrual cycles and hormone levels (Anckaert et al., 2021; Fehring et al., 2006), a within-subjects study design will more appropriately test how natural fluctuations in hormones can impact an individual's emotional memory across the cycle. In fact, within-subjects designs have been suggested as the gold standard for menstrual cycle research (Schmalenberger et al., 2021). Thus, additional research investigating the relationship between menstrual cycle phase and emotional memory from a within-subjects design is warranted (as concluded by Gamsakhurdashvili et al., 2021). After all, the intraindividual effect reflects the true nature of the phenomenon of interest—whether an individual's changes in hormones across the menstrual cycle impact emotional memory. Thus, implementing a within-subjects design will help to determine if emotional memory performance changes within women as their hormones fluctuate from one menstrual cycle phase to another.

Other Potential Contributing Factors

Other factors beyond the basic methodological design (i.e., between versus within designs) warrant consideration in evaluating the relationship between sex hormones and emotional memory. Prior studies of sex hormones and emotional memory have largely ignored the potential influences of menstrual symptoms (e.g., pain), mental health symptomatology, and sleep, all of which have been implicated in memory.

Menstrual Symptoms

A large majority of reproductive age women report experiencing symptoms surrounding menstruation including physical symptoms of pain/cramping in the early follicular phase that dissipate during other phases (Schoep et al., 2019). Menstrual pain has been associated with negative impacts on attention (Keogh et al., 2014), and experiencing pain more broadly is associated with memory deficits. For example, compared to pain-free individuals, individuals experiencing chronic pain have been shown to have worse working and verbal episodic memory (Oosterman et al., 2011). Thus, it is important to consider if menstrual cycle phase-related differences in emotional memory remain when controlling for menstrual symptoms such as pain.

Mental Health Symptomatology

Mental health symptoms have been shown to fluctuate with hormones across the menstrual cycle. Symptoms such as depression generally worsen during low hormone phases while anxiety tends to increase during the luteal phase and as progesterone levels increase (Handy et al., 2022; Reynolds et al., 2018). These observed patterns are important as symptomatology has been shown to impact memory. For example, even subclinical depressive symptoms have been positively linked to negativity bias of attention, interpretation, and memory (Everaert et al., 2014). Additionally, individuals with anxiety (both clinical and subclinical levels) exhibited recall bias toward threatening information (Mitte, 2008). Further, acute stress has been shown to exhibit both enhancing and impairing effects on episodic memory including emotional memory (Shields et al., 2017). Thus, the potential impact of mental health symptoms such as depression, anxiety and stress should be controlled to determine if any observed differences in emotional memory between high and low hormone phases are distinct from simultaneous changes in mental health symptomatology.

Sleep

Sleep is known to impact consolidation of general episodic memory and emotional memory (Andreano & Cahill, 2010; Inostroza & Born, 2013) and to be impacted by sex hormones as evidenced by changes in sleep quality across the menstrual cycle (Baker & Lee, 2018). Therefore, it is unclear if the observed influence of sex hormones on emotional memory is independent from parallel changes in sleep. Prior studies have not investigated whether observed hormonal effects persist when covarying for sleep; however, it has been noted as a limitation and potential source of bias in prior studies (Hsu et al., 2021).

Current Study

Considering the reliance on between-subjects designs with multiple methodological inconsistencies (particularly menstrual cycle phases used for group comparison), it remains unclear if the effect of menstrual cycle phase on emotional memory performance is an artifact of between-subjects designs or if there is a within-person fluctuation in emotional memory performance that may be due to hormone changes across the menstrual cycle. Thus, we designed the present study with both within- and between-subjects components. We also examined a subset of contraceptive users who were not expected to experience large fluctuations in hormone levels over the course of their monthly cycle that served as another means to examine whether hormone levels underlie any observed differences in emotional memory performance. The proposed research is intended to inform future study designs and elucidate a potential risk factor for women's development of disorders related to emotional memory such as PTSD.

To address our aims, the proposed research employed a between-subjects design using data from the first appointment sets (described below) to allow for comparison to the majority of previous studies on menstrual cycle/sex hormones and emotional memory. We also prospectively

followed participants to examine the relationship between menstrual cycle phase and emotional memory recall via a within-subjects design and explored whether effects held above potential confounds (i.e., menstrual symptoms, mental health symptomatology, sleep). The study was conducted in healthy women during the most hormonally distinct points in their menstrual cycles (i.e., early follicular and midluteal phases; Knudtson & McLaughlin, 2019) and measured recall memory given that effects of sex hormones appear to have been better detected in studies of recall memory (Hsu et al., 2021). Although stress paradigms have been shown to amplify menstrual cycle effects, the evocative nature of visual stimuli appears sufficient to elicit, albeit smaller, effects. For this reason, and given the questionable feasibility of repeating stress paradigms, we did not include a stressor paradigm.

Specific aims and hypotheses were as follows:

Aim 1: Examine the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional stimuli in naturally cycling women via between-subjects design.

Hypothesis 1: There will be a main effect of valence whereby naturally cycling women across menstrual cycle phase will recall more negatively valenced stimuli compared to neutral stimuli in cross-sectional analyses conducted using the first appointment set.

Hypothesis 2: There will be a significant interaction between menstrual cycle phase and valence whereby women in the higher hormone midluteal phase will recall more negatively valenced stimuli compared to women in the lower hormone early follicular phase in cross-sectional analyses conducted using the first appointment set.

Aim 2: Examine the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional memory in naturally cycling women via within-subjects design.

Hypothesis 3: There will be a main effect of valence whereby naturally cycling women will recall more negatively valenced stimuli compared to neutral stimuli regardless of cycle phase in longitudinal analyses conducted using both cycle phases.

Hypothesis 4: There will be a significant interaction between menstrual cycle phase and valence whereby women will recall more negatively valenced stimuli when in the higher hormone midluteal phase compared to when they are in the lower hormone early follicular phase in longitudinal analyses conducted using both cycle phases.

Aim 3: Examine the relationship between contraceptive phase (i.e., placebo, active pill) and recall of emotional memory via within-subjects design in the subsample of contraceptive users.

Hypothesis 5: There will be a main effect of valence whereby more negatively valenced stimuli will be recalled by contraceptive users; however, given the presumed stability of contraceptive users' hormone levels, emotional memory performance will be equivalent across contraceptive phases.

Aim 4 (Exploratory): Explore if the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional memory in within-subjects designs remains when controlling for menstrual symptoms, changes in mental health symptomatology, and sleep.

Hypothesis 6: The significant interaction between menstrual cycle phase and valence will remain when controlling for menstrual symptoms, mental health symptoms and sleep in longitudinal analyses conducted using both cycle phases.

Aim 5 (Exploratory): Explore the relationship between salivary levels of estradiol and progesterone and emotional memory performance.

Hypothesis 7: There will be a significant interaction between each salivary hormone and valence such that higher levels of hormones will be associated with recall of more negatively valenced stimuli in longitudinal analyses conducted using both cycle phases.

Method

The following procedures and results reflect part of a larger, ongoing experimental investigation of psychological processes across the menstrual cycle approved by the Kent State University Institutional Review Board (ID: 372) and Institutional Biosafety Committee (ID: KSUDD01242023-P34).

Participants

Participants were 51 women aged 18-35 years old recruited via flyers around campus and the surrounding community, and via the department of psychological sciences subject pool of undergraduate students enrolled in psychology courses. The primary sample was comprised of 41 naturally cycling women who self-reported having regular menstrual cycles. A smaller sample of 10 oral contraceptive users served as a control group. Participants had to be fluent in English, report monthly menstruation (or placebo week withdrawal bleeding for oral contraceptive users) and regular cycle lengths that were 24-32 days in length. Participants across groups were excluded for the following reasons: self-reported menarche less than three years prior to the study, medical diagnoses that are known to impact sex hormones (e.g., endometriosis, polycystic ovary syndrome (PCOS), hyper/hypothyroid), self-reported mental health diagnoses, taking medications known to impact hormone levels, women who were pregnant, trying to become pregnant, breastfeeding or were unsure of pregnancy status, women who were menopausal or amenorrheic, taking hormone replacement or hormone therapy, or who used emergency contraception in the last month. Additional exclusion criteria for naturally cycling women included use of hormonal birth control within the last three months, irregular

cycles, and/or cycle lengths outside of range of 24-32 days. Women in the oral contraceptive control group had to be taking monophasic, combined birth control pills, report consistency in taking the contraceptive pill, and must have taken their current prescription for at least three months.

A total of 412 initial online screeners were completed by naturally cycling women. Of these, 129 met eligibility criteria and were contacted to participate in the study. Eight potential participants explicitly declined participation and 74 did not reply to multiple outreach attempts. Forty-seven naturally cycling women consented to participate in the study. Three naturally cycling participants withdrew, and one was considered withdrawn due to lost contact, prior to attending any study appointments. One withdrew and five dropped out halfway through the study. One participant dropped out before completing the second virtual visit and is excluded from within-subjects analyses due to missing the outcome variable of interest as a result. Additionally, two participants (one completer and one who dropped out halfway) reported initiating hormonal contraceptives prior to their first appointments and were thus excluded from all analyses. No participants were excluded for missing greater than 20% on a questionnaire or for missing data quality checks. This resulted in a final sample of 41 naturally cycling participants for the primary between-subjects analyses and 35 for the primary within-subject analyses.

Three hundred and four initial online screeners were completed by oral contraceptive users. Of these, 50 met eligibility criteria and were contacted to participate in the study. Three explicitly declined participation and 33 did not reply to multiple outreach attempts. Fourteen contraceptive users consented to participate. Of these, two withdrew and two were considered withdrawn due to lost contact before participating. No participants were excluded for missing

greater than 20% on a questionnaire or for missing data quality checks. This resulted in a final control sample of ten women for primary analyses.

Procedure

Once participants were determined to meet eligibility criteria for the study following completion of the online screening (hosted on Qualtrics), they were contacted via email regarding interest in the study and to set up a phone call to provide a detailed description of the study, obtain informed consent via online link, and schedule appointments. Participants were randomized to begin the study in either the early follicular or midluteal phase and were scheduled accordingly based on the participant's reported dates of start of last menstruation. Participants had four total sessions over the course of the menstrual cycle that were divided into two "sets" of appointments—one set during each cycle phase comprised of 1. encoding session and 2. recall session. In accordance with multiple previous studies (e.g., Nielsen, Ahmed, et al., 2013; Nielsen et al., 2015; Nielsen, Segal, et al., 2013) appointments were conducted between 12:00pm and 6:00pm. Prior to the first appointment of each set, referred to as the encoding session, participants were asked to refrain from alcohol use and exercise for 24 hours and refrain from caffeine, nicotine and food intake for three hours. During the encoding session, participants came into the laboratory and completed self-report questionnaires on Qualtrics. Questionnaires included measures of symptomatology (e.g., anxiety, depression, stress), menstrual symptoms (e.g., pain), as well as behaviors that could impact saliva samples (e.g., last meal, exercise, substance use). Following questionnaire completion, participants provided salivary estradiol and progesterone samples via passive drool. Participants were then shown one of two sets of neutral and negatively valenced photos from the International Affective Picture System (IAPS; Lang et al., 2008); IAPS photo sets were counterbalanced across participants/phases via randomization.

Two days (M_{hours}=50.65, SD_{hours}=8.11) after the encoding session, participants had a virtual study session, referred to as the recall session, over Microsoft Teams and completed a free recall test of images where they were asked to describe as many images as they could remember from the prior study visit. During this visit, participants also completed a brief self-report survey including questions about sleep over the previous two nights. This procedure was then repeated for the second set of appointments during the other cycle phase with the other set of IAPS photos they had not yet seen (time between session sets: M_{days}=15.84, SD_{days}=8.13). During the second recall session, participants also rated the valence and arousal of ten photos they had previously seen. Participants were compensated for their time via electronic gift cards.

Measures

Demographic Variables

Standard self-report demographic questions were administered during online screening to assess sex, age, race/ethnicity, current medications, and history of mental health diagnoses ("Have you ever been given a mental health diagnosis?").

Menstrual Cycle Information

Information about participants' menstrual cycle and related physical health was gathered as part of the online screening via self-report questions, and components (i.e., dates of menses) were reassessed as needed throughout the study for scheduling. Questions included height, weight, age at first menarche, history of pregnancies and births, medical diagnoses that may impact menstrual cycles (e.g., endometriosis, PCOS, hyper/hypothyroid), hormonal contraceptive use (i.e., whether using hormonal contraceptive, type, and duration; recent use of emergency contraceptives) and regularity of use ("How regularly do you take your birth control?" from 1-very regularly to 7-very irregularly and "On average how many days of birth

control do you miss per week? from 0, 1, 2, or 3 or more, with ratings ≥4 on the regularity question and/or missing more than two pills per week indicating irregular pill use), regularity of menstrual cycles ("How regular is your cycle?" from 1-very regular to 7 very irregular with ratings ≤3 indicating cycle regularity), and typical length of menstrual cycle and of menses. Additionally, date of onset of most recent menstrual period and estimated start date of next menses was collected and used to schedule appointments after randomization for included participants. Given the variation in cycle lengths, we applied conservative day counts used in prior studies (see Gamsakhurdashvili et al., 2021a for review) of days 1-4 for early follicular phase and days 18-24 for midluteal phase.

Sex Hormones

Salivary estradiol and progesterone levels were collected via Salimetrics (Carlsbad, CA) passive drool collection kits in accordance with manufacturer's assay kit protocols during both encoding visits. Each participant was provided instructions and monitored during self-collection of about 300 µL of saliva. The sample was stored in a -80°C freezer within 30 minutes of collection. Samples were then shipped to Salimetrics (Carlsbad, CA) for enzyme immunoassay (ELISA). According to the manufacturer, detection ranges of estradiol and progesterone assays were 1 - 32 pg/mL and 10- 2430 pg/mL, respectively with sensitivities of 0.1 pg/mL and 5 pg/mL, respectively. Average intra-assay coefficients of variation were 7.13% and 6.20% for estradiol and progesterone, respectively. Inter-assay coefficients of variation were 7.45% for estradiol and 7.55% for progesterone. Along with saliva sample collection, participants were asked about compliance with behavioral guidelines prior to the appointment that may explain outlying values due to impact on assays including time of last exercise and last consumption of food, alcohol, caffeine, and nicotine. No levels of sex hormones were below the assay kit

threshold for detection. Two samples did not have sufficient quantity for duplicate testing, and thus the level from the first assay repetition was used in analyses.

Emotional Memory

Participants were shown a total of two sets of photos (i.e., Set A and Set B), one per cycle phase encoding session (i.e., early follicular, midluteal), and the order in which participants saw the sets was counterbalanced. Although many prior studies measured surprise free recall, given that the recall test could only be a surprise on the first set of appointments, prior to the presentation of images, participants were instructed to pay attention to the photos because they would be asked about the photos later, similar to Nielsen et al., 2015, to avoid substantial influence of surprise versus anticipated recall. During each encoding session, participants were shown a total of 70 images—35 neutrally valenced and 35 negatively valenced photos from the International Affective Picture System (IAPS; Lang et al., 2008). Images were selected from those used in previous studies of the relationship between menstrual cycle phase and emotional memory (Felmingham, Fong, et al., 2012; Gamsakhurdashvili et al., 2021b; Pompili et al., 2016); however, we removed and supplemented some images with different IAPS images to ensure no two photos could be identified by a similar description (e.g., there was only one photo that can be described as an angry dog). Images were carefully separated to ensure the two photo sets were equal in terms of women's normed ratings of valence and arousal for neutral and negative photos (See Table 1 for details). The presentation time of images has ranged from two seconds (Bayer et al., 2014) to ten seconds (Nielsen, Segal, et al., 2013) in prior research, thus we presented images for five seconds each, consistent with the most recent study in the area of sex hormones and emotional memory (Gamsakhurdashvili et al., 2021b). Images were separated by a one second fixation cross, and photo sets were presented in video format to ensure timing consistency.

In order to ensure that recall occurs during the same menstrual phase as photo viewing, memory performance was measured by the number of pictures freely recalled accurately two days after encoding. During virtual recall sessions, participants were asked to provide typed descriptions of as many images that they could recall from two days prior. Participants were proctored by research assistants during memory recall. They were sent a link to a Qualtrics survey which prompted them to "please briefly describe an image you can remember from the last lab session", and they were provided a text box to type in a description of the first recalled image. The participant was then prompted by the question "Do you remember any other images? Please do not guess" and with selection of "yes" was then given another text box to describe another image recalled and so on until reaching the point of not recalling more images and instead indicating "no" to recalling additional images. Two independent raters, blind to cycle phase and contraceptive status, coded participant responses. Consistent with prior studies (Ertman et al., 2011; Felmingham, Fong, et al., 2012; Gamsakhurdashvili et al., 2021b; Nielsen et al., 2015; Nielsen, Segal, et al., 2013), participant responses that clearly described a specific image from the photo set presented during the most recent encoding session were coded as correctly recalled. If it was the participant's second recall session and she recalled an image from the first photo set it was coded as a relevant intrusion and not counted as correct. Other responses that did not align with any image from the study were coded as an irrelevant intrusion and regarded as incorrect. The current study focused on numbers of correctly recalled photos per valence and a ratio of negative photos correctly recalled out of total number of photos correctly recalled.

Manipulation Check. On the final visit of the study (i.e., second recall session), after all other measures were completed, participants were shown ten photos, randomly selected from

both photo sets consisting of five neutral and five negative photos, intermixed. The selection of photos was the same for all participants. Participants were asked to rate the valence and arousal of the photos on a one to nine Likert scale consistent with the IAPS (Lang et al., 2008) for comparison to check whether stimuli were behaving as intended.

Mental Health Symptomatology

The 21-item Depression, Anxiety, and Stress Scale (DASS-21) is a valid and reliable self-report measure composed of three subscales assessing recent symptoms of depression (e.g., "I couldn't seem to experience any positive feeling at all"), anxiety (e.g., "I felt I was close to panic"), and stress (e.g., "I found it hard to wind down"; Lovibond & Lovibond, 1995) that was administered at each encoding session. Consistent with prior research examining the scale's use in healthy college samples, the total score was used to represent a general measure of negative emotions experienced in the last week (Osman et al., 2012). Each item is rated on a 4-point Likert Scale from 0 ("did not apply to me at all") to 3 ("applied to me very much or most of the time"). Scores on items were doubled and summed so higher total scores indicated greater symptomatology. The scale had excellent internal consistency in this study during the early follicular phase (α=0.91) and good internal consistency during the midluteal phase (α=0.89).

Menstrual Symptoms

The Menstrual Symptoms Questionnaire (MSQ; Chesney & Tasto, 1975) is a reliable self-report measure of menstrual symptoms comprised of 24 items covering premenstrual symptoms (e.g., "For several days *before* my period I feel exhausted, lethargic or tired"), psychophysiological changes surrounding menstruation (e.g., "I feel weak and dizzy *during* my period;" "I have cramps that *begin* on the first day of my period;" "I feel tense and nervous *before* my period"), and pain during menses (e.g., "*Beginning* on the first day or so of my period,

I have pains which may diminish or disappear for several minutes and then reappear;" "I take a prescription drug for the pain *during* my period"). Each symptom is rated from 1 ("never") to 5 ("always") with higher summed scores indicating more menstrual symptoms (Negriff et al., 2009). As the questions are phrased to refer to the most recent cycle, only ratings during the encoding session of the early follicular phase were used in the present study. The MSQ demonstrated acceptable internal consistency (α=0.75).

Sleep Quality

Sleep quality was measured using the Insomnia Severity Index (ISI), a 7-item self-report questionnaire with established validity and reliability (Bastien et al., 2001) that demonstrated good internal consistency in the present study during each cycle phase (early follicular: α=0.87, midluteal: α=0.89). The index captured participants' potential difficulty with initiating and maintaining sleep as well as their perception of their sleep (e.g., general satisfaction with sleep, distress related with sleep difficulties, and interference of sleep problems with daily functioning and overall quality of life). Each item is rated on a 0-4 scale and summed to create a total score ranging from 0-28 with higher scores indicating greater severity of insomnia and thus worse sleep quality. The ISI was administered during each recall session and the timeframe was altered to assess sleep problems during the last two nights to assess sleep specifically during the period of memory consolidation.

Data Analytic Plan

Power Analysis

A *post hoc* power analysis was conducted using G*Power (Faul et al., 2007) for the primary aim of examining within-subjects differences in emotional memory across the menstrual cycle in naturally cycling women. The 2 (menstrual cycle phase) x 2 (image valence) ANOVA:

repeated measures, within factors power analysis revealed that a sample size of 35 participants yielded 52% power to detect a small to medium effect (defined as η_p^2= 0.03, Cohen's *f*= 0.18 equivalent to effect size Cohen's *d*= 0.36), but afforded 83% power to detect a medium effect (η_p^2= 0.06, Cohen's *f*= 0.25 equivalent to Cohen's *d*= 0.50). While some prior studies of emotional memory in naturally cycling women reported effect sizes between 0.32 (Zoladz et al., 2015) and 0.52 (Ertman et al., 2011), most studies did not report effect sizes. Further, this literature is equivocal given the mixed findings complicated by heterogenous methods which made it difficult to determine an expected effect size. Despite limited power analyses in prior literature, most studies had total samples of less than 70 for between-subjects designs. Those that had larger samples also involved more groups due to the additional testing of physiological stressors. Thus, our sample size for the within-subjects design was adequately powered and in line with prior literature. However, our between-subjects analysis (*n*=41) was likely underpowered.

Given that the sample of oral contraceptive users served as a control group, we did not plan for specific power, and it was meant to serve as a check on the role of hormone fluctuation given this group was not anticipated to exhibit large fluctuations.

Handling of Missing Data

Missing data were handled in a couple of ways. Given the nature of the primary variables of interest (i.e., menstrual cycle phase, salivary hormone levels, memory recall), values cannot be imputed, and participants missing these data were excluded from relevant analyses. In exploratory analyses involving self-report questionnaires (i.e., DASS-21, MSQ, ISI), missing data were imputed when scales were missing 20% or less of the total scale. A total of 10 values were imputed using the individual's mean of available items for that particular scale or subscale.

No participants were missing greater than 20% of items on a questionnaire which would have necessitated exclusion in relevant analyses. Additionally, throughout the self-report measures, we had five data quality checks (i.e., questions instructing participants to select specific answers). Data from participants who failed one or two quality checks were reviewed for patterns of mis-responding and it was determined that exclusion from analyses was not warranted. No participants incorrectly responded to three or more quality checks in a session set, which would have resulted in exclusion from analyses.

Preliminary Analyses

Unless otherwise specified, analyses were run using SPSS Version 26.0 (IBM Corp., 2019). Descriptive statistics including frequencies were examined to ensure that data fell within the expected values for each measure. Variables were examined for normality and assumptions for each analysis. Further, we examined for outliers (values greater than three standard deviations from the mean) and examined for impact on both data distribution and outcomes. Extreme values with a meaningful impact on assumptions or outcomes were excluded from relevant analyses.

Chi- square analyses and *t*-tests were conducted to assess for differences in demographics across groups. Group comparisons were conducted between menstrual cycle phases of naturally cycling women for both cross-sectional and longitudinal analyses, between contraceptive phase groups, and between naturally cycling and contraceptive users to investigate potential group differences. Chi-square analyses were conducted for categorical variables of race, ethnicity, and university affiliation. *T*-tests were conducted for comparison of continuous variables of age, body mass index (BMI), mental health symptomatology, menstrual symptoms, and sleep quality. However, given that we only utilized early follicular menstrual symptoms in the present study,

we did not compare menstrual symptoms for the cross-sectional analysis in naturally cycling women. We also conducted *t*-tests to assess whether hormone levels (i.e., estradiol and progesterone) differed between groups.

The manipulation check was carried out by a series of *t*-tests that compared participants' ratings of valence and arousal of a subset of images categorized as neutral and negative images in the IAPS catalogue (Lang et al., 2008). Additionally, we conducted 2x2 ANOVA analyses across repeated measures samples to check randomization and assess for potential effects of order of appointments (i.e., first versus second session, irrespective of randomized cycle phase) or stimuli set (i.e., photo set A versus B) on memory of neutral or negative stimuli with intention of including any effects as covariates in primary analyses.

Primary Analyses

Consistent with prior studies (e.g., Ertman et al., 2011; Felmingham, Fong, et al., 2012; Nielsen et al., 2014), an analysis of variance (ANOVA) framework was used to test study aims.[1] Aim one was tested in the naturally cycling sample with a cross-sectional 2x2 mixed-model ANOVA analyzing the effect of valence of the visual stimuli (i.e., neutral versus negative) and menstrual cycle phase (i.e., early follicular versus midluteal) on memory using data from the first set of appointments. Neutral valence and the early follicular phase served as the reference

[1] This ANOVA framework was chosen to be consistent and comparable to prior research on emotional memory recall with similar scoring and analyses (e.g., Ertman et al., 2011; Felmingham, Fong, et al., 2012; Nielsen et al., 2014) and because data were observed to behave as if approximately normally distributed. However, given that the outcome variable is a count variable (and thus inherently not normally distributed), mixed effects Poisson regressions are more appropriate (Coxe et al., 2009). Therefore, mixed effects Poisson regressions were also conducted to examine primary and exploratory aims. These analyses all led to the same conclusions as the ANOVA analyses; therefore, ANOVA and similar linear mixed effects regression results are presented in this document for ease in interpretation and comparison to prior studies.

groups. The main effects of valence and menstrual cycle phase as well as the interaction, which would indicate an effect of phase on emotional memory performance, were examined.

Aim two was tested in the naturally cycling sample with a repeated measures 2x2 ANOVA examining the effect of stimuli valence (i.e., neutral versus negative) and menstrual cycle phase (i.e., early follicular versus midluteal) on recall. Again, reference groups were the neutral valence and early follicular phase. The main effects of valence and menstrual cycle phase as well as the interaction were examined, whereby a significant interaction would indicate an effect of menstrual cycle phase on emotional memory within women.

Aim three was conducted in the oral contraceptive sample using the same repeated measures 2x2 ANOVA set up analyzing the effect of stimuli valence (i.e., neutral versus negative) and contraceptive phase (i.e., placebo/early follicular versus active/midluteal) on memory. The neutral valence and the placebo pill/early follicular phase served as the reference groups. A nonsignificant interaction would indicate that emotional memory performance did not change on account of time and valence. Additionally, to further test for the absence of a contraceptive pill phase effect, a test of equivalence using the two one-sided tests method (Lakens, 2017) was conducted. Equivalence tests were run in R (R Core Team, 2024) utilizing the "TOSTER" package (Lakens, 2017). Given the *t* test nature of this method, emotional memory was scored as the number of negatively valenced images correctly recalled out of total number of images correctly recalled for the purposes of the equivalence test.

Exploratory Analyses

Aim four concerned the naturally cycling sample. To identify covariates for aim four, ratings of mental health symptomatology and sleep were compared between the early follicular and midluteal phases using paired samples *t*-tests. If there was a significant change in ratings, the

change score from early follicular to midluteal (calculated as midluteal ratings minus early follicular ratings) would be used as a covariate in the analysis of covariance (ANCOVA) if it was also correlated with change in emotional memory (operationalized as number of negative images recalled out of total number recalled for this purpose). Because only menstrual symptom ratings collected during the early follicular phase were used, menstrual symptoms would only be included as a covariate if they correlated with change in emotional memory. Any significant change scores and menstrual symptom ratings correlated with emotional memory change were to be entered as covariates in separate repeated measures 2x2 ANCOVAs examining the effect valence of stimuli (i.e., neutral versus negative) and menstrual cycle phase (i.e., early follicular versus midluteal). A significant interaction would indicate that emotional memory performance changed on account of time and valence when accounting for covariates.

Aim five was examined separately but identically in the naturally cycling and contraceptive samples for each hormone (i.e., estradiol and progesterone). A series of linear mixed effects regressions predicting memory recall from the dichotomous predictor of valence of visual stimuli and continuous hormone levels (measured during early follicular and midluteal phases), and their interaction was conducted. A significant interaction between hormone level and valence would indicate that emotional memory changed as the hormone level changed across the cycle. The hormone levels in the early follicular phase and the neutral valence served as the reference groups. Models were conducted in STATA 14.1 (StataCorp, 2015) using the mixed procedure, maximum likelihood estimation, and the repeated measures method for degrees of freedom with random intercepts at the person level.

Results

Descriptive Statistics

Demographic and descriptive statistics are reported in Tables 2 and 3. Naturally cycling participants were, on average, 20.34 (SD=3.30) years old. The majority were white (73%), undergraduate (93%) college students. Similarly, oral contraceptive users were 20.80 (SD=2.49) years old on average, primarily white (90%), and the majority were undergraduate students (70%).

Preliminary Analyses

All data fell within expected values for each measure and, except for sleep quality during both cycling phases in the naturally cycling group, appeared approximately normally distributed (skewness <|2|) and met the assumption of sphericity given that there were only two levels of each variable. Further examination revealed one outlier with notably worse sleep quality across phases, almost maxing out the scale indicating a potentially unreliable response, and its removal resulted in an approximately normal distribution at both timepoints in the menstrual cycle. Thus, this outlier was excluded from all sleep analyses. Another potential outlier was identified in the recall of neutral photos during the midluteal phase. However, it did not impact the distribution and results were consistent across analyses conducted with and without it; therefore, it was retained in all analyses. Similarly, three naturally cycling women exhibited a decrease in progesterone between the early follicular and midluteal phases of their menstrual cycles; however, excluding them did not result in any meaningful change and thus they were also retained. Finally, three participants (two naturally cycling and one oral contraceptive user) were

excluded from within-person analyses utilizing the proportion operationalization of emotional memory (i.e., the ratio of negative recall to total recall) given that they did not recall any images correctly during one recall visit and it was not possible to calculate a proportion score with zero as a denominator.

Group comparisons are reported in Tables 2-4. No differences in demographic, mental health symptomatology, menstrual symptoms, or sleep quality were observed across sample groupings (all *p*s>0.05). However, levels of sex hormones were significantly different between sample groupings. More specifically, within the first session set, levels of estradiol and progesterone were significantly different between participants in the early follicular and midluteal phase, while only progesterone was significantly different within the naturally cycling group from one phase to the other and between the naturally cycling and oral contraceptive samples (see Tables 2-4).

A 2x2 ANOVA revealed that, while there was a significant main effect of valence ($p<0.001$, $\eta_p^2=0.62$), there was no main effect of session set ($p=0.216$, $\eta_p^2=0.04$) or interaction between valence and session set on memory recall ($F(1, 44)=0.01$, $p=0.913$, $\eta_p^2<0.001$). Similarly, a 2x2 ANOVA examining the potential influence of photo set on memory recall revealed a significant main effect of valence ($p<0.001$, $\eta_p^2=0.62$), but no significant main ($p=0.292$, $\eta_p^2=0.03$) or interactive effect of photo set ($F(1, 44)=1.70$, $p=0.199$, $\eta_p^2= 0.04$). Thus, neither session set nor photo set was retained as a covariate in primary analyses.

Paired samples *t*-tests revealed that participants rated negatively valenced photos (M=2.17, SD=0.95) as less pleasant compared to neutral photos (M=2.90, SD=1.51; $t(44)=3.18$, $p =.003$). Furthermore, participants also rated negative photos (M=6.08, SD= 1.45) as more arousing than neutral photos (M=2.41, SD=1.22; $t(44)=-16.23$, $p <0.001$).

Primary Analyses

Aim 1: Examine the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional stimuli in naturally cycling women via between-subjects design.

A 2 (within factor: valence) x 2 (between factor: cycle phase) mixed model ANOVA using data from naturally cycling women during the first session set revealed a main effect of photo valence on the number of images correctly recalled ($F(1, 39)=24.28$, $p<0.001$, $\eta_p^2=0.38$), such that negative photos (M=4.90, SE=0.34) were recalled more than neutral photos (M=2.64, SE=0.34; see Figure 1). However, there was no significant main effect of menstrual cycle phase on memory ($F(1, 39)=0.78$, $p=0.381$, $\eta_p^2=0.02$) nor was there a significant interaction between valence and cycle phase ($F(1, 39)=0.70$, $p=0.409$, $\eta_p^2=0.02$).

Given the non-significant interaction effect, an equivalence test was conducted comparing women in the early follicular phase to those in the midluteal phased during session set one on the proportion of negative recall out of total recall. Equivalence bounds were set to the smallest detectable effect size comparing samples of n=16 and n=25 (Lakens, 2017), -0.81 and 0.81, according to G*Power *post hoc* sensitivity analysis (Faul et al., 2007). The equivalence test revealed that that the menstrual cycle groups were not significantly equivalent on emotional memory performance ($t(39)=1.45$, $p=0.0779$) suggesting that the midluteal group recalled a greater proportion of negative photos than the early follicular group.

Aim 2: Examine the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional memory in naturally cycling women via within-subjects design.

A 2 (valence) x 2 (cycle phase) repeated measures ANOVA within naturally cycling women revealed a main effect of photo valence on the number of images correctly recalled ($F(1, 34)=45.44$, $p<0.001$, $\eta_p^2=0.57$), such that negative photos (M=4.66, SE=0.37) were recalled more than neutral photos (M=2.27, SE=0.22; see Figure 2). However, again, there was no significant main effect of menstrual cycle phase ($F(1, 34)=1.18$, $p=0.285$, $\eta_p^2=0.03$) nor an interaction between valence and cycle phase ($F(1, 34)=0.002$, $p=0.965$, $\eta_p^2<0.001$).

An equivalence test was conducted to further investigate the non-significant interaction effect comparing the proportion of recall of negative photos out of total recalled within naturally cycling women from one cycle phase to the other. Given that two women recalled no images at one time point, $n=33$ for this follow-up and equivalence bounds were set accordingly to -0.44 and 0.44, the smallest detectable effect size (Lakens, 2017) for this sample size (Faul et al., 2007). Within naturally cycling women, emotional memory performance was significantly equivalent across cycle phases ($t(32)=-1.98$, $p=0.0282$).

Aim 3: Examine the relationship between contraceptive phase (i.e., placebo, active pill) and recall of emotional memory via within-subjects design in the subsample of contraceptive users.

A 2 (valence) x 2 (pill/cycle phase) repeated measures ANOVA in oral contraceptive users revealed a main effect of photo valence, whereby more negative photos were correctly recalled (M=6.45, SE=0.94) than neutral photos (M=2.85, SE=0.44; $F(1, 9)=31.19$, $p<0.001$, $\eta_p^2=0.78$; see Figure 3). Menstrual cycle phase trended toward a significant main effect on memory ($F(1, 9)=3.80$, $p=0.083$, $\eta_p^2=0.30$); however, the interaction between valence and cycle phase was not significant ($F(1, 9)=0.02$, $p=0.903$, $\eta_p^2=0.002$).

Given the expectation of a non-significant interaction effect, an equivalence test was conducted comparing emotional memory performance within oral contraceptive users from one

pill/menstrual cycle phase to the other. Due to one woman not recalling any images during one cycle phase, equivalence bounds were set to the smallest detectable effect size (Lakens, 2017) for n=9 (-0.91 and 0.91; Faul et al., 2007). The equivalence test revealed that performance during the two cycle phases was significantly equivalent within oral contraceptive users ($t(8)$=-2.107, p=0.0341).

Exploratory Analyses

Aim 4: Explore if the relationship between menstrual cycle phase (i.e., early follicular, midluteal) and recall of emotional memory in within-subjects designs remains when controlling for menstrual symptoms, changes in mental health symptomatology, and sleep.

Despite there being no significant main or interactive effects for menstrual cycle phase on memory within the naturally cycling women, potential covariates were explored for potential influence. Paired samples t tests revealed no significant change in mental health symptomatology or sleep quality across the menstrual cycle within naturally cycling women (ps>0.05; see Table 4). Given the lack of significant change, change scores were not explored as covariates in ANCOVAs.

Although menstrual cycle phase did not exhibit a memory effect, and no differences were observed in menstrual symptoms, mental health symptomatology, or sleep from one phase to another, we further examined each potential covariate for a significant relationship with emotional memory (negative images out of total recalled) at each phase and change in emotional memory; however, none emerged (see Table 5). Therefore, none of these variables were explored as potential covariates in an ANCOVA.

Aim 5: Explore the relationship between salivary levels of estradiol and progesterone and emotional memory performance.

Naturally Cycling. A linear mixed effects regression revealed a significant relationship between photo valence and memory recall (B=2.39, SE=0.36, 95% CI [1.67, 3.10]) that remained even when hormone levels were added into the models (see Table 6). However, estradiol was not significantly related to memory recall overall (B=0.04, SE=0.35, 95% CI [-0.65, 0.74]) or through an interaction with valence (B=0.03, SE=0.57, 95% CI [-1.10, 1.16]). Progesterone had a similar nonsignificant main (B<0.001, SE=0.001, 95% CI [-0.002, 0.003]) and interactive effect (B=0.001, SE=0.002, 95% CI [-0.003, 0.01]) with valence in predicting memory recall.

Oral Contraceptive Users. Valence again significantly predicted memory recall (B=3.60, SE=0.73, 95% CI [2.10, 5.10]) in linear mixed effects regressions in oral contraceptive users and remained even with the addition of hormone levels (see Table 7). No significant associations between estradiol or progesterone and memory recall emerged overall (estradiol: B=-1.02, SE=0.78, 95% CI [-2.61, 0.58]; progesterone: B=-0.01, SE=0.005, 95% CI [-0.02, 0.004]). Moreover, there was no significant interaction between valence and estradiol (B=-2.02, SE=1.12, 95% CI [-4.32, 0.28]) or valence and progesterone (B=-0.01, SE=0.01, 95% CI [-0.02, 0.002]).

Discussion

The present study extended the investigation of the relationship between menstrual cycle phase (i.e., early follicular and midluteal) and recall of emotional memory to look within the same group of women across the cycle, which is the most appropriate design for menstrual cycle research (Schmalenberger et al., 2021). It also sought to compare these results to those of previous between-person analyses utilizing cross-sectional data from the first half of the study for each participant. Furthermore, it included a control sample of oral contraceptive users for comparison. Results revealed an emotional memory effect whereby all women recalled negatively valenced stimuli more than neutral. However, across all our group comparisons, results revealed no differences in emotional memory based on menstrual cycle or contraceptive pill phases and subsequently no significant relationship with salivary hormone levels (i.e., estradiol and progesterone). Therefore, while results supported our hypothesis that the contraceptive users would not exhibit a significant hormonal change from one phase to the other, our other hypotheses that women in the high hormone midluteal phase would exhibit a stronger emotional memory effect were not supported.

In order to compare our results to prior literature, we first conducted between-subjects analyses of naturally cycling women using data collected during the first session set. We compared outcomes between naturally cycling women who were randomized to either the early follicular or midluteal phase of their cycle for their first appointments. Women in the early follicular phase during session set one had lower levels of both estrogen and progesterone compared to women in the midluteal phase as expected (Knudtson & McLaughlin, 2019).

Supporting hypothesis one, results indicated that naturally cycling women in the first appointment session set recalled more negatively valanced stimuli compared to neutral stimuli. This is consistent with prior literature of the phenomenon of emotional memory broadly (Anderson et al., 2006; Cahill & McGaugh, 1995; Christianson, 1992; Kensinger, 2004, 2009; LaBar & Cabeza, 2006; Levine & Pizarro, 2004; McGaugh, 2004; Todd et al., 2012) and prior studies indicating the effect is particularly strong in women (Cahill, 2003; Canli et al., 2002; Felmingham, Tran, et al., 2012; Hamann, 2005). Contradicting our second hypothesis, there was not a significant impact of menstrual cycle phase on memory recall. However, the two cycle phase groups were also not equivalent in their emotional memory performance which indicates that there may be an effect of cycle phase that we were not sufficiently powered to detect given our small sample size for the between-subjects analyses. In other words, results suggest that if we were sufficiently powered, we may find an effect of menstrual cycle phase on emotional memory which would be consistent with the slight majority of prior between-subjects research (Ertman et al., 2011; Felmingham, Tran, et al., 2012; Nielsen et al., 2014, 2015; Nielsen, Segal, et al., 2013; Zoladz et al., 2015).

In longitudinal analyses the enhancement of emotional memory was again observed across the menstrual cycle, regardless of phase, which is consistent with our third hypothesis. However, hypothesis four, that women would exhibit a greater emotional memory effect in the high hormone midluteal phase compared to the low hormone early follicular phase, was not supported. In fact, emotional memory was the same across the different phases. This is partially consistent with the one existing within-subjects study that found that there was no difference in accuracy of recognition by phase but inconsistent with its finding that women exhibited a higher recollection memory for negative stimuli during the low hormone follicular phase than the high

hormone luteal phase (Bayer et al., 2014). While it can be difficult to compare to prior studies given design and methodological heterogeneity, these results suggest that, despite some evidence from between-subjects designs (Ertman et al., 2011; Felmingham, Tran, et al., 2012; Nielsen et al., 2014, 2015; Nielsen, Segal, et al., 2013; Zoladz et al., 2015), there is not an effect of cycle phase on emotional memory recall within women across their menstrual cycles. Although between-subjects designs enable the examination of emotional memory performance without practice effects or the possible influence of unequal stimuli sets, given individual differences in menstrual cycles (Fehring et al., 2006) and the notion that the menstrual cycle and its impact are inherently a within-person phenomenon, within-subjects designs are considered the gold-standard for studying the menstrual cycle (Schmalenberger et al., 2021).

Hypothesis five, that more negatively valenced stimuli would be recalled overall but that emotional memory performance would be equivalent across phases in the subset of oral contraceptive users was supported. As expected, this subsample had significantly lower levels of progesterone compared to naturally cycling women and did not exhibit significant changes in hormones from one phase to the other (Blumenthal & Edelman, 2008; Rivera et al., 1999). Furthermore, analyses revealed that the emotional memory effect was present and equal in both pill phases as predicted. While these subsample analyses were underpowered due to small sample size, results are consistent with the one prior study that also failed to find a difference in emotional memory performance between women in the placebo versus active pill phase even though hormone levels were significantly different across these phases (Mordecai et al., 2017). Considering that the naturally cycling women in our study were also observed to not exhibit a change in emotional memory across the cycle, results lend some additional evidence that there is potentially not a difference between naturally cycling and oral contraceptive users as suggested

by a few between-subjects studies (Nielsen et al., 2011; Nielsen, Segal, et al., 2013; Person & Oinonen, 2020).

Our sixth hypothesis, that a menstrual cycle effect on emotional memory would remain even when accounting for menstrual cycle symptoms and changes in mental health symptoms and sleep, could not be fully explored because we did not see a change in emotional memory due to menstrual cycle phase. However, we also did not see an association between menstrual cycle symptoms, mental health symptoms, or sleep within our sample across the menstrual cycle. Thus, given that we did not see a change in any variables of interest within naturally cycling women across the menstrual cycle, it could be that an effect did not emerge because there was not the expected change in these other variables (Baker & Lee, 2018; Handy et al., 2022; Reynolds et al., 2018; Schoep et al., 2019) which have the potential to influence emotion and memory processes (Andreano & Cahill, 2010; Everaert et al., 2014; Inostroza & Born, 2013; Keogh et al., 2014; Mitte, 2008; Oosterman et al., 2011; Shields et al., 2017). Thus, unfortunately, results do not enable us to disentangle the potential relationship between these variables across the menstrual cycle.

The lack of a significant relationship between salivary levels of estradiol and progesterone and emotional memory recall within both the naturally cycling women and contraceptive users also does not support our seventh hypothesis. Within the oral contraceptive users, it may be that we were simply underpowered to detect a relationship between hormone levels and emotional memory given our very small sample size. However, the lack of relationship within this sample may also be due to the relative stability in both hormone levels and emotional memory performance observed. If so, this would suggest that suppression of ovulation by contraceptives may have blocked elevations in hormone levels and emotional

memory (Blumenthal & Edelman, 2008; Rivera et al., 1999). In the naturally cycling women, considering that there was no difference in emotional memory performance within women from one cycle phase to the other, it makes sense that we did not observe a relationship with hormone levels, though this is contrary to what we expected to find. While it is possible that the lack of significant change in estradiol levels in our naturally cycling sample across the cycle (Knudtson & McLaughlin, 2019) may have contributed to the lack of change in emotional memory, prior within- and between-subjects studies that explored the relationship between hormone levels and emotional memory directly failed to find a significant association between emotional memory and estradiol (Bayer et al., 2014; Ertman et al., 2011; Ferree et al., 2011). Thus, although we cannot rule out the potential relationship, the absence of a significant association between estradiol and emotional memory in our study appears consistent with prior literature. More surprisingly, our sample did exhibit the expected increase in progesterone levels during the midluteal compared to the early follicular phase (Knudtson & McLaughlin, 2019), yet no relationship between progesterone and emotional memory was found. While this is consistent with the prior within-subjects study (Bayer et al., 2014), it deviates from the association between progesterone and negative recall observed in prior between-subjects studies (Ertman et al., 2011) and the meta-analytic suggestion of a relationship between progesterone and emotional memory recall (Hsu et al., 2021).

There are a couple possible explanations for the lack of an observed effect within the naturally cycling women across the menstrual cycle. Although we were appropriately powered to detect medium effects and equivalence tests revealed comparable emotional memory effects within women from one phase to the other, it is possible that the impact of hormones on memory is a smaller effect, particularly within a person, than originally thought; perhaps too small to be

detected with the current sample size. Furthermore, although no significant impact of session order or photo set was detected, it could be that each aspect of the design had a small impact that collectively inhibited our ability to detect a small to medium menstrual cycle effect. Additionally, given that we only observed a significant change in progesterone, and not a simultaneous increase in estradiol (Knudtson & McLaughlin, 2019), it is possible that we accidentally ran women closer to ovulation than the midluteal phase (Knudtson & McLaughlin, 2019). However, given that prior studies have only reported a link between progesterone (Ertman et al., 2011), not estradiol (Bayer et al., 2014; Ertman et al., 2011; Ferree et al., 2011), and negative memory, it is unlikely that this fully explains the present results if emotional memory is tied to progesterone levels.

The lack of effect of menstrual cycle phase and hormone levels in our study may also be due to the possibility that physiological arousal is a necessary component of the relationship between sex hormones and emotional memory, and that the images were not as evocative as intended. In fact, some clarity begins to emerge in the between-subjects emotional memory studies that implemented acute stressor paradigms in an attempt to mimic higher arousal stressors. A number of studies have found three-way interactions between valence, menstrual cycle phase, and stressor condition, albeit in inconsistent directions (Felmingham, Tran, et al., 2012; Nielsen et al., 2014, 2015). Activation of the physiological stress response as an essential component is supported by the broader context when we consider that PTSD is theorized to develop from overconsolidation of memory on account of stress/hyperarousal (Pitman & Delahanty, 2005) and that encoding is enhanced by stress (Cahill et al., 2003; Hall & Berntsen, 2008; Payne et al., 2006; Smeets et al., 2008). Furthermore, fluctuations in circulating sex hormones have been associated with the stress response such that higher cortisol responses are

associated with higher levels of sex hormones (Andreano et al., 2008; Andreano & Cahill, 2010; Goldstein et al., 2005; Kirschbaum et al., 1999). Given that no within-subjects examinations of an interactive effect of valence, menstrual cycle phase/sex hormones, and stressor on memory exists in the literature, it remains unknown if the addition of a stressor would cause a change in the strength of emotional memory to emerge within a person across the cycle. Given the equivocal directions even when a stressor is added in between-subjects paradigms, future research should investigate the role of stress within a sample across the cycle to account for the potential influence of individual differences.

It also remains possible that our results are accurate and that previous between-subjects designs yielded different results and conclusions than what is observed within women. In fact, our results revealed that there were no significant effects of menstrual cycle phase on emotional memory recall in any of our hormone groupings, but equivalence testing suggests that with a larger sample, we may find a difference in our between-subjects design. If we were to detect a between-subjects difference with a larger sample and still not observe a difference in the within-subjects design, this would suggest that between-subjects studies of the menstrual cycle are not representative of the true effect within most women. Regardless of whether a between-subjects effect was to emerge with a larger sample, the lack of similar effects in a within-subjects design would underscore the need to conduct more within-subjects studies in order to be able to determine if it truly is a menstrual cycle/sex hormone level effect (Schmalenberger et al., 2021).

If current results hold with a larger sample size, and in replication studies, this would suggest that the relationship between sex hormones and emotional memory is more nuanced and not simply a relationship between hormone levels and recall. Moreover, it would suggest that it may not simply be a between- or within-person effect, but perhaps it is both—it may be a

between-person difference in within-person change. Considering that there are individual differences in variability in menstrual cycles (Fehring et al., 2006) and in the magnitude of hormonal fluctuations (Anckaert et al., 2021), it may be that a subset of women experience enough of a change to exhibit a change in emotional memory while others do not. Future research should directly investigate this possibility and plan to power for more sophisticated statistical approaches that will allow for the modelling of individual differences in differing hormonal fluctuations and the relationship with memory performance.

Although the present study worked to rigorously test emotional memory across the menstrual cycle, it is not without limitation. First, small sample size limited our ability to adequately simulate the between-subjects analysis using first session data and to detect any potential unexpected effects within oral contraceptive users. Additionally, our sample was predominantly white women who were highly educated, and reported very regular menstruation; therefore, it remains unclear how results may or may not generalize to the greater population. We relied on self-report of mental health diagnoses and did not conduct diagnostic interviews, thus we cannot be sure our sample did not include individuals with mental health diagnoses. Furthermore, although we attempted to apply more conservative cycle inclusion criteria and more stringent day counts, we still relied on self-report of menstruation start dates and day counts for cycle phase determination and scheduling. While this is likely sufficiently accurate for the early follicular phase, the best way to determine the midluteal phase would be to measure actual ovulation via an at-home luteinizing hormone test (Schmalenberger et al., 2021). We also only tested women at two timepoints during the cycle as opposed to the recommended three or more to allow for appropriate modeling of random effects (Schmalenberger et al., 2021). Furthermore, we did not have a measure of attention nor evocativeness of each image so as not to

disrupt encoding; however, it limits our ability to check for the potential influence of attention. Moreover, the test-retest reliability of our emotional memory paradigm is unknown given that it has not been previously tested.

Despite these limitations, the present study included multiple methodological strengths that should be replicated in future research. To date, it is the first known attempt to investigate the relationship between menstrual cycle phase and emotional memory recall using a within-subjects design. In doing so, we demonstrated the feasibility of examining emotional memory recall within-subjects without a clear confound of a practice effect. Future research with larger samples and more measurements across the cycle is needed to confirm current results and to address the limitations and unanswered questions of the present study. More specifically, future studies should more accurately and reliably determine cycle phases in accordance with recommended guidelines (Schmalenberger et al., 2021). Furthermore, the role of an added stress paradigm should be explored within-subjects. Additionally, future research should employ more advanced statistical methods that are more accurate for count data (Coxe et al., 2009) and that enable the modeling of potential individual differences. This would allow for the examination of potential between-individual differences in within-individual changes in hormones and subsequent influence on emotional memory.

The present study was the first to our knowledge to investigate emotional memory recall within women across their menstrual cycle, and the first to attempt a direct comparison to previous between-subjects designs. While no significant effects of menstrual cycle phase or sex hormones on memory emerged, results from the present study, at a minimum, highlight the need for additional within-subjects exploration of the relationship between sex hormones and potential underlying mechanisms of PTSD development, such as emotional memory formation. This may

further elucidate whether women's increased risk for symptomatology following trauma is linked to sex hormone levels or the magnitude of change in hormones across the cycle. At this time, we cannot determine if the link between sex hormones and emotional memory emerges only in the presence of a stressor or as an artifact of between-subjects methodologies. Thus, it remains unclear whether a relationship between sex hormones and emotional memory does exist within most women (thus representing a fluctuating change in risk across the cycle), or if a specific subset of women is particularly at risk due perhaps to the magnitude of change in their individual hormone levels across the cycle.

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Table 1. Photo Set Comparisons

Comparison Across Photo Sets					
	Photo Set A	Photo Set B			
	Mean (SD)	*Mean (SD)*	*t*	*df*	*p*
Neutral Photos					
Valence	5.50 (0.68)	5.51 (0.71)	-0.06	68	0.952
Arousal	3.70 (1.02)	3.67 (0.99)	0.13	68	0.899
Negative Photos					
Valence	2.39 (0.63)	2.39 (0.72)	0.02	68	0.985
Arousal	5.96 (0.97)	5.97 (0.89)	-0.03	68	0.976
Overall					
Valence	3.94 (1.69)	3.95 (1.72)	-0.01	138	0.991
Arousal	4.83 (1.51)	4.82 (1.45)	0.05	138	0.963
Comparison Within Photo Sets					
	Neutral Photos	Negative Photos			
	Mean (SD)	*Mean (SD)*	*t*	*df*	*p*
Valence					
Photo Set A	**5.50 (0.68)**	**2.39 (0.63)**	**-19.85**	**68**	**<0.001**
Photo Set B	**5.51 (0.71)**	**2.39 (0.72)**	**-18.27**	**68**	**<0.001**
Overall	**5.50 (0.69)**	**2.39 (0.67)**	**-27.08**	**138**	**<0.001**
Arousal					
Photo Set A	**3.70 (1.02)**	**5.96 (0.97)**	**9.47**	**68**	**<0.001**
Photo Set B	**3.67 (0.99)**	**5.97 (0.89)**	**10.20**	**68**	**<0.001**
Overall	**3.68 (1.00)**	**5.96 (0.92)**	**13.989**	**138**	**<0.001**

Note: Significant differences are bolded.

Table 2. Menstrual Cycle Phase Comparison of Naturally Cycling Participants in Cross Sectional Analyses

	Total (*n*=41)	Early Follicular Phase (*n*=16)	Midluteal Phase (*n*=25*)	Cycle Phase Comparison			
		n (%)	*n (%)*	X^2	*df*	*p*	Fisher's Exact
Race				2.34	5	0.801	
Asian	2 (5)	0 (0)	2 (8)				
Black/African American	3 (7)	1 (6)	2 (8)				
White	30 (73)	13 (81)	17 (68)				
Biracial/Multiracial	2 (5)	1 (6)	1 (4)				
Other	3 (7)	1 (6)	2 (8)				
Unknown	1 (2)	0 (0)	1 (4)				
Ethnicity				2.94	1	0.086	0.120
Hispanic	8 (20)	1 (6)	7 (28)				
Not Hispanic	33 (80)	15 (94)	18 (72)				
University Affiliation				2.85	2	0.241	
Undergraduate Student	38 (93)	15 (94)	23 (92)				
Graduate Student	2 (5)	0 (0)	2 (8)				
Other	1 (2)	1 (6)	0 (0)				
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*t*	*df*	*p*	
Age	20.34 (3.30)	19.25 (1.53)	21.04 (3.92)	-1.74	39	0.090	
BMI	24.27 (3.77)	22.88 (3.58)	25.16 (3.68)	-1.94	39	0.059	
Estradiol (pg/mL)	**2.91 (0.68)**	**2.50 (0.72)**	**3.17 (0.53)**	**-3.44**	**39**	**0.001**	
Progesterone (pg/mL)	**422.17 (215.26)**	**270.16 (137.07)**	**519.46 (200.55)**	**-4.36**	**39**	**<0.001**	
DASS-21	26.70 (18.38)	31.17 (20.05)	23.84 (17.02)	1.25	39	0.217	
ISI	6.88 (4.33)	6.88 (3.56)	6.88 (4.86)	<0.001	38	1.000	

Note: Significant differences are bolded. **n*=34 for midluteal phase ISI due to removal of outlier. BMI=Body Mass Index, DASS-21=Depression and Anxiety Stress Scale-21, ISI=Insomnia Severity Index

Table 3. Comparison of Demographics and Potential Covariates Between Naturally Cycling Women and Oral Contraceptive Users in Repeated Measures Analyses

	Naturally Cycling (*n*=35*)	Oral Contraceptive (*n*=10)				
	n (%)	*n* (%)	X^2	*df*	*p*	Fisher's Exact Test
Race			2.46	5	0.782	
Asian	2 (6)	0 (0)				
Black/African American	2 (6)	0 (0)				
White	26 (74)	9 (90)				
Biracial/Multiracial	2 (6)	1 (10)				
Other	2 (6)	0 (0)				
Unknown	1 (3)	0 (0)				
Ethnicity			1.98	1	0.16	0.312
Hispanic	6 (17)	0 (0)				
Non-Hispanic	29 (83)	10 (100)				
University Affiliation						
Undergraduate Student	32 (91)	7 (70)	3.09	2	0.213	
Graduate Student	2 (6)	2 (20)				
Other	1 (3)	1 (10)				
	Mean (SD)	*Mean (SD)*	*t*	*df*	*p*	
Age	20.63 (3.48)	20.80 (2.49)	-0.15	43	0.885	
BMI	24.55 (3.81)	25.47 (6.14)	-0.58	43	0.863	
Estradiol (pg/mL)						
Early Follicular	2.79 (0.64)	2.87 (0.53)	-0.39	43	0.702	
Midluteal	2.95 (0.64)	2.97 (0.73)	-0.10	43	0.923	
Progesterone (pg/mL)						
Early Follicular	330.92 (125.76)	302.10 (97.19)	0.67	43	0.508	
Midluteal	**494.54 (183.35)**	**337.85 (128.46)**	**2.52**	**43**	**0.015**	
DASS						
Early Follicular	23.97 (15.92)	26.80 (30.57)	-0.28	10.43	0.784	
Midluteal	20.11 (13.13)	27.27 (24.54)	-1.23	43	0.225	
ISI						
Early Follicular	6.44 (3.84)	9.30 (5.50)	-1.87	42	0.068	
Midluteal	5.85 (3.18)	8.50 (5.34)	-1.21	42	0.056	
MSQ-EF	68.26 (10.67)	62.19 (11.49)	1.56	43	0.126	

Note: Significant differences are bolded. **n*=34 for ISI due to removal of outlier. BMI=Body Mass Index, DASS-21=Depression and Anxiety Stress Scale-21, ISI=Insomnia Severity Index

Table 4. Comparison of Demographics and Potential Covariates Within Naturally Cycling Women and Oral Contraceptive Users in Repeated Measures Analyses

		Early Follicular Phase	Midluteal Phase			
	n	*Mean (SD)*	*Mean (SD)*	*t*	*df*	*p*
Naturally Cycling						
MSQ-EF only	35	68.26 (10.67)				
DASS 21	35	23.97 (15.92)	20.11 (13.13)	1.64	34	0.110
ISI	34	6.44 (3.84)	5.85 (3.18)	1.04	33	0.304
Estradiol (pg/mL)	35	2.79 (0.64)	2.95 (0.64)	-1.51	34	0.141
Progesterone (pg/mL)	**35**	**330.92 (125.76)**	**494.54 (183.35)**	**-5.97**	**34**	**<0.001**
Oral Contraceptive						
MSQ-EF only	10	62.19 (11.49)				
DASS 21	10	26.80 (30.57)	27.27 (24.54)	-0.11	9	0.919
ISI	10	9.30 (5.50)	8.50 (5.34)	1.21	9	0.259
Estradiol (pg/mL)	10	2.87 (0.53)	2.97 (0.73)	-0.40	9	0.696
Progesterone (pg/mL)	10	302.10 (97.19)	337.85 (128.46)	-1.26	9	0.240

Note: Significant differences are bolded. **n*=34 for ISI due to removal of outlier. BMI=Body Mass Index, MSQ=Menstrual Symptom Questionnaire, DASS-21=Depression and Anxiety Stress Scale-21, ISI=Insomnia Severity Index

Table 5. Correlation Table of Variables of Interest in Repeated Measures Analyses in the Naturally Cycling Sample (*n*=32-35)

	1	2	3	4	5	6	7	8	9	10	11	12
1. EF Emotional Memory	--											
2. ML Emotional Memory	0.11	--										
3. Emotional Memory Change	**-0.76**	**0.57**	--									
4. EF MSQ	-0.04	-0.07	<0.001	--								
5. EF DASS-21	-0.03	-0.001	-0.05	0.21	--							
6. ML DASS-21	0.16	0.07	-0.04	0.06	**0.56**	--						
7. EF ISI	-0.07	0.21	0.20	-0.21	0.17	0.14	--					
8. ML ISI	0.25	0.07	-0.09	-0.02	0.27	0.28	**0.58**	--				
9. EF Estradiol	0.01	0.06	0.05	-0.01	0.25	0.25	**0.38**	**0.36**	--			
10. ML Estradiol	0.17	0.23	0.02	-0.21	0.07	0.33	0.22	**0.36**	**0.53**	--		
11. EF Progesterone	0.04	0.06	0.06	-0.09	0.09	0.21	**0.43**	0.31	**0.80**	**0.36**	--	
12. ML Progesterone	**0.35**	0.10	-0.18	-0.15	0.10	0.24	0.16	0.06	**0.52**	**0.50**	**0.50**	--

Note: Significant correlations are bolded. EF= early follicular phase, ML= midluteal phase, Emotional Memory = correct recall of negative images/total recall, Emotional Memory Change= ML-EF emotional memory scores, MSQ=Menstrual Symptom Questionnaire, DASS-21=Depression and Anxiety Stress Scale-21, ISI=Insomnia Severity Index

Table 6. Results of Linear Mixed Effects Regressions Predicting Memory Performance from Valence and Salivary Hormones in Naturally Cycling Women (*n*=35)

	Model 1				Model 2				Model 3			
Estradiol												
Fixed Effects	B	SE B	*t*	*p*	B	SE B	*t*	*p*	B	SE B	*t*	*p*
Intercept	**2.27**	**0.30**	**7.46**	**<0.001**	**2.15**	**1.05**	**2.05**	**0.048**	2.20	1.33	1.65	0.108
Valence	**2.39**	**0.36**	**6.60**	**<0.001**	**2.39**	**0.36**	**6.61**	**<0.001**	2.30	1.67	1.38	0.171
Estradiol					0.04	0.35	0.12	0.907	0.03	0.45	0.06	0.954
V x E									0.03	0.57	0.05	0.958
Random Effects	Variance	SE	95% CI		Variance	SE	95% CI		Variance	SE	95% CI	
Residual	4.57	0.63	3.48-5.99		4.56	0.63	3.48-5.98		4.56	0.63	3.48-5.98	
Intercept (person-level)	0.96	0.53	0.33-2.81		0.96	0.53	0.33-2.82		0.96	0.53	0.33-2.82	
Progesterone												
Fixed Effects	B	SE B	*t*	*p*	B	SE B	*t*	*p*	B	SE B	*t*	*p*
Intercept	**2.27**	**0.30**	**7.46**	**<0.001**	**2.01**	**0.58**	**3.46**	**0.001**	**2.25**	**0.72**	**3.14**	**0.004**
Valence	**2.39**	**0.36**	**6.60**	**<0.001**	**2.39**	**0.36**	**6.61**	**<0.001**	**1.90**	**0.92**	**2.06**	**0.042**
Progesterone					<0.001	0.001	0.53	0.598	<0.001	0.002	0.03	0.979
V x P									0.001	0.002	0.57	0.567
Random Effects	Variance	SE	95% CI		Variance	SE	95% CI		Variance	SE	95% CI	
Residual	4.57	0.63	3.48-5.99		4.56	0.63	3.48-5.98		4.55	0.63	3.47-5.96	
Intercept (person-level)	0.96	0.53	0.33-2.81		0.95	0.52	0.32-2.80		0.95	0.52	0.32-2.80	

Note: Significant findings are bolded.

Table 7. Results of Linear Mixed Effects Regressions Predicting Memory Performance from Valence and Salivary Hormones in Oral Contraceptive Users (*n*=10)

	Model 1				Model 2				Model 3			
Estradiol												
Fixed Effects	B	SE B	*t*	*p*	B	SE B	*t*	*p*	B	SE B	*t*	*p*
Intercept	**2.85**	**0.72**	**3.95**	**0.003**	**5.82**	**2.38**	**2.44**	**0.037**	2.89	2.83	1.02	0.334
Valence	**3.60**	**0.73**	**4.92**	**<0.001**	**3.60**	**0.72**	**5.03**	**<0.001**	**9.50**	**3.34**	**2.84**	**0.008**
Estradiol					-1.02	0.78	-1.30	0.203	-0.01	0.94	-0.01	0.989
V x E									-2.02	1.12	-1.80	0.082
Random Effects	Variance	SE	CI		Variance	SE	CI		Variance	SE	CI	
Residual	5.35	1.38	3.22-8.87		5.12	1.32	3.09-8.50		4.62	1.19	2.78-7.66	
Intercept (person-level)	2.54	1.77	0.65-9.94		2.45	1.70	0.63-9.58		3.05	2.08	0.71-9.38	
Progesterone												
Fixed Effects	B	SE B	*t*	*p*	B	SE B	*t*	*p*	B	SE B	*t*	*p*
Intercept	**2.85**	**0.72**	**3.95**	**0.003**	**4.60**	**1.64**	**2.80**	**0.021**	2.69	1.91	1.41	0.193
Valence	**3.60**	**0.73**	**4.92**	**<0.001**	**3.60**	**0.74**	**4.89**	**<0.001**	**7.29**	**2.16**	**3.38**	**0.002**
Progesterone					-0.01	0.005	-1.17	0.251	0.0004	0.01	0.09	0.930
V x P									-0.01	0.01	-1.81	0.082
Random Effects	Variance	SE	CI		Variance	SE	CI		Variance	SE	CI	
Residual	5.35	1.38	3.22-8.87		5.43	1.54	3.26-9.03		5.31	1.43	3.13-9.00	
Intercept (person-level)	2.54	1.77	0.65-9.94		1.92	1.54	0.40-9.22		2.61	1.96	0.60-11.41	

Note: Significant findings are bolded.

Figure 1. Memory Recall of Neutral and Negative Images Between Women in the Early Follicular Phase and Women in the Midluteal Phase During the First Session Set (n_{EF}=16, n_{ML}=25).

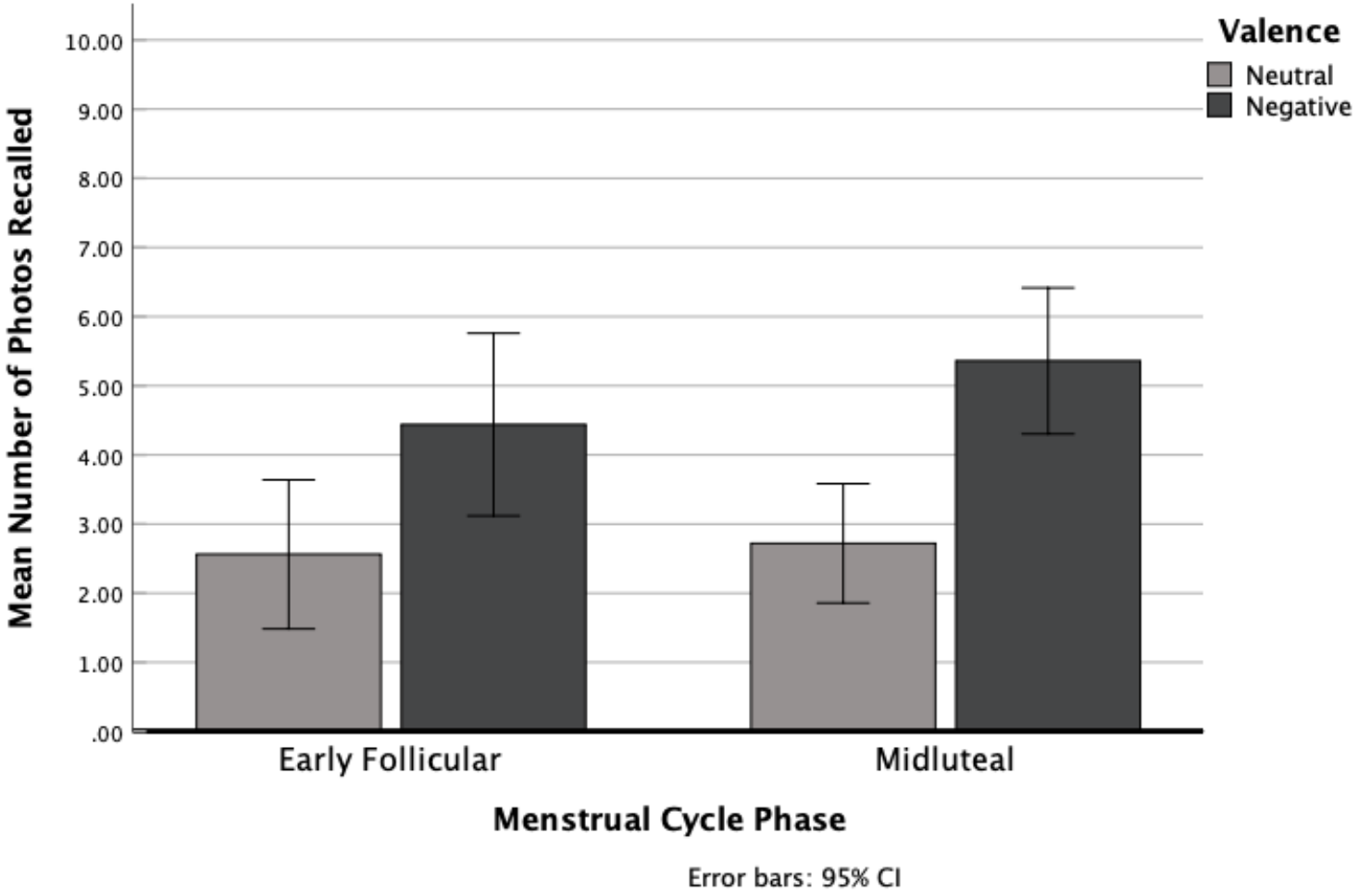

Figure 2. Memory Recall of Neutral and Negative Images Within Naturally Cycling Women During the Early Follicular and Midluteal Phase (*n*=35).

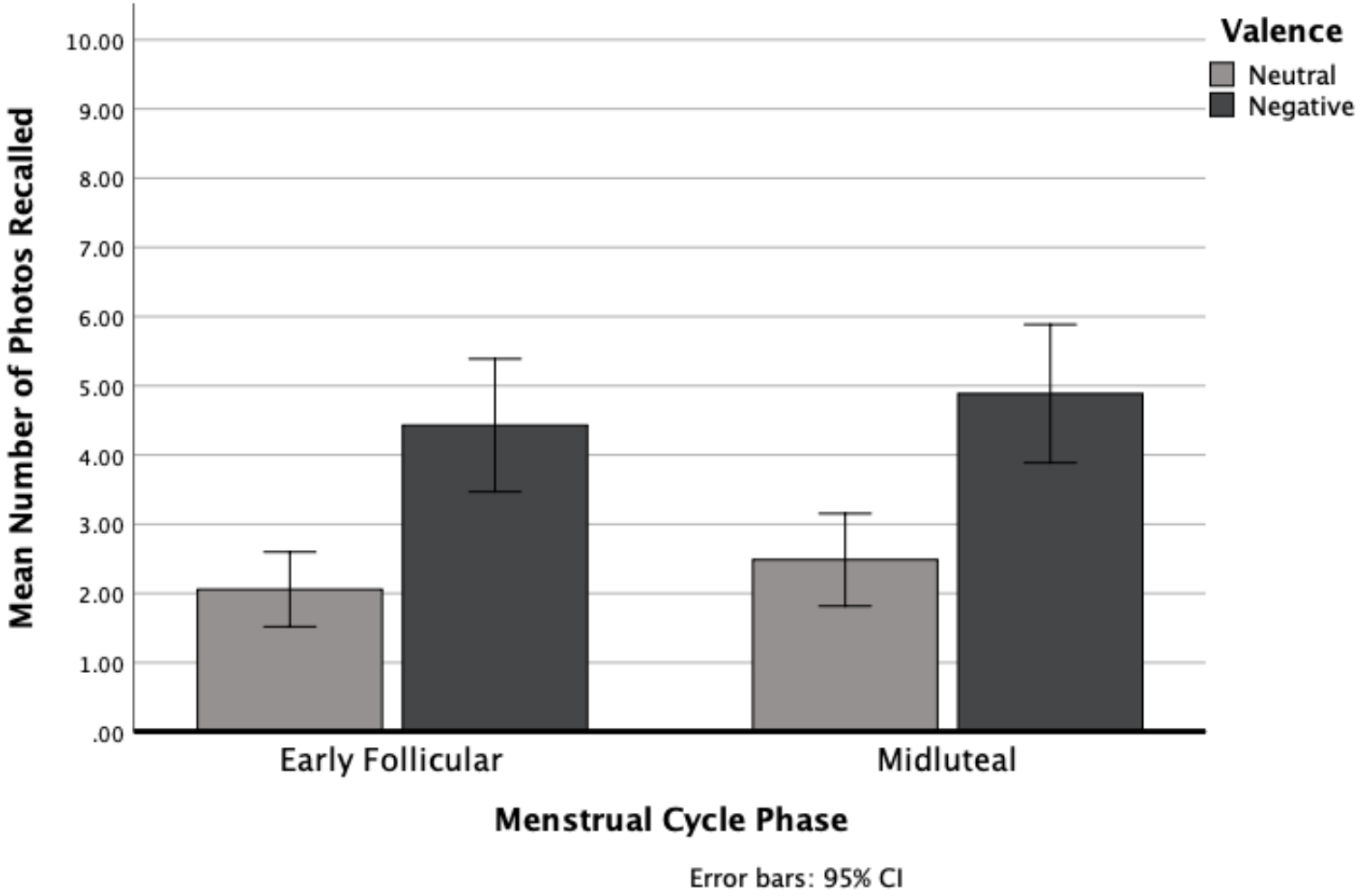

Figure 3. Memory Recall of Neutral and Negative Images Within Oral Contraceptive Users During the Early Follicular and Midluteal Phase (*n*=10).