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ANALOGUE TRAUMA EXPOSURE AND EMOTIONAL MEMORY INTRUSIONS THE ROLE OF OVARIAN HORMONES

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ABSTRACT

The gender difference in the development of reexperiencing symptoms of posttraumatic stress disorder (PTSD) may be partly explained by the influence of gonadal hormones on memory consolidation for stressful events. Circulating levels of ovarian hormones may influence the encoding of stressful memories, via their modulation of stress-response systems. This study augments existing research asserting that absolute levels of circulating ovarian hormones determine risk for the development of memory intrusions by also considering the prospect that cyclical fluctuations in estradiol and progesterone may facilitate re-experiencing. The low hormone early follicular (EF) phase of the menstrual cycle and hormonal contraceptive (HC) use, which eliminates cyclical fluctuations in endogenous estradiol and progesterone, may serve to diminish the risk naturally cycling women face for severe stress responding and the subsequent development of intrusive memories. To replicate existing research and contextualize potential protective effects, the development of memory intrusions following trauma film stressor exposure was assessed and compared among men (n = 27), HC users (n = 41), naturally cycling (NC) women in the EF (n = 24), late follicular (n = 20), ovulatory window (n = 14), and luteal phases (n = 21) for a 5-day period to determine whether low ovarian hormone levels confer a protective effect among women. Contrary to hypotheses, this study found no support for this prospect; rather, stressor exposure during the window around ovulation increased risk for the occurrence more frequent intrusive memories. Enhanced stress responsivity may have particular utility around ovulation as a means to promote evolutionary fitness.

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Introduction

Overview

With little consensus, researchers have attempted to explain why the burden of living with posttraumatic stress disorder (PTSD) falls disproportionately on women (e.g., Carter-Snell & Hegadoren, 2003; Olff, Langeland, Draijer & Gersons, 2007; Rasmusson & Friedman, 2002; Stein, Walker, & Forde, 2000; Tolin & Foa, 2008; Yehuda, 1999). Despite the fact that men are more likely than women to experience a significant traumatic event over the course of their lifetimes (61% compared to 51%; Kessler, Chiu, Demler, & Walters, 2005), women are more than twice as likely as men to develop PTSD in response to trauma (Kessler et al., 2005). Further, women are approximately four times more likely than men to suffer from chronic PTSD (Tolin & Breslau, 2007) and the severity of their re-experiencing symptoms (e.g., sudden and uncontrollable recollections regarding the trauma) is greater (Hourani Williams, Bray, & Kandel, 2016; Olff et al., 2007). Gender differences in post-trauma cognitions (Freedman et al., 2002), women's greater inclination toward self-blame (Tolin & Foa, 2002), and differences in the type of trauma women and men typically endure (Breslau, Chilcoat, Kessler, Peterson, & Lucia, 1999) have been purported as explanations for this difference. Yet, none is sufficient to account for the magnitude of the gender discrepancy (Tolin & Breslau, 2007). A singular explanation of this gender difference is unlikely, and any number of etiological pathways may result in the same expression of PTSD symptomatology (Olff, de Vries, Güzelcan, Assies, & Gersons, 2007; Yehuda, 1999). However, the most consistent evidence explaining the development of PTSD is for the impact of stress-response hormones on the way that trauma memory is consolidated (Ehlers & Clark, 2000; Foa & Hearst-Ikeda, 1996; Halligan, Clark & Ehlers, 2002; Horowitz, 1975; Horowitz, 1976; Pitman, 1989; Siegel, 1995; Wolf, 2008). Further, several lines of

research converge to suggest that trauma memories vary by sex (Canli, Desmond, Zhao, & Gabrieli, 2002; Davis, 1999; Hourani et al., 2016; Olff et al., 2007). As such, the unique contribution of male and female biology to peri-traumatic stress and memory processes may explain substantial variance in the PTSD gender difference (e.g., Breslau, 2001; Breslau, 2009; Cahill, 2003; Kudielkaa & Kirschbaum, 2005; Kirschbaum, Kudielka, Gaab, Schommer & Hellhammer, 1999; Olff, et al., 2007; Phillips & Sherwin, 1992).

In PTSD, trauma memories are extreme emotional fear memories, which are thought to be facilitated by an abnormal biological profile that is indicative of a threat state. This profile consists in part of elevated levels of stress-response hormones cortisol (CORT) and noradrenaline (NA), which have been implicated in peri-traumatic memory consolidation (i.e., the process by which trauma relevant information is stored within long-term memory) and PTSD symptom development (e.g., McCleery & Harvey, 2004; Van Stegeren, Wolf, Everaerd, & Rombouts, 2007). Re-experiencing symptoms, notably "flashbacks," or spontaneous intrusive recollections, have been consistently associated with these hormones during, and in the hours after, trauma when memory consolidation takes place (e.g., Buchanan & Lovallo, 2001; de Kloet, Oitzl, & Joëls, 1999; Ehlers and Clark, 2000; Feldner, Monson & Friedman, 2007; Lupien & McEwen, 1997; McGaugh, 2004; Pitman, 1989; Pitman, et al., 2002). The process by which stress hormones facilitate the consolidation of extremely vivid sensory memories (often devoid of context) that recur spontaneously has been dubbed emotional memory over-consolidation (Ehlers & Clark, 2000; Lupien & McEwen, 1997; McGaugh, 2004; Pitman, 1989; Pitman et al., 2002).

A wealth of research suggests that gender differences exist in the secretion of the stress hormones that facilitate emotional memory over-consolidation, and that these stress hormones

are regulated by circulating sex steroids. Although the process is not entirely understood, research has found that the female ovarian hormones estradiol and progesterone, which vary in elevation across the menstrual cycle (see Figure 1), are capable of modulating stress-responsive CORT and NA release bi-directionally (Bayer, Schultz, Gamer, & Sommer, et al., 2014; Kajantie & Phillips, 2006; Kirschbaum, et al., 1999; Kudielka & Kirschbaum, 2005; Walder, Statucka, Daly, Axen, & Haber, 2012; Viau, 2002). Indeed, stress-responsive CORT and NA secretion appear to exhibit menstrual cycle-bound fluctuations (Du, Riemersma & Dart, 1995; Kajantie & Phillips, 2006; Kirschbaum et al., 1999; Wolf, Schommer, Hellhammer, McEwen, & Kirchbaum, 2001). In contrast, men, who have low levels of estradiol and progesterone (comparable to women in the early follicular phase; Kudielka & Kirschbaum, 2005; Phillips & Sherwin, 1992), do not display cyclic variability in stress hormone release (Kirschbaum et al., 1999). Together, this implies that women may experience elevations in circulating stress-response hormones, and thus greater risk for memory over-consolidation following stressor exposure, during specific stages of the menstrual cycle (Andreano, Arjomandi, & Cahill, 2008; Bryant Creamer, O'Donnell, Silove, & McFarlane, 2011; Cheung, Chervonsky, Felmingham, & Bryant, 2013; Ertman, Andreano, & Cahill, 2011; Felmingham, Fong & Bryant, 2012; Ferree, Kamat, & Cahill, 2011). Indeed, two independent research groups reported that elevated sex steroids predicted cortisol elevations in response to exposure to negative images (a proxy for stressful experiences), which in turn predicted greater frequencies of memory intrusions. However, one group found this effect for progesterone (Felmingham et al., 2012), while the other group found the effect for estradiol (Cheung et al., 2013), thus questioning the proposition that women are at increased risk for memory over-consolidation during a particular stage of the menstrual cycle.

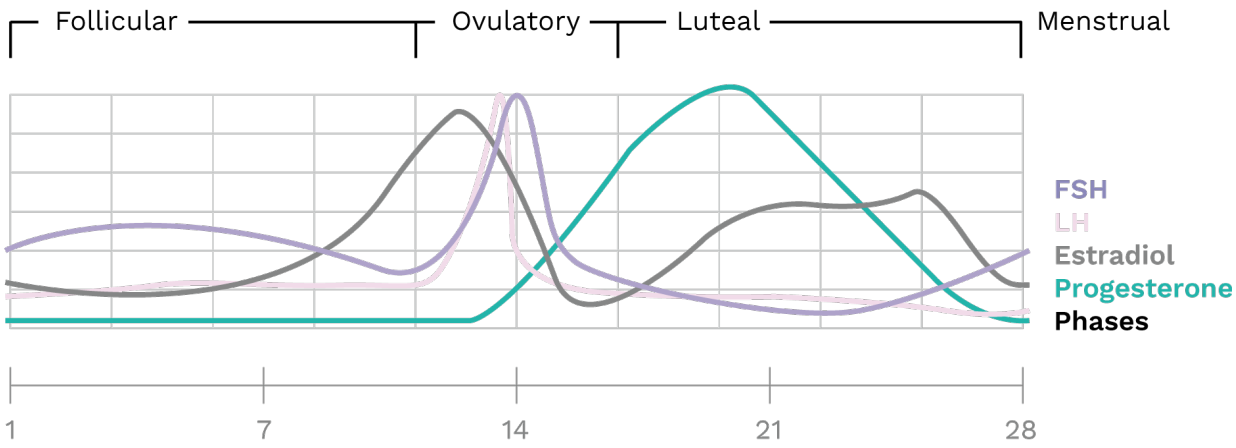

Figure 1. Ovarian Hormones Across the Menstrual Cycle. Reprinted from *The Science Behind*, by Ava Science Inc., April 19, 2016, retrieved from http://www.avawomen.com/ Copyright 2016 by Ava Science Incorporated.

Similarly, because steady low-level ovarian hormones may be protective against stress-responsive hypothalamic-pituitary-adrenal (HPA) and autonomic arousal (Boisseau et al., 2013; Kudielka & Kirschbaum, 2005; Roche, King Cohoon, & Lovallo, 2013; Rohleder, Wolf, Piel, & Kirschbaum, 2003), researchers have speculated that low-level hormones should protect against the development of memory intrusions (Ferree & Cahill, 2009; Nielson, Amhed, & Cahill, 2013; Neilson, Segal, Wordon, Yim, & Cahill, 2013). Specifically, researchers have suggested that stress exposure during the *early* follicular phase (when both progesterone and estradiol are maintained at their lowest levels for approximately five days) may pose the least risk for the over-consolidation of vivid emotional details of stressful events, relative to the rest of the cycle (Andreano & Cahill, 2010; Neilson et al., 2013). However, existing studies have grouped participants according to the entire follicular phase, which is associated with two very distinct periods corresponding with hormonal extremes: the cycle's lowest and peaking estradiol levels. Thus, whether the EF phase may truly be protective has not been tested directly.

It is also possible that it is not the absolute levels of estradiol and progesterone that may put women at risk for enhanced stress-responsivity and memory over-consolidation, but ovarian hormone fluctuations themselves. This prospect is supported by the fact that researchers have been unable to agree on a critical window (and associated levels of estradiol and progesterone) during which stress exposure is most likely to lead to intrusions among women. Several attempts to do this have captured the majority of the menstrual cycle as vulnerability periods, with each research group espousing a different window of risk (Bayer et al., 2014; Bryant et al., 2011; Cheung et al., 2013; Ferree & Cahill, 2009; Ferree, et al., Cahill, 2011; Soni, Curran, & Kamboj, 2013). Further, though women release less stress-responsive CORT than men throughout the follicular phase (days 1-14) and comparable levels during the luteal phase (days 15-28; Kirschbaum et al., 1999; Kudielka & Kirschbaum, 2005), they may be more vulnerable to its effects. As Felmingham and colleagues (2012) theorized, women may experience greater sensitivity to the effects of stress-induced cortisol than men, facilitating enhanced threat processing. A proposed explanation for this is the cyclical off-and-on again binding of estrogen to neuronal receptors, which may dysregulate the glucocorticoid system, such that cyclical estrogen surges and withdrawals facilitate glucocorticoid neuronal toxicity, and make women more vulnerable to stress responsivity (Seeman, 1997). Largely via the same mechanism, fluctuations in ovarian hormones across the cycle have been theorized to explain women's enhanced propensity toward a number of other anxiety disorders associated with the body's stress response systems (Maguire, Stell, Rafizadeh, & Mody, 2005; Seeman, 1997; Toufexis, Myers, & Davis, 1996).

More probable than either ovarian hormone levels or fluctuations being the culprit of enhanced risk, however, is the prospect that the combination of high levels and periodic

fluctuations both contribute to risk for the development of memory intrusions. The present study was designed to elucidate whether the inhibition of ovarian hormone fluctuations and maintenance of chronic low levels convey protection against peri-traumatic emotional memory over-consolidation processes. Hormonal contraceptives (HCs) dull the naturally occurring fluctuations in estradiol and progesterone across the menstrual cycle, maintaining both hormones at chronic low levels (Fleischman, Navarrete, & Fessler, 2010). Accordingly, HC use has been found to dampen naturally occurring corticosteroid and noradrenergic activation during stressful events (Boisseau et al., 2013; Kirschbaum et al.1999; Kudielka & Kirschbaum, 2005; Otterstette, et al., 1999; Neilson et al., 2013b; Roche et al., 2003). Given evidence that HCs inhibit stress system reactivity, the emotional memory over-consolidation hypothesis of PTSD would imply that HC use should also stifle emotional memory over-consolidation. Preliminary evidence by one research group is supportive of this prospect. Unlike naturally cycling women, HC users exhibit diminished recall for the specific negative stimulus details typically associated with memory over-consolidation (Neilson, Ertman, Lakhani, & Cahill, 2011), even when simultaneously exposed to physiologic stress (used to simulate trauma; Neilson, et al., 2013b). Additionally, HC use and taking emergency contraceptives (ECs, which are similar in chemistry and mechanism to HCs; Frye, 2006) immediately following a sexual assault has been associated with fewer PTSD re-experiencing symptoms six months later (Ferree, Wheeler, & Cahill, 2012)..

While these are the only studies to have examined this question, their methodologies raise validity concerns. First, estimates of total memory intrusions experienced were assessed retrospectively after either seven-days (Neilson et al., 2011, 2013b) or six-months (Ferree et al., 2012), thus subjecting estimates to potential biases in participants' recall. Second, frequency of memory intrusions was not directly assessed, but rather approximated by measurement of

memory detail (Neilson et al., 2011, 2013b) or overall PTSD re-experiencing symptoms (Ferree et al., 2012), including additional symptoms such as nightmares, general distress, and emotional and physiological reactivity to trauma reminders. Third, in Ferree and colleagues' (2012) study, HC users were more likely than others to participate in therapy during the follow-up period (p = .06 with a medium effect size), which may better explain their lower re-experiencing symptoms at follow-up, but this factor was not accounted for in the analyses. However, it is possible that the HC group was more inclined than their naturally cycling counterparts to seek treatment, as a function of blunted stress responsivity and thus less avoidance. Fourth, as an alternative to the interpretation that ECs and HCs conveyed a protective effect via biological mechanisms, it is possible that naturally cycling women who declined ECs exhibited enhanced trauma reactivity due to the stress associated with fear of pregnancy. Finally, Ferree and colleagues (2012) did not account for their finding that women using HCs were significantly more likely than naturally cycling women to have consumed alcohol at the time of the assault, which has been found to dull physiological arousal and decrease risk for PTSD development (Maes, Delmeire, Mylle, & Altamura, 2011).

Overall, research on hormonal factors accounting for women's enhanced vulnerability for traumatic re-experiencing suffers from a number of limitations. Most importantly, although estradiol and progesterone levels are comparable during HC use and the EF phase (days 1-5), no researchers have examined potential differences in stress reactivity among HC users and naturally cycling women during this period. Investigation of potential differences in intrusion development among women in the low estradiol EF phase, women across the rest of the cycle, and HC users may help elucidate the role that ovarian hormone levels vs. fluctuations play as contributors to risk. Methodologically, a number of studies in this area included analysis of detail

relative to gist characteristics of emotional memories as a proxy for re-experiencing. While it is true that intrusive memories have a vivid sensory quality, examination of the frequency of memory intrusions is more generalizable to the development of traumatic re-experiencing than analysis of detail. Moreover, the association between intrusion frequency and detail associated with stressful event recall has not been assessed empirically. Additionally, stimuli used to simulate analogue trauma often have little external validity. For example, exposure to a sad story or negatively valenced photographs may not induce enough stress to facilitate the development of memory intrusions in most participants; thus, findings may reflect individual differences in anxiety proneness, rather than propensity towards traumatization. Finally, as described, the effect of HCs on inhibiting the development of memory intrusions has been examined in only two studies that each had significant validity concerns, and no study has explored the effect of HCs compared to naturally cycling women during the earlier follicular phase, despite the likelihood that this period would be protective.

The Present Study

The present study was aimed at further elucidating the role of the menstrual cycle and HC use in the development of post-trauma intrusive memories. The study was designed to examine frequency of emotional memory intrusions following analogue trauma exposure, and their putative relationship to hormonal status in HC users and naturally cycling women from an undergraduate student population. Cycle phase divisions among naturally cycling women were designed to capture specific windows around peak ovarian hormones, in an effort to compare the cycle's lowest and most elevated hormone levels without the noise incurred by fluctuations within the larger phases. A comparison group of men was also included to contextualize relative risk experienced across groups of women. In a controlled environment, participants were

exposed to an analogue trauma film that was realistic in nature, and a manipulation check was employed to ensure that the stimulus was emotionally evocative for participants. For this purpose, physiological indicators of stress reactivity (changes in heart rate and blood pressure) were monitored throughout the laboratory session, and changes in state anxiety and affect from baseline to post-stimulus were assessed via self-report. Because the theory of memory over-consolidation posits that trauma leads to intrusive memories via central mechanisms (particularly CORT and NA release), rather than peripheral or cognitive mechanisms, components of the manipulation-check were not used as independent variables in primary analyses.

The theoretical prospect that low levels of ovarian hormones may be protective was tested empirically. A decision was made not to collapse across the remainder of the menstrual cycle when comparing women in the EF phase to other naturally cycling women for several reasons. While the low hormone EF phase is hypothesized to be protective against developing emotional memory intrusions, this prospect relies heavily on research evidence that high levels of ovarian hormones enhance intrusion frequency, such that the EF phase may not be protective relative to the *entirety* of the cycle. There is also disagreement in the literature with regard to whether high levels of estradiol or high levels of progesterone (implicating distinct windows of risk) drive this effect. Further, high estradiol and high progesterone have been implicated in intrusion frequency, but there is no evidence as to whether risk is additive (with rising levels being associated with increasingly greater stress responsivity and intrusions), or dependent on some threshold of elevation for an individual (e.g., 75% of peak pre-ovulatory estradiol level). Thus, collapsing across the menstrual cycle equates to collapsing across the variance among groups in the mechanisms (estradiol and progesterone) presumed to underlie this process, and may prevent the detection of any protective EF effect.

The same logic applies to the comparison of HC use with potential discrete windows of high risk among naturally cycling women. This is particularly relevant if high levels are found to be greater determinants of risk than fluctuations, in predicting more frequent and detailed intrusions. In addition, the low level ovarian hormone conditions (HC and EF) were not combined for several reasons. First, despite espousal of its potential protective effects, this was the first study to assess empirically whether stressor exposure during the EF phase buffers against intrusion development. Further, it is unknown whether the additional presence of synthetic ovarian hormones in HC users may impact the memory over-consolidation process. Finally, combination of the low ovarian hormone groups would prevent teasing apart fluctuations from levels, and the overall objective to compare the two groups in terms of putative protective utility.

As such, the following groups were compared in terms of frequency of intrusive memories and intrusion detail over a 5-day period: EF, late follicular, ovulatory, luteal, HC users, and men. Given the mixed findings in the literature, there was no prediction as to which group of naturally cycling women would be most at risk for the development of frequent and detailed memory intrusions following stressor exposure. However, it was expected that both low hormone groups would experience somewhat fewer and less detailed intrusions relative to all other women, appearing similar to men. Overall, it was hypothesized that women in the late follicular, luteal, and ovulatory phases would all display more frequent and detailed intrusions than women in both the EF and HC groups, supporting a protective effect for a low hormone group. Additionally, it was predicted that HCs would convey a greater protective advantage than the EF phase. A statistically significant finding for the protective nature of HCs (which keep both estradiol and progesterone at chronic low levels and inhibit fluctuations) compared to all

other groups, including EF, would support a model of risk in which both absolute levels and fluctuations in ovarian hormones influence stress memory over-consolidation.

As previously mentioned, memory detail, relative to gist, is often used a proxy for re-experiencing within this literature, yet the relationship between intrusion frequency and degree of detail has not been assessed empirically. Thus, a supplemental aim of this study was to demonstrate the existence of a significant relationship between intrusion frequency and prevalence detailed, relative to gist, memories.

Methods

Participants

Participants were 151 undergraduate students recruited from the psychology department "subject pool" at The Pennsylvania State University (n = 151). The average age at participation was 18.83 (SD = 1.057) years and participants ranged from 18 to 24 years of age. Most participants, 119 (77.27%) identified as White, and 7 (4.55%) identified as Black, 18 (11.69%) as Asian, 2 (1.30%) as Hispanic, 5 (3.23%) as Mixed Race, and 3 (1.94%) declined to answer. Following a mass screening of all potential participants for sex, HC use, trauma history, and exclusion criteria (see below), naturally cycling women across the menstrual cycle (n = 81), women using HCs (n = 41); and a comparison group of men (n = 29) were recruited. Two participants (one man, and one naturally cycling woman) withdrew from study procedures. One man was excluded due to substantial protocol deviations made to accommodate his illness during the first lab session, and one naturally cycling woman was excluded due to inability to reliably confirm her menstrual cycle phase (detailed below). As such, the final sample included 147 participants (27 men, 41 HC users, and 79 naturally cycling women).

Exclusion criteria included irregular menstrual cycles among naturally cycling women, regular smoking, endocrine disorders, current psychotropic medication use, or a BMI above 30 based on self-reported height and weight, all due to the potential hormonal confounds these conditions may have posed to relevant outcome data Individuals who screened positively for PTSD based on established liberal criteria (Sheeran & Zimmerman, 2002) using the Posttraumatic Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997) were also excluded so as participation may have been an uncomfortable, or symptom exacerbating, experience for them. For the same reasons, women who experienced sexual assault were excluded at screening, as the laboratory stressor contained relevant interpersonal violent content.

Procedures

Recruitment. Eligible participants were called or emailed a description of the study and basic procedures involved. During a telephone interview with a research assistant, interested participants received additional information about the study and completed further screening and scheduling procedures. Women using HCs and men were scheduled as available. Naturally cycling women recorded and self-reported the dates of two most recent episodes of menses, and were scheduled by projected cycle phase in accordance with the recommendations set forth by Hampson and Young (2008). The mean cycle length for naturally cycling women was 29.06 (*SD* = 3.5) days. Efforts were made to schedule naturally cycling women across the entirety of the menstrual cycle, including: early follicular (n = 24), late follicular (n = 20), ovulatory window (n = 14), and luteal (n = 21) phases.

Laboratory Sessions. Participants presented for a one-hour appointment at the Relationships and Stress Research Lab. Women were asked not to eat or drink for an hour prior to their appointments. Because they may have denied previous trauma during screening for

confidentiality reasons, during informed consent procedures, every participant was informed that the study stimulus contained graphic physical and sexual content, and if sexual assault was relevant to a participant in any way, study staff urged him or her not to participate. Following the informed consent procedures, participants rinsed their mouths with water and were instructed in the saliva collection technique by a research assistant. A 2mL salivary sample was obtained from each participant in a salivette tube using the passive drool method.

Prior to exposure to the analogue trauma film, a minimum of five heart rate and blood pressure readings were taken every 2 minutes while participants completed questionnaires regarding current anxious affect, reproductive health history, and relevant medical conditions. These physiological measures were used to establish a baseline and to habituate participants to the recording device. Following, participants viewed a ten-minute film stressor that depicted graphic violence. Participants were asked to watch the screen for the duration of the clip, and to try not to look away or obstruct their vision with their hands. Heart rate and blood pressure readings were taken at 2-minute intervals throughout the film stressor and for 4 minutes afterward, while participants filled out post-film questionnaires examining emotional arousal and state anxiety. At this point, participants were asked if they had seen any of the clip previously, none of whom had. Participants were then given instructions to record any spontaneous intrusive recollections related to the clip content for a 5-day period, including the day of the laboratory appointment.

Measures

Salivary Assays. Salivary samples were frozen at -40 degrees C (Hampson & Young, 2008) and a proportion of samples were assayed for estradiol and progesterone levels, including 56% of naturally cycling women and 12% of hormonal contraceptive users. Given budget

constraints only a portion of participants' salivary samples were assayed. These assays were used as a manipulation check to confirm the phase projections derived from self-reported menstrual cycle tracking. The vast majority of assays were allocated to naturally cycling women (n = 45) given the propensity of HCs to keep both ovarian hormones at low levels throughout the cycle. Samples chosen for assay were prioritized according to the following: 1) To facilitate comparison of low ovarian hormones with elevations, the ovulatory window (n = 11; 79% assayed) was overrepresented, ensuring appropriate capture of the estradiol peak and early luteal progesterone rise; 2) the late follicular (n = 12; 60% assayed) and luteal phases (n = 14; 66% assayed) were prioritized next, so as to confirm their hormonal profiles were distinguishable (on average) from the ovulatory group and each other; 3) EF samples were chosen last (n = 8; 33% assayed), as women were expected to most accurately report this phase, given that all but 3 women (2 at day -2, 1 at day -1) were menstruating at the time of participation. Further, both hormones were expected to be low, and exhibit less overlap in estradiol and progesterone levels than across the other phases. Salivary samples were assayed using *DRG International Salivary Kits*.

Salivary concentrations of circulating estradiol and progesterone have been validated as a means to approximate menstrual cycle phase (Ellison, 1993; Hofman, 2001; Gandara, LeResche & Mancl, 2007), and were thus used to confirm self-reported phase. Given the substantial normative variation of estradiol and progesterone levels across women at various cycle phases, and research indicating that hormones tend to be at the higher end of cycle phase norms in younger women (Hampson & Young, 2008), no participants were reassigned to a different phase on the basis of assay results. As mentioned previously, a single participant, having among the lowest levels of progesterone among all individuals sampled, despite reporting being in the mid-

luteal phase (the progesterone peak), was excluded based on substantial deviation from established norms (guidelines established by Salimetrics, 2011), as cycle phase could not be reasonably validated.

Trauma film paradigm. Trauma film paradigm methodology (Lazarus & Alfert, 1964; Lazarus, Opton, 1964; Lazarus, Opton, Nomikos, & Rankin, 1965) has proven successful for inducing analogue PTSD symptoms in a laboratory setting for up to a week (Holmes & Bourne, 2008). The procedure consists of watching a film clip that simulates traumatic life events illustrating "death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence" as defined by PTSD diagnostic criteria (APA, 2013; Holmes & Bourne, 2008), and has been effective in evoking autonomic stress responses (Folkins, Lawson, Opton, & Lazarus, 1968; Holmes & Bourne, 2008; Holmes Brewin, & Hennessy, 2004) and subsequent re-experiencing symptoms (Butler, Wells & Dewick, 1995; Holmes & Bourne, 2008; Horowitz, 1975) similar to those associated with post-trauma sequelae (Holmes & Bourne, 2008). This procedure has been used extensively in investigating peri-traumatic cognitive processes and stress-related memory intrusions (Butler, Wells & Dewick, 1995; Ferree & Cahill, 2009; Ferree, Kamat, & Cahill, 2011; Holmes & Bourne, 2008; Horowitz, 1975; Laposa & Alden, 2008; Nixon, Cain, Nehmy, & Seymour, 2009; Nixon, Nehmy, & Seymour, 2007; Verwoerd, Wessel, Jong, & Nieuwenhuis, 2009).

The present study used a ten-minute film clip that features a compilation of scenes from the Gaspar Noe movie *Irreversible,* containing graphic physical and sexual violence. This film has been previously validated as a stressor (Nixon et al., 2007; Nixon et. al, 2009) effectively producing an average of 7.2 intrusive memories among men and women during the week following viewing (Nixon et. al, 2009). In addition, this trauma film stimulus is both relatable

and realistic in nature, featuring scenes of a young woman leaving a party, walking alone at night, then being physically and sexually assaulted in an alleyway by a stranger. The film also features graphic physical assault of one man by another. Therefore, unlike many trauma film paradigms that have used footage from motor-vehicle accidents and emergency rooms, this stressor includes the context of the trauma and depicts typical activities relevant to undergraduate students (e.g., going to parties, walking home alone) that may be more likely to resonate with them.

Memory diary. All participants were provided with a paper memory diary, which is considered the most appropriate way to ensure accurate recording in the trauma film literature (Holmes & Bourne, 2008). The memory diary included printed instructions to remind individuals of what constitutes an intrusion (i.e., a spontaneous, not deliberately recalled, thought, image, or dream) and each page of the diary was devoted to recording the content of each intrusion experienced. The use of a memory diary facilitates ease of immediate recording, thus enhancing the accuracy and validity of study data. The paper memory diary was provided for personal use, and participants were asked to transfer recorded information for each intrusion onto secure website containing questions identical to those in the paper diary. Researchers retrieved all intrusion data exclusively from the website; paper diaries were not collected. Many participants entered data into the website in real time if they had convenient access to the Internet when intrusions occurred, as was approved by study staff. Entries were coded by ID numbers, which were provided to participants during the initial lab visit. A trained research assistant reviewed memory-recording procedures with each participant, and problem-solved ways to ensure that individuals remembered to document intrusions as they occurred.

Demographic and Health Questionnaire. Participants were asked a series of basic demographic questions including sex, age, and ethnicity. Participants were also asked for estimated height and weight to determine BMI, and about specific medical conditions relevant to reproductive health, namely regularity of menstrual periods (for women) and diagnoses of endocrine disorders.

Physiological reactivity. An automated heart rate and blood pressure monitor was used to measure physiological status before, during, and after the analogue trauma stimulus. Such monitors have been used frequently for research purposes. They tend to be highly reliable (Mundt, Chambless, Burnham, & Heiss, 1992) and ensure standardization of cardiovascular measures, minimizing the errors associated with manual devices (Hoyt & Wolf, 1984).

State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Changes in anxiety from baseline to post stressor exposure were measured using the State Anxiety subscale of the STAI. The subscale consists of 20 items designed to assess individuals' degree of anxious affect "right now, at this moment" (e.g., "I feel tense," "I am worried"). Participants were instructed to rate each item on a 4-point Likert scale ranging from "not at all" to "very much so." The STAI has evidenced excellent internal consistency and good convergent validity with other measures of state anxiety (Spielberger, 1983). Given the temporal nature of the state construct, it expectedly exhibits lower test-retest reliability (average $r = .70$; Barnes, Harp, & Jung, 2002). Within this sample, the STAI demonstrated good internal consistency ($\alpha = .82$).

Positive and Negative Affect Schedule. PANAS-X (Watson & Clark, 1994). The PANAS-X is a 60 item measure assessing current degree of endorsement of 11 positive and negative affective states: fear, sadness, guilt, hostility, shyness, fatigue, surprise, joviality, self-

assurance, attentiveness, and serenity. Each affect consists of 3 to 8 different items (e.g., "serenity" includes "calm," "relaxed," and "at ease"). Individual items are rated on a Likert scale ranging from 1 "very slightly or not at all" to 5 "extremely." The PANAS-X demonstrates good convergent validity (r = .85 - .91) with the Profile of Mood States (Watson & Clark, 1994). While the questionnaire instructs individuals to rate each item based on the "extent you have felt this way during the past few weeks," for the purpose of this study, participants were only asked to rate current affect following exposure to the film clip. The PANAS-X 10-item negative affectivity subscale demonstrated good internal consistency within this sample (α = .86), while internal consistency of the 10-item positive affectivity subscale was acceptable (α = .70).

Data Preparation

Cycle phase determinations. Naturally cycling women were categorized into phases based on self-reported cycle day and length. Phase determinations were made in accordance with previous research (Lester, Keel, & Lipson, 2003; Elder, Lipson, & Keel, 2007; Klump et al., 2013), but amended to capture interest in the low hormone early follicular phase, categorize the entirety of the cycle, and correct for potential error in self-reporting. That is, the first day of menses was designated +1 and the prior day -1, thus anchoring the following groups: a) days -2 to +5, early follicular, capturing the lowest levels of estradiol and progesterone across the cycle (n = 24), b) days +6 to -17, late follicular, defined by elevated estradiol and low progesterone (n = 20), c) days -16 to -12, ovulatory, capturing peak estradiol and an early rise in progesterone and representing the fertile window for the majority of women (n = 14; Wilcox, Dunson, & Baird, 2000), and d) days -11 to -3, luteal, capturing the progesterone peak (n = 21).

Phase classifications deviate slightly from prior research in a few key respects. Previous divisions have included either the premenstrual (defined by -3 to +1; e.g., Klump et al., 2013) or

early follicular (days 1-5; e.g., Ferree, Kamat, & Cahilll, 2011) periods, as indicated by the substantive research question under investigation. Given that the objective of the current study was to capture the lowest levels of estradiol and progesterone, and given significant research evidence indicating that hormone levels are comparable from two days premenstrual through the early follicular phase (Stricker et al., 2006), all 7 days were included for the purposes of our research and labeled "early follicular" for conceptual clarity. As such, the luteal phase was truncated by 2 days. Additionally, the ovulatory phase was extended by one day from traditional measurement (Lester, Keel, & Lipson, 2003; Elder, Lipson, & Keel, 2007; Klump et al., 2013) to include one day prior (-16), thus enhancing the chances of appropriately capturing the cycle's estradiol peak given recent gynecological research indicating that the majority of women ovulate anywhere between 16 and 12 days prior to their next menstrual period (Arélin et al., 2015; Pletzer, 2015). These changes to prior classifications allowed for clustering of the lowest levels, moderate levels, and highest levels of hormones respectively.

Intrusion coding. A trained graduate or undergraduate student research assistant reviewed the content of each recorded memory intrusion to confirm its validity, as defined by a clear association with the trauma film. Intrusions that were not associated with the film content, broadly defined, were excluded from analysis (n = 5). Then, individual intrusions were categorized as primarily gist or detail based on an amalgam of previously operationalized procedures (Adolphs, Denburg, & Tranel, 2001; Lamb et al., 1996; Neilson et al., 2013; Seidlitz & Diener, 1998). As such, gist was defined as narrative elements central to the events of the film or without which the story would be incomplete (e.g., woman was attacked by a man in tunnel; man punched through car window to attack driver). Details were considered peripheral descriptive elements unessential to the plot (e.g., woman was wearing a yellow dress; tunnel was

lit by red lights). Recorded intrusive memories were one to three sentences long, and were classified as either gist or detail memories by four undergraduate research assistants trained as coders. At least three out of four independent coders agreed on the classification of each intrusion. When three were unable to agree, the intrusions were discussed by study personnel to determine consensus.

Manipulation check. Effectiveness of the stimulus was verified by physiological and psychological symptom measures; to be deemed a stimulus responder, a participant needed to have met at least one criteria under any response category (biological, self reported physio, affective). Biological responding was operationalized in two ways. Informed by literature concerning resting heart rate acceleration in response to acute stress (van Rosendael et al., 2016), a participant was considering a responder if he or she 1) reached a peak heart-rate of at least 85bpm while viewing the analogue trauma film and 2) this represented an increase of at least 5 beats per minutes from baseline. Further, a participant exhibiting a change in 20 mm HG to either systolic or diastolic BP was considered a responder (Ehring, Ehlers, Cleare, & Glucksman, 2008; Matthews, Zhu, Tucker, & Whooley, 2006). As these constituted the only measured autonomic responses, participants who endorsed sweating, feeling lightheaded, rapidity of breathing, or tightening in their chests in response to the stimulus, were also deemed responders.

Psychological responding was defined via significant changes in self-reported state anxiety from baseline to post analogue trauma film or by at least moderate endorsement of guilt or fear on the PANAS-X subscales. Increases in self-reported state anxiety were assessed for clinical significance in accordance with reliable change index (RCI; Jacobson & Truax, 1991) procedures. The RCI is a widely used metric for determining whether a symptom score change at the individual level is statistically reliable, and thus attributable to a treatment condition (Wise,

2004). A participant was deemed a stimulus responder if his or her RCI score *(PostSTAI-PreSTAI) / (PreSTAIsd) *(sqrt(1-$R_{preSTAIpostSTAI}$))* exceeded the cut point of 1.96 (indicative of a significant change at $\alpha = .05$). Given the association between experiencing hostility (e.g., Orth & Wieland, 2007) and the development of post-trauma sequelae, a score of at least 18 of 30 (moderate endorsement) of the PANAS-X hostility subscale (angry, irritable, hostile, scornful, disgusted, loathing) was defined as responsivity. Similarly, based on the independent association between endorsement of extreme fear and post-trauma sequelae (Brewin, Andrews, & Rose, 2000) a score of at least 18 of 30 (moderate endorsement) of the PANAS-X fear subscale (afraid, scared, frightened, nervous, jittery, shaky) was also deemed responding. All but two participants demonstrated some reactivity in at least one of these areas (see Table 1). Given that exclusion of these 2 non-responders did not change the results of analyses or associated effect sizes, their data were retained.

Table 1

Manipulation Check: Number and Percentage of Responders to Analogue Trauma Film

HR	BP	Physio SR	Anxiety	Hostility	Fear	None
57	35	133	65	67	60	2
38.78%	23.80%	90.48%	44.22%	45.58%	40.82%	1.36%

Note. HR = heart rate. BP = blood pressure. Physio SR = self report of physiological symptoms. 108 participants (73.20%) exhibited responsivity in two or more domains.

Analyses

A one-way analysis of variance (ANOVA) was conducted to examine whether intrusion frequency differed as a function of hormonal status grouping. Five participants were identified as outliers on the dependent variable using the three overarching groupings (1 man, 2 naturally cycling women, and 2 HC users). Potential outliers were detected by using Tukey's hinges

(Tukey, 1977) and confirmed as being more than 2.5 SDs from the group mean. Analyses revealed the same pattern of results with and without inclusion of the outliers; both were statistically significant and produced identical effect sizes. As such, in order to present more conservative results and minimize standard error, outliers were assigned the value of the next highest value of their individual groups. Although group sizes were unequal, ANOVA is robust against this, particularly when all major assumptions are met: independence, normality, and homogeneity of variance. Independence is assumed, based on study design. A visual inspection of the histograms, Q-Q plots, and box plots at each level of the independent variable did not imply significant deviations from normality. This was supported by calculations of skewness and kurtosis for each group, using the rule of thumb that skewness and kurtotic values between -2 and +2 are acceptable for ANOVA testing (George & Mallery, 2010). Homogeneity of variance was confirmed via Levene's test (Levene's statistic (5,141) = .440; p = .820).

Percentages of memories that were coded as detailed, relative to gist, were calculated for each participant. Given violations of homogeneity of variance in group distributions of percent gist and detail, a Welch Robust Test for Equality of Means was run to assess differences in percent of detail memories experienced across groups. For the purposes of analyzing group differences in prevalence of detailed memories, original scores were used to calculate percentages for the 5 participants who were outliers on intrusion number.

Results

Ovarian Hormone Status: Confirmatory Assays

Ovarian hormone assays reflected the expected trend of capturing peak estradiol during the ovulatory phase, the highest levels of progesterone during the luteal phase, lower levels of

both hormones during the early follicular phase, and the lowest levels of both hormones among HC users. Mean group levels of estradiol and progesterone across conditions are plotted in Figure 2 and listed in Table 2. There were no significant differences in estradiol levels across groups; ovulatory estradiol levels among women were compared to levels among women in the EF phase (p = .239; d = 3.02), women in the late follicular phase (p = .965; d = .78), women in the luteal phase (p =. 687; d = 1.36), and among HC users (p = .215; d = 4.11). Luteal progesterone differed significantly from progesterone levels among HC users (p = .002; d = 5.07), women in the EF phase (p = .001; d = 4.82), women in the late follicular phase (p = .004; d = 3.43) and women in the ovulatory window (p = .032; d = 2.53).

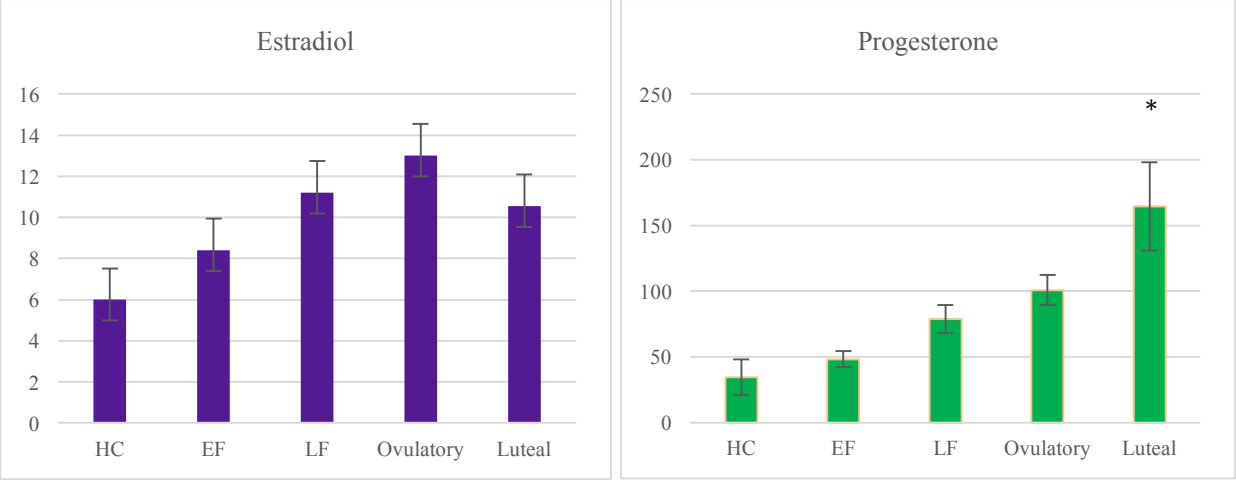

Figure 2. Mean salivary progesterone and estradiol levels across groups (pg/ml)

Table 2

Mean Estradiol and Progesterone Levels Among Groups

Ovarian Hormones	Group				
	Hormonal Contraceptives	Early Follicular	Late Follicular	Ovulatory	Luteal
Estradiol	5.99 (1.3)	8.40 (.71)	11.57 (1.60)	13.00 (2.03)	10.55 (1.54)
Progesterone	34.42 (13.6)	48.21 (5.95)	78.83 (10.74)	100.83 (11.53)	164.46 (33.62)

Note. There was no significant difference among salivary estradiol levels across groups, F (4,47) = 1.75; p = .156; η^2 = .14. Luteal phase progesterone levels differed significantly from all other groups, F (4,47) = 5.00; p = .002; η^2 = .32.

Intrusive Memories

The mean number of intrusions experienced by all participants was 4.06 (SD = 3.13) with a range from 0 to 12 and a 95% CI of 3.55 to 4.57. Participants (including untransformed outliers) reported a total of 649 intrusions; 91.16% reported at least one intrusion.

A one-way ANOVA illustrated that there was at least one significant difference between groups, F (5,146) = 2.28; p = .050; η^2 = .07. Post hoc tests using Fisher's LSD revealed that the ovulatory group (M = 6.5, SD = 3.48) differed significantly from all other groups: Early follicular (M = 4.17, SD = 3.25; d = .69), late follicular (M = 3.45, SD = 2.67; d = .98), luteal (M = 4.05, SD = 3.03; d=.75), HC users (M = 3.98, SD = 3.31; d = .74), and men (M = 3.30, SD = 2.55; d = 1.05). Mean intrusion number across groups is plotted in *Figure 3.*

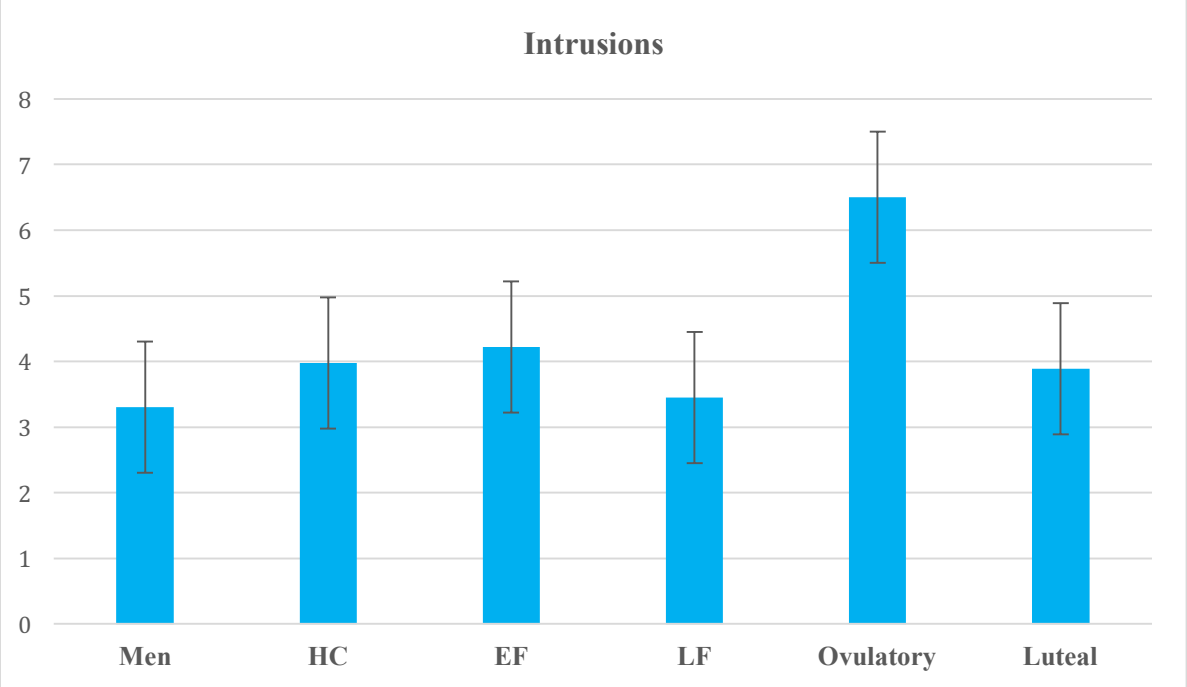

Figure 3. Five-day intrusion means across groups of naturally cycling women, HC users and men

Gist and Detail

Of the total number of intrusions reported, 386 (59.48%) were classified as gist memories and 263 (40.52%) as detailed memories. Intrusion number was positively correlated with percent of detailed intrusions (r = .221; p < .001); intrusion number was not significantly correlated with percent of gist intrusions (r = .061; p = .441).

On average, 33.08% (SD = 35.00) of a participant's intrusions were classified as detailed, rather than gist. Among participants in the EF phase, an average of 24.61% (SD = 32.87) of intrusions were detailed, in the late follicular phase 49.25% (SD = 44.22), in the ovulatory window 39.08% (SD = 27.01), in the luteal phase, 25.21% (SD = 23.94), in HC users 30.00% (SD = 33.63), and in men 36.34% (SD = 39.86) of intrusions were detailed. A one-way ANOVA revealed no significant difference across groups with regard to the percentage of memories that were detailed rather than gist, *Welch's* F (5, 56.98) = 1.394; p = .240; η^2 = .04. Percentage detailed intrusions across groups are plotted in Figure 4.

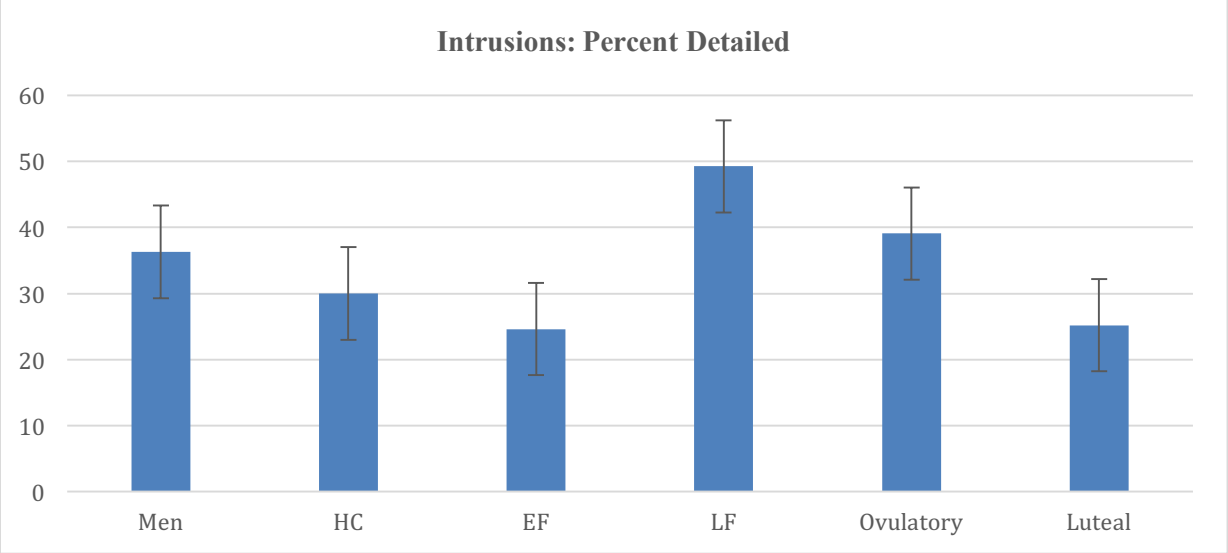

Figure 4. Average percent of intrusions classified as detailed, across groups

Discussion

Results and Potential Interpretations of Findings

It was hypothesized that both ovarian hormone levels and fluctuations contribute to risk for the development of memory intrusions, and as HCs keep hormones at low levels and suppress fluctuations, the HC group was predicted to have the fewest, and least detailed, intrusions among all groups. Contrary to study predictions and limited previous research (Andreano & Cahill, 2010; Ferree, Wheeler, & Cahill, 2012; Neilson et al., 2011, 2013b), stressor exposure during neither the low hormone EF phase, nor among those using HCs, was *uniquely* protective against the development of emotional memory intrusions. Relative to all other naturally cycling women, those in the EF and HC groups did not exhibit fewer memory intrusions, or a smaller percentage of detailed intrusions. As such, given the null findings with regard to the putative protective nature of HCs, this study provides no evidence that ovarian hormone fluctuations, or suppression thereof, are directly related to the development or prevention of intrusive memories. These findings diverge from Neilson and colleagues' finding that HC use is associated with less detailed memories for emotional events (2011, 2013b), and Ferree and colleagues' finding that HCs may be protective against the development of re-experiencing symptoms (2012).

As the EF phase was not found to be any more protective than the late follicular or luteal phases, this research also provides no indication that low level ovarian hormones offer specific protection against the development of memory intrusions. Rather, the unexpected finding that women who participated during the ovulatory phase displayed significantly more intrusions than all other groups suggests a unique window of vulnerability, around the time that estradiol peaks and progesterone begins to rise. This finding corroborates in part, an aforementioned line of

research, that has implicated elevated estradiol and the ratio of estradiol to progesterone, respectively, in driving risk for memory over-consolidation (Cheung et al, 2013; Soni et al., 2013).

Interestingly, Soni and colleagues (2013) assessed development of emotional memory intrusions during distinct limited periods of the menstrual cycle, and found support for elevated risk during a "post-ovulatory" early luteal window. However, in contrast to a number of researchers (Elder et al., 2007; Klump et al., 2013; Lester et al., 2003), this group defined a somewhat earlier ovulatory phase, and thus luteal phase (operationalizing days -9 to -13 as the early luteal phase). As such, there are 2 days of overlap between the present study's ovulatory phase and the aforementioned study's early luteal phase. Further, 27% (n = 4) of the present study's ovulatory group participated on cycle days that overlapped with Soni et al.'s (2013) early luteal phase providing partial corroboration that this window of risk exists. As neither this research group, nor Soni and colleagues (2013) assayed estradiol and progesterone throughout the entirety of the cycle, as would be necessary to definitively identify the day each participant ovulated, both studies relied on estimates, using likelihood windows based on self-reported menstrual tracking and participation day hormone levels. Thus, it is possible that both study windows capture various participants during ovulation, right after, or right before. Regardless, both studies support the general prospect that the time around ovulation seems to be a significant period, driving risk for emotional memory over-consolidation.

Identification of the ovulatory window as a period of risk has potential theoretical implications. The day of ovulation represents a woman's peak of fertility, during which conception is most probable. As such, from an evolutionary standpoint, the period around ovulation may serve as a critical window during which threat is salient for women and stress

responsivity, as indicated by emotional memory over-consolidation, is enhanced. Providing additional support that women may be hypersensitive to environmental threat during the ovulatory period exclusively, research evidences that women can most accurately identify emotional expressions of anger (Derntl, Exner, Fernbach, Moser, & Habel, 2008) and fear (Derntl et al., 2008a,b; Pearson & Lewis, 2005), which are accompanied by enhanced amygdala activity (Dert et al., 2008b), just prior to ovulation. This ability to perceive threat dissipates across the luteal phase, as both amygdala activity and accurate identification of fear and anger have been negatively correlated with progesterone level (Dert et al., 2008b).

Given the neuroendocrine and sympathetic nervous system activity presumed to underlie it, memory over-consolidation may be a functional byproduct of enhanced ovulatory stress sensitivity; this stress hyper-sensitivity could help moderate conception under perilous environmental conditions. Indeed, given that ovulation is largely under neuroendocrine control (Berga & Naftolin, 2012) and the intricate process of co-regulation between the HPA and HPG axes, it has long been believed that this crosstalk developed specifically for the purpose of enhancing evolutionary fitness (Kudielka & Kirschbaum, 2005). Prevention of ovulation by neuroendocrine response to chronic external stressors, hypothalamic anovulation, is not uncommon (Kalantaridou, Makrigiannakis, Zoumakis, & Chrousos, 2004), and high levels of salivary alpha-amylase (a norepinephrine metabolite) have also been found in women unable to conceive (Louis, et al., 2011). Further, even single episodes of stress can disrupt ovulatory processes; higher NE release during the ovulatory window has been found to temporarily reduce fertility across those days exclusively (Louis et al., 2011). While taken together, this study and the aforementioned one by Soni and colleagues (2013) support enhanced risk for emotional memory intrusions around ovulation, whether this risk occurs in response to stress right before,

during, and/or right after ovulation has yet to be articulated. Should this vulnerability window capture peri-ovulation, the presence of emotional memory intrusions from the hours to days after acute stress exposure may serve as reminders of an unsafe environment, long after the hyper-aroused body has returned to homeostasis.

Given that average progesterone was relatively high among the ovulatory sample, it is likely that for some women, the days immediately following ovulation, rather than ovulation itself, was captured. However, this would not preclude the possibility of an evolutionary mechanism at play. Following fertilization, the egg has several days to implant within the uterus, and research supports that this process can be disrupted by glucocorticoids (Csemiczky, Langren, & Collins, 2000; Kalantaridou, et al., 2004), and to a lesser extent norepinephrine (Smeenk, et al., 2005) under stressful circumstances. Further, very high levels of cortisol in the days after successful implantation have been associated with spontaneous abortion (Arck, 2001; Nepomnaschy Welch, McConnell, Low, Strassmann, & England, 2006). The salience of emotional memory intrusions, should they occur immediately after ovulation may too serve as reminder of threat, facilitating vigilance in a woman who had just conceived. Wolohan et al. explain their finding that luteal phase women are faster to respond to and engage with emotional and social cues as a potential biological mechanism geared toward fetal protection (2013). Due to the use of single-time point assays, and reliance on self-reported menstrual tracking (see page 31 for in depth discussion of limitations), this study was unable to directly assess estradiol and progesterone themselves as predictors of emotional memory over-consolidation; as such, the aforementioned discussion is largely speculative, based on the preliminary evidence that stress response processes related to ovulation may be implicated in this process. However, as informed by prior literature, it is very possible that increased frequency of intrusive memories following

acute stressor exposure may be one of several means by which elevations in cortisol and noradrenaline promote evolutionary fitness, in this case potentially via cognitive threat salience and resultant behavioral vigilance.

To assess empirically a frequently presumed relationship within the literature, intrusion frequency was compared to prevalence of detailed, relative to gist, intrusions. Upon forced recall tests, researchers often present gist memory as evidence of low risk for re-experiencing, and representative of a lack of memory over-consolidation. Based on this literature, it would be highly unlikely for such a large percentage of intrusions, as was apparent in this data, to be gist-based. As such, the fact that more than half of the intrusive memories in this study were gist based challenges the assumptions that re-experiencing is always best captured by remembered detail. Further, while a significant relationship between intrusion number and detailed content was supported, this association was small. Thus, using degree of detail associated with recall for emotional experiences may be a methodologically insubstantial way of extrapolating toward risk for frequent intrusive memories. This is the first study to examine the relationship between intrusive memories and detail associated with them, and does so within a nonclinical population. Thus, this finding demands replication; empirical validation of the assumptions with which trauma research operates is crucial for advancement of the field.

This study improved on previous methodologies in several respects. In utilizing a stimulus that was realistic in nature, to which many participants exhibited a visceral reaction, extreme emotional stress reactivity (as evident in trauma) may have been better approximated. This is supported by the manipulation check, as participants exhibited a high degree of physiological and emotional responsivity, both objectively measured and self-reported. Further, to improve accuracy and generalizability of the data, real-time intrusion recording procedures

were employed rather than retrospective estimates, and the recording period was extended to 5 days from the typical 48 hours following stressor exposure. In addition, this study examined intrusion frequency and intrusion detail together, scrutinizing the often employed assumption that memory detail is representative of re-experiencing, an assumption that study results call into question.

Limitations

This study also suffers from a number of limitations. Among those more common to this literature, group sizes were relatively small and the study's primary finding is based on the smallest group size (n = 14), potentially diminishing generalizability of results to the larger population. In addition, the study population was an undergraduate convenience sample. Use of a nonclinical sample precludes knowledge of whether the process of emotional memory over-consolidation may operate differently in those at higher risk for psychopathology. Informed by prior literature supporting a significant sex difference, this study included men as a means to contextualize relative risk, but had inadequate power to test the sex difference that is often presumed (rather than demonstrated) within this literature. Perhaps most significant, group designation relied on self-reported menstrual cycle data. As previously mentioned, women are considerably poor reporters of dates of menstruation and cycle length. Attempts were made to combat this, in having women track their cycles for two consecutive months, and assaying estradiol and progesterone to confirm the possibility of being in projected phase on the date of participation. However, only a portion of salivary samples were assayed for estradiol and progesterone levels (56% of naturally cycling women had saliva assayed), and single time point salivary estradiol assays are notoriously unreliable and have recently been deemed insubstantial

for independently establishing phase (Barrett, Thune, Lipson, Furberg, & Ellison, 2013; Rajeswari, Mathan, & Swaminathan, 2014). Given the normative inter- and across- individual variability associated with fluctuating estradiol and progesterone, collection of circulating ovarian hormone levels over an entire menstrual cycle is undoubtedly the most accurate way to make phase determinations. Within this sample, both ovarian hormones tended to represent the higher norms for each phase and substantial overlap in levels was evident across phases, as is consistent with research on younger women. But again, these were single time point assays, and salivary estradiol assays, in particular, need to be contextualized within the range of levels obtained over an individual's entire cycle to be meaningful. Indeed, among the most important tenets of ovarian hormone research is the reality that variability in levels, in particular what constitutes high and low levels, is a function of the individual (Hampson & Young, 2008).

Given that research regarding how HCs impact stress and memory processes is nascent, this study may also suffer from unknown limitations. HC users were homogenous with regard to being on combined-type oral contraceptives (containing synthetic estradiol and progesterone). However, the relationship between levels of circulating ovarian hormones and neural levels is largely un-explicated. It is possible, for example, that taking HCs depresses plasma levels of estradiol while elevating levels in the brain, altering the cascade of HPA activity and memory processes. Is it also possible that factors such as pill type, presence of specific levels of exogenous ovarian hormones, and duration of HC use influence emotional memory over-consolidation via CORT and NA regulation. Failure to control for these factors, in addition to cursory knowledge of the influence of HCs on neurobiological processes beyond those implicated in reproductive health, prevents drawing the firm conclusion that HCs *never* exhibit a protective effect. Indeed, it is possible that certain contraceptive types used for a certain duration

of time, may be protective. Additionally, study findings indicate enhanced risk for emotional memory over-consolidation during ovulation, the very process that HCs are designed to suppress. Thus, in that regard, HCs do provide a protective effect. Finally, relevant to this study in particular, there was no way to monitor HC use (including time of day that women took their pills), and assays among this group were particularly limited (12% of HC users had saliva assayed). As such, the finding that HCs do not buffer against intrusion development compared to all naturally cycling women could be a function of medication noncompliance. Thus, while this study did not support a prophylactic effect for HC use on intrusion development, too little is known about the influence of HCs at the neural level, and the various factors which may moderate such influence, to draw the firm conclusion that they are never protective.

Conclusions and Future Directions

This research provides some preliminary evidence that ovarian hormone fluctuations are not implicated in risk toward emotional memory over-consolidation, and that low levels of ovarian hormones (although not tested directly) may not be protective against the development of intrusive memories. In addition, this study suggests that the window around ovulation may represent a period of particular vulnerability during which stress reactivity is enhanced. Replication of this research utilizing full cycle assay data and a larger sample of NC women (particularly in the ovulatory phase) is necessary to draw any firm conclusions with regard to vulnerability toward stress reactivity and intrusion development across the menstrual cycle. To extend this literature, future research may also employ assessment of changes from rest in circulating levels of stress-responsive CORT and SAA release following stimulus exposure, so as to confirm whether the theory of emotional memory over-consolidation is the appropriate

paradigm from which to understand intrusive memory development among naturally cycling women. Given literature regarding the direct effects of estradiol on neural areas implicated in memory generally, it is also possible that a distinctive mechanism is at play. Consistent with the tenet of equifinality, stress-responsivity during the window around ovulation, and the neurobiological and psychological processes associated with it, may account for one distinctive pathway toward risk for intrusion development, and PTSD development more generally, following trauma exposure.

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