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Identification of a narrow post-ovulatory window of vulnerability to distressing involuntary memories in healthy women

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ABSTRACT

Psychological disorders characterised by intrusive memories are more prevalent in women than men. The biological, social and cognitive processes underlying this gender-difference have yet to be fully elucidated. Some evidence suggests that (fluctuations in) ovarian hormone levels are responsible for altered sensitivity to emotional stimuli during certain phases in the menstrual-cycle and this may form the basis of a specific vulnerability to psychological disorders in women. The post-ovulatory (luteal) phase has been identified as a period of particular vulnerability to the development of Post-Traumatic Stress Disorder (PTSD).

Using an experimental model of PTSD, we examine whether differences are detectable between discrete phases in the menstrual-cycle in the experience of intrusive memories. Women (18–35 years-old) in one of three tightly-defined periods within the menstrual cycle – mid-follicular ($n = 15$), early-luteal ($n = 15$) and late-luteal ($n = 11$) – provided saliva samples for ovarian-hormone assay and watched a distressing film. Subsequent intrusive memories, assessed using a daily online-diary, occurred significantly more frequently in the early-luteal group compared to mid-follicular and late-luteal groups. Intrusion frequency was negatively correlated with the estradiol-to-progesterone ratio, but not estradiol or progesterone alone, suggesting that the interactive effect of low estradiol and high progesterone at encoding contributes to the observed effect. Our results support the need for further research in a clinical context with naturally-cycling women who experience a traumatic event, since assessment of days-since-last-menses and ovarian hormone levels may help to identify those at greatest risk of developing re-experiencing symptoms akin to those seen in psychological disorder such as depression and PTSD.

1. Introduction

Recurrent, involuntary negative thoughts and images are a common feature of many psychiatric disorders (Brewin, Gregory, Lipton, & Burgess, 2010; Reynolds & Brewin, 1998). Anxiety and mood disorders characterised by such intrusive memories are significantly more prevalent among women than men (e.g. Breslau, Davis, Peterson, & Schultz, 1997; Kendler, Thornton, & Prescott, 2001; McLean & Anderson, 2009). A number of psychosocial and biological factors have been implicated in this gender imbalance (McLean & Anderson, 2009).

The observation that prevalence of psychological disorders fluctuates across the life span in women (e.g. Ditlevsen & Elklit, 2010) may hold some clues about the nature of biological risk factors. In particular, periods of vulnerability coincide with significant changes in ovarian hormone levels, for example during and after pregnancy as well as menopause. More commonly, vulnerability to psychological symptoms follows a cyclical pattern which is temporally tied to fluctuations in progesterone and estradiol (e.g. Nillni, Toufexis, & Rohan, 2011).

Recent studies suggest that menstrual phase may influence the encoding and/or retrieval of negative emotional events via data-driven, sensory representations which are encoded at the expense of contextualised episodic memories (Bryant et al., 2011; Ferree & Cahill, 2009 Ferree, Kamat, & Cahill, 2011). The typical menstrual cycle in humans ranges from between 25 and 35 days (see Nillni et al., 2011). In the modal example of a 28 day cycle, day 14 marks ovulation, an event preceded by the follicular-, and followed by the luteal-phase. Many healthy women experience predictable fluctuations in physical sensation and mood across their menstrual cycle (Clayton, 2008). In particular, the late luteal phase (i.e. the week prior to menstruation) is commonly linked to increased likelihood of mood swings, sleep disturbances, anxiety and depressive symptoms (Steiner, Peer, Macdougall, & Haskett, 2011) with approximately 80% of healthy women regularly experiencing at least one premenstrual symptom (Wittchen, Becker, Lieb, & Krause, 2002). Taken as a whole, the luteal phase is also associated with increased physiological responsivity to psychological stressors in healthy women (Kirshbaum, Kudielka, Gaab, Schommer, & Hellhammer,

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1999) as well as exacerbation of symptoms in women with depression (Kornstein et al., 2005) and social anxiety disorder (van Veen, Jonker, van Vliet, & Zitman, 2009).

The cycling nature of psychological and physical symptoms is closely linked to variations in ovarian hormones, particularly progesterone (along with its neuroactive metabolite, allopregnanolone) and estradiol. These hormones have been implicated in the amelioration (e.g. Wirth, 2011), as well as exacerbation (e.g. Bäckström et al., 2011) of stress responses. The nature of the dependence of psychological symptoms on ovarian hormone levels therefore remains unclear. An elegant way to examine this dependence is by examining the effects of a stressful life event at different phases of the menstrual cycle, while ovarian hormone levels vary naturalistically.

Recent research on the effect of cycle phase on involuntary memories suggests that women experiencing a stressful or traumatic event during the luteal phase have reported a greater number of negative intrusive thoughts than those who have such experiences in the follicular phase (Bryant et al., 2011; Ferree & Cahill, 2009; Ferree et al., 2011). These findings have significant clinical implications because they suggest the presence of a temporal 'window of vulnerability' that may be targeted in efforts to prevent the onset of psychological disorders (e.g. PTSD) in women. The idea of a window of vulnerability representing a 'window of opportunity' for prevention or treatment is a familiar one to PTSD researchers. For example, Holmes and colleagues (Holmes, James, Kilford, & Deeprose, 2010) showed that participants viewing distressing film footage who engaged in a visuospatial task within a critical timeframe (30 min–4 h) during which memory consolidation occurs, were inoculated against the formation (or recall) of unpleasant involuntary memories of the film. Clearly the entire luteal phase represents a substantial period of vulnerability (14 days). It is therefore of interest to determine whether there are specific periods of especially elevated risk for intrusive memories within the luteal phase. Furthermore, it is important to use an experimental protocol that allows the identification of intrusive memories that have characteristics relevant to psychopathology. For example, intrusive memories in PTSD depression and social anxiety are often characterised by *sensory* phenomena (i.e. as predominantly mental *images*) rather than verbal processing. These phenomena should be assessed – as far as possible – in the absence of cuing by other (explicit) memory tasks (Brewin et al., 2010).

Here we used the stressful film paradigm (Holmes & Bourne, 2008) to compare involuntary recollection of distressing film footage over a 72 h period in three separate groups, each consisting of participants in a discrete phase of their menstrual cycle: mid follicular, early luteal and late luteal. No previous clinical or experimental study has examined the effect of a stressful life event (or simulation of such an event) on the expression of psychological symptoms in two distinct *and short* epochs within the luteal phase (compared to a short period in the follicular phase).

Whilst previous studies have compared memory effects in follicular and luteal phases as a whole, predictable fluctuations in ovarian hormone levels during the luteal phase suggest that it can be characterised as having an early and late phase separated by the 'progesterone peak.' (e.g. Gandara, Leresche, & Mancl, 2007). For example, while progesterone levels are low in the mid follicular phase, they rise and fall (at different rates) in the early and late luteal phases respectively. On the other hand, estradiol levels are expected on average, to be similar across these three cycle phases over the specific periods of assessment chosen for this study (see below). Since these distinct patterns of hormone activity may give rise to differential memory effects, we also examined the relationship between intrusion frequency and salivary estradiol and progesterone levels separately, as well as their interaction in the form of the estradiol–progesterone (E:P) ratio. We distinguished between sensory and verbal intrusions and assessed intrusion frequency in the absence of any additional (prior) memory test related to the distressing film in order to avoid biasing of intrusion estimates. These methodological considerations are refinements of the methods used by Ferree et al. (2011) who showed a greater number of 'spontaneous intrusive recollections' over the course of the entire luteal period compared to the follicular. A more temporally fine-grained understanding of the luteal phase in onset or maintenance of key psychological symptoms may help to efficiently target preventative interventions towards individuals most vulnerable to psychological disorder.

2. Method

2.1. Participants and design

The study was advertised on a university internet site as an investigation of emotional information processing. Participants who responded to the advert underwent screening via an internet survey, to ensure they met inclusion criteria. These were to have fluency in English, predictable menstrual cycle length of between 26 and 34 days (Nillni et al., 2011), and daily access to a mobile phone and internet. Exclusion criteria were use of hormonal contraception within the past three months, history of mental health difficulty requiring treatment (psychologically/pharmacologically), and phobia of blood, injury or injection. Before participating, all participants were informed of the distressing nature of the film and were told that graphical scenes may be remembered involuntarily after the experiment. The study was approved by the University College London/University College London Hospital Ethics Committee. At the end of the study, all participants received £20 in compensation for their time. Forty-five participants aged between18 and 35 ($M = 23.34$; $SD = 3.86$) completed the study. An independent group design was used where participants were tested during one of three discrete periods in the menstrual cycle (mid follicular, early luteal or late luteal). Cycle length was taken into account when determining menstrual phase, therefore all participants were asked to measure one full cycle (i.e. number of days between menses in two consecutive cycles) prior to taking part in the study. For a 28-day cycle, the three periods were as follows: mid follicular: days 7–11 (25–39% of way through cycle), early luteal: days 16–20 (57–71% of cycle) and late luteal: days 24–28 (86–100% of cycle). For cycle lengths longer or shorter than 28 days, cycle phase was adjusted proportionately (e.g. in a 25-day cycle the early luteal phase (57–71% of cycle) would be days 14–17). Overall, the average mid follicular test day (±SEM) was: day 9 ± 0.45; early luteal: day 17 ± 0.34; late luteal: day 24 ± 0.47.

Three participants were excluded (all in the late luteal group): two due to diary non-compliance and one with outlying intrusion values (>2 SDs). Final analysis involved data from 42 women, with $n = 11$ in the late luteal phase, and $n = 15$ in both mid follicular (36.5%) and early luteal groups. Participants attended the laboratory for two sessions separated by one week.

Upon arrival at session 1, participants read the relevant information sheet and provided written informed consent. After providing a saliva sample, an unrelated task involving facial affect recognition was completed. Standardised questionnaires were then administered to determine level of equivalence between groups on psychological variables, which are either associated with risk of development of PTSD symptoms (trait anxiety) or are relevant to physical and psychological premenstrual symptoms (ASI; PMTS-VAS; see Section 2.3 below). A number of additional visual analogue scale (VAS) measures of current emotional states (see Section 2.3) were taken immediately before and after participants watched the stressful film.