



# How Reward and Emotional Stimuli Induce Different Reactions Across the Menstrual Cycle

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## Abstract

Despite widespread belief that moods are affected by the menstrual cycle, researchers on emotion and reward have not paid much attention to the menstrual cycle until recently. However, recent research has revealed different reactions to emotional stimuli and to rewarding stimuli across the different phases of the menstrual cycle. The current paper reviews the emerging literature on how ovarian hormone fluctuation during the menstrual cycle modulates reactions to emotional stimuli and to reward. Behavioral and neuroimaging studies in humans suggest that estrogen and progesterone have opposing influences. That is, it appears that estrogen enhances reactions to reward, but progesterone counters the facilitative effects of estrogen and decreases reactions to rewards. In contrast, reactions to emotionally arousing stimuli (particularly negative stimuli) appear to be decreased by estrogen but enhanced by progesterone. Potential factors that can modulate the effects of the ovarian hormones (e.g., an inverse quadratic function of hormones' effects; the structural changes of the hippocampus across the menstrual cycle) are also discussed.

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In life, we often encounter hedonic stimuli, such as happy faces, appealing animals, money, car accidents, and stressful events. These hedonic stimuli sometimes induce strong physiological arousal (i.e., emotional arousal) that modulates subsequent cognitive processing (for a review see Mather & Sutherland, 2011). Some hedonic stimuli (e.g., money; high-calorie foods) can also serve as reinforcers (i.e., reward), increasing the frequency of behaviors that lead to their acquisition (e.g., Berridge, 2003; Kringelbach, 2005). Given the importance of these stimuli in our life, reward and emotion have been intensively examined in many fields, such as social neuroscience, cognitive science, affective neuroscience, behavioral economics, and neuroeconomics.

While traditional studies in these areas examined common patterns across different people regardless of their sex, a growing body of research demonstrates sex differences in how people react to and process rewards and emotional stimuli (see Andreano & Cahill, 2009; Cahill, 2006; Caldú & Dreher, 2007; Hamann & Canli, 2004; Kajantie & Phillips, 2006; Kudielka & Kirschbaum, 2005 for reviews). One possible reason for these sex differences is that ovarian hormones alter reactions to emotional stimuli and to rewards. For example, the same emotional stimuli may induce different arousal reactions and neural responses in brain regions modulating arousal depending on ovarian hormone levels. Brain regions involved in reward processing might also respond differently depending on ovarian hormone levels. To address these possibilities, in the current paper, we review behavioral and neuroimaging findings on the effects of the menstrual cycle on reactions to emotional stimuli and to rewards.

Before further discussing the effects of ovarian hormones, we first describe our definitions of emotional stimuli and reward. Emotional stimuli are often characterized based on two orthogonal dimensions (Russell & Carroll, 1999): valence (positive or negative) and

physiological arousal. Previous studies revealed that the amygdala, which is a key region for emotion (Phelps & LeDoux, 2005), responds to the intensity of physiological arousal induced by positive or negative stimuli (Anderson et al., 2003; Kensinger & Corkin, 2004; Shabel & Janak, 2009). However, the amygdala does not respond to the intensity of neutral stimuli (Winston, Gottfried, Kilner, & Dolan, 2005). This valence by intensity interaction is consistent with the notion that both arousal and valence are important aspects of emotional stimuli.

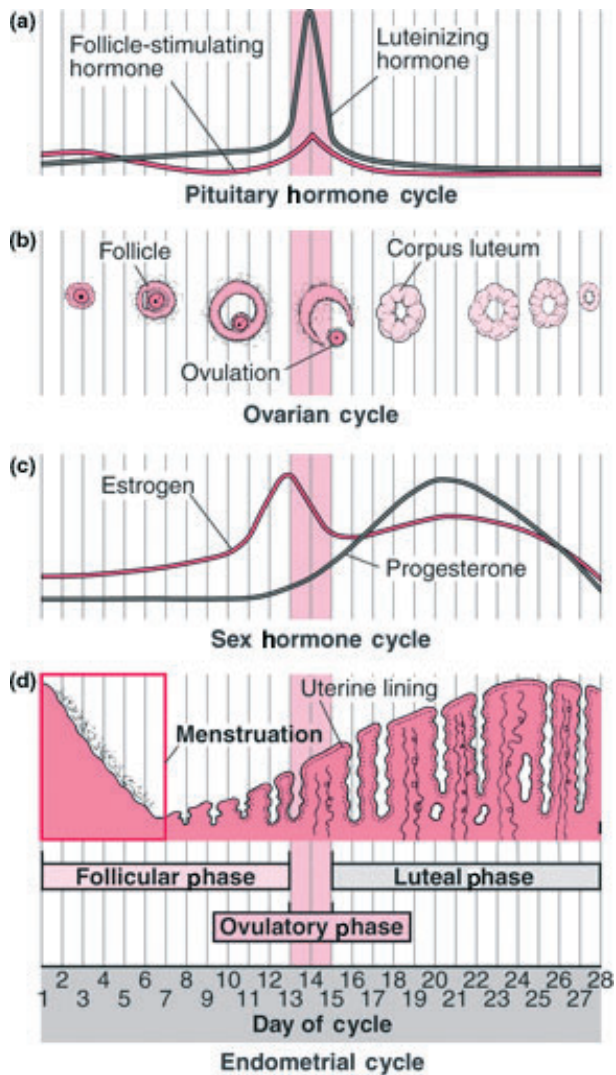
In contrast, reward has been defined as an instrumental reinforcer which triggers ‘wanting’ or craving (i.e., incentive salience) and increases the frequency of behaviors contingent with it (e.g., Berridge & Robinson, 2003; Berridge, Robinson, & Aldridge, 2009). Reward has been associated with brain regions involved in dopaminergic processing, such as the striatum (including nucleus accumbens), globus pallidus, and ventral tegmental area (Berridge, 2003; Berridge et al., 2009). Rewards overlap with emotional stimuli (particularly emotionally positive stimuli), as they can produce emotional consequences (e.g., earning money could be a reinforcer but might also evoke emotional arousal). In fact, rewards sometimes activate the amygdala (Camara, Rodriguez-Fornells, & Munte, 2009). Likewise, emotionally positive stimuli sometimes activate the reward-related regions in the brain (Phan, Wager, Taylor, & Liberzon, 2002).

However, emotional stimuli do not always serve as reinforcers and do not necessarily have strong incentive salience. For example, seeing people celebrating their victory at the Olympics can induce emotional arousal, but does not necessarily alter one’s behavior or induce craving for victory. Similarly, rewards can serve as reinforcers even when they do not have positively valenced meanings (Berridge, 2003; Berridge et al., 2009). In the current paper, therefore, “reward” is defined as an instrumental reinforcer which increases the frequency of contingent behaviors while evoking feelings of ‘wanting’ or craving. In contrast, we use the term “emotional stimuli” to refer to valenced stimuli that induce physiological arousal (regardless of positive or negative valence), affecting cardiovascular activity, heart rate, skin response, and pupil dilation. Emotional stimuli induce multiple reactions, including physiological arousal, stress hormones, amygdala activity, and subjective feelings. Similarly, rewards can alter physiological states (e.g., heart rate), activity in reward-related regions in the brain, and subjective experiences. In the current paper, we review the effects of ovarian hormones without discriminating these different aspects of reactions.

### **Ovarian Hormone Changes across Menstrual Cycle**

The human menstrual cycle lasts 28 days on average and is divided into follicular and luteal phases. The follicular phase begins with the onset of menstruation on day 1 and continues until ovulation (typically on day 14), and the luteal phase begins at ovulation and continues until the onset of menstruation (typically days 15–28; Figure 1).

The early follicular phase begins with release of gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary to secrete follicle-stimulating hormone (FSH: Barr, 1999; Raven, Johnson, Singer, & Losos, 2005; Rimsza, 2002). FSH stimulates the growth of a number of ovarian follicles that secrete estrogen as they mature. When one of the developing follicles becomes dominant, it starts to secrete large amounts of estrogen. This sharp increase in estrogen causes positive feedback effects on the hypothalamus and the pituitary gland, which results in a surge of luteinizing hormone (LH) and then ovulation. During the luteal phase, the postovulatory dominant ovarian follicle transforms into a corpus luteum, which in turn produces both progesterone and



**Figure 1** The human menstrual cycle. Day 1 of the cycle is defined as the first day of menstruation, with ovulation occurring on day 14 in a typical 28-day cycle. The follicular phase starts on day 1 and continues until ovulation, which is followed by the luteal phase. The menstrual cycle in healthy women is associated with (a) pituitary hormone changes, (b) development of ovarian follicles, (c) changes in estrogen and progesterone level, and (d) changes in the thickness of the uterine lining (From *The Merck Manual Home Health Handbook*, edited by Robert S. Porter. Copyright © 2004–2011 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. Retrieved on 10 May 2011 from: <http://www.MerckManuals.com/home>).

estrogen. The combination of these two ovarian hormones helps the endometrium thicken and become more vascular. If fertilization does not occur, the corpus luteum cannot survive. As the corpus luteum regresses, estrogen and progesterone levels drop and FSH begins to rise to initiate follicular growth for the next cycle.

Thus, the absolute levels of estrogen and progesterone, and the ratio of these hormone concentrations, change over the regular menstrual cycle. Both progesterone and estrogen levels are low during the early follicular phase, while the late follicular phase is characterized by a marked increase in secretion of estrogen. Finally, progesterone levels rise during

the early luteal phase, peaking in the mid-luteal phase, in parallel with a second estrogen peak.

### **Research Examining Effects of Ovarian Hormones**

Although estrogen and progesterone are best known for their effects on the female reproductive organs (e.g., uterus; ovary), they cross the blood-brain barrier (Henderson, 1997; Wirth, 2011) and affect brain functions as well (e.g., McEwen, 2002). For example, the hypothalamus, which plays an important role in regulation of the menstrual cycle (as described above), has both estrogen and progesterone receptors. Many other brain regions that are not crucial for reproduction also show progesterone receptor expression (Brinton et al., 2008), such as the amygdala, brainstem, hippocampus, cerebellum, and frontal cortex. Among those areas, the amygdala is a key region in emotional processing (e.g., Phelps, 2006). The amygdala also has both ER $\alpha$  and ER $\beta$  estrogen receptors (e.g., Weiser, Foradori, & Handa, 2008). In fact, the amygdala has one of the highest densities of estrogen receptors in the brain (Merchenthaler, Lane, Numan, & Dellovade, 2004; Shughrue & Merchenthaler, 2001). These findings suggest that both estrogen and progesterone influence reactions to emotional stimuli. In addition, other brain regions, such as the ventral tegmental area, hippocampus, and cerebellum, also express at least one of the estrogen receptors (McEwen, 2002; Weiser et al., 2008). Given that the ventral tegmental area plays a crucial role in processing of reward (Berridge, 2003; Berridge et al., 2009), females may show different responses to reward depending on the cycle.

To address these effects of the ovarian hormones in humans, past studies categorized the menstrual cycle into several phases and compared women's reactions to emotional or rewarding stimuli in one phase with other phases. Some studies distinguished the follicular vs. luteal phases. Given that both estrogen and progesterone levels are higher in the luteal than in the follicular phase on the average, however, these studies cannot discriminate the effects of estrogen and progesterone. Thus, other studies have defined menstrual phase more specifically, with smaller ranges of dates of testing. For example, studies examining the effects of estrogen compare females in the late follicular mid-cycle phase (high estrogen and low progesterone) with the early follicular phase (low estrogen and low progesterone). In contrast, studies addressing the effects of progesterone compare the luteal phase (high estrogen and high progesterone) vs. the late follicular phase (high estrogen and low progesterone). Furthermore, researchers sometimes administer progesterone or estrogen to females in the early follicular phase. The exogenous administration of the ovarian hormones seems especially useful to understand the role of progesterone independently from estrogen, because there is no phase involving low estrogen and high progesterone in the regular menstrual cycle.

The phases of the cycle have been defined in various ways. Some studies have relied on self-reports of the dates of menstruation. Other studies have identified the day of ovulation by having participants measure their body temperature or their urinary LH levels. Given possible individual differences and potential menstrual cycle variations within the same women (e.g., Allende, 2002), these methods are sometimes combined with hormone assays based on plasma or saliva samples to verify the definition of the phase. While these methodological issues are important (see Turner & de Wit, 2006 for a related discussion), the field is new and the number of relevant studies is still small. Therefore, we review studies irrespective of the methods used to define and verify the cycle phases.

In the following sections, we first describe findings from past studies examining the effects of the menstrual cycle on reactions to rewards, and then findings on reactions to

emotionally arousing stimuli in healthy women. Each section starts with reviewing previous studies that simply compared the follicular phase (days 1–14) and the luteal phase (days 15–28). To understand the roles of estrogen and progesterone, we then describe studies examining the effects of these hormones separately with finer cycle categorizations or exogenous administrations of the ovarian hormones.

### **Effects of Ovarian Hormones on Reactions to Reward**

Females showed greater physiological and subjective effects of cocaine (Evans & Foltin, 2006; Evans, Haney, & Foltin, 2002), amphetamine (Justice & de Wit, 1999) and nicotine (Gray et al., 2010) during the follicular phase than during the luteal phase. Neuroimaging research also revealed that monetary reward induced greater activity in the striatum in the follicular than luteal phase (Dreher et al., 2007). However, it is not clear whether the decreased reactions to reward during the luteal phase were due to estrogen or progesterone, both of which are elevated in this period. To address this question, we review studies examining the effects of these hormones separately.

#### *Estrogen enhances reactions to reward*

Animal studies suggest that estrogen enhances reactions to rewards (Becker & Hu, 2008; Lynch, Roth, & Carroll, 2002). In one study (Hu, Crombag, Robinson, & Becker, 2004), for example, female ovariectomized rats were given estrogen before self-administration sessions, in which they were allowed to nose poke to obtain a cocaine infusion. The results indicated that ovariectomized rats with estrogen self-administered larger amounts of cocaine more frequently than did ovariectomized rats without estrogen. Estrogen was also revealed to increase behavioral sensitization (Becker & Hu, 2008; Galankin, Shekunova, & Zvartau, 2010; Hu & Becker, 2003) and dopamine release in reward-related regions in the brain (e.g., striatum; Becker, 1990).

Studies in humans demonstrated similar enhancement effects of estrogen on reactions to rewards. When receiving doses of *d*-amphetamine, for instance, females reported that they liked the effects of drug more strongly in the late follicular phase (high estrogen and low progesterone) than the early follicular phase (low estrogen and low progesterone; Justice & De Wit, 2000a). In addition, exogenous estrogen administration to females with low progesterone increased subjective effects of *d*-amphetamine (e.g., “want more”; feeling “high”; Justice & de Wit, 2000b; Lile, Kendall, Babalonis, Martin, & Kelly, 2007). Taken together with findings from animal studies, it appears that estrogen enhances reactions to reward stimuli.

#### *Progesterone counters facilitative effects of estrogen*

However, estrogen no longer has facilitative effects on reactions to rewards when progesterone is high. As described in previous sections, estrogen administration to ovariectomized female rats increased self-administration of cocaine (e.g., Hu et al., 2004). When estrogen and progesterone were given together, however, progesterone diminished the facilitative effects of estrogen (Jackson, Robinson, & Becker, 2006; Larson, Anker, Gliddon, Fons, & Carroll, 2007). These results are consistent with recent findings that progesterone down-regulates the estrogen receptor (e.g., Aguirre, Jayaraman, Pike, & Baudry, 2010), and suggest that progesterone counters the facilitative effects of estrogen

(Anker, Larson, Gliddon, & Carroll, 2007; Quinones-Jenab & Jenab, 2010; Yang, Zhao, Hu, & Becker, 2007).

Studies in humans provide additional support that progesterone opposes the effects of estrogen. In line with the facilitative roles of estrogen, estrogen level was positively correlated with the magnitude of subjective (e.g., feeling “high”; elation) and physiological (e.g., heart rate) stimulation of amphetamine during the follicular phase (Justice & de Wit, 1999; White, Justice, & de Wit, 2002). But when progesterone was high (i.e., during the luteal phase), the level of estrogen no longer had a positive correlation with the magnitude of amphetamine’s stimulation (Justice & de Wit, 1999; White et al., 2002).

A recent neuroimaging study also reported consistent evidence (Frank, Kim, Krzemien, & Van Vugt, 2010). In this study, female participants viewed images of high-calorie-rewarding foods (e.g., cakes, cookies, ice cream) and of low-calorie foods (e.g., steamed vegetables) when they were hungry. During the late follicular phase, high-calorie foods induced greater activity in reward-related regions (e.g., nucleus accumbens) than did low-calorie foods. However, nucleus accumbens activity did not differ between high- and low-calorie foods in the luteal phase. Given the hormone patterns of the late follicular (high estrogen and low progesterone) and the luteal phase (high estrogen and high progesterone), these results seem consistent with the idea that progesterone counters facilitative effects of estrogen.

#### *Progesterone decreases reactions to reward by itself*

In addition to its countering effects on estrogen, past studies have revealed that progesterone can decrease reactions to reward even when estrogen is low (Evans, 2007; Quinones-Jenab & Jenab, 2010). While intact animals show strong preference for a chamber associated with cocaine, for example, progesterone administration diminished the preference for the cocaine-paired chambers in ovariectomized female rats (Russo et al., 2003) and in male rats (Romieu, Martin-Fardon, Bowen, & Maurice, 2003). Studies in humans also reported similar findings. When progesterone was administered to females with low estrogen, for instance, it attenuated physiological and subjective (e.g., feeling “high,” “willing to pay”) effects of cocaine (Evans & Foltin, 2006; Sofuoglu, Babb, & Hatsukami, 2002). Administration of progesterone also reduced urges to smoke cigarettes in female smokers during the early follicular phase (Sofuoglu, Mouratidis, & Mooney, 2011). Because those studies addressed the effects of progesterone when estrogen is low, they suggest that progesterone decreases reactions to rewards not only by countering the effects of estrogen, but also by itself.

#### *Summary*

In summary, it appears that estrogen and progesterone have opposing effects on reactions to rewards. That is, both animal and human studies indicate that estrogen enhances reactions to rewards. In contrast, studies suggest that progesterone counters the facilitative effects of estrogen and decreases reactions to rewards. As we described above, females tend to show stronger reactions to rewards during the follicular phase than during the luteal phase (Dreher et al., 2007; Evans & Foltin, 2006; Evans et al., 2002; Gray et al., 2010; Justice & de Wit, 1999; Sofuoglu, Dudish-Poulsen, Nelson, Pentel, & Hatsukami, 1999). Given studies reviewed in this section, it appears that progesterone is crucial to explain the decreased reward sensitivity during the luteal phase.



## Effects of Ovarian Hormones on Reactions to Emotionally Negative Stimuli

Next, we turn to the question whether and how ovarian hormones influence reactions to emotionally arousing stimuli. As we mentioned above, emotional stimuli involve stimuli inducing physiological arousal, irrespective of whether they are positive or negative. However, the majority of past studies on ovarian hormones employed only negative and neutral stimuli. Therefore, we focus on findings about reactions to negative stimuli in this section.

As with reward, previous studies revealed that females react to emotionally negative stimuli differently in follicular vs. luteal phases. Compared with the follicular phase, for example, females in the luteal phase showed increased stress hormones after stressful tasks (Altemus, Roca, Galliven, Romanos, & Deuster, 2001; Childs, Dlugos, & De Wit, 2010a; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Roca et al., 2003; Tersman, Collins, & Enoth, 1991), showed stronger amygdala activity when anticipating pain (Choi et al., 2006), and interpreted mildly negative faces as strongly negative (Derntl, Kryspin-Exner, Fernbach, Moser, & Habel, 2008). Studies of daily moods also reported increased negative moods during the luteal phase than the follicular phase (Allen, Allen, & Pomerleau, 2009; Reed, Levin, & Evans, 2008; Sanders, Warner, Backstrom, & Bancroft, 1983). Because these studies cannot discriminate the effects of the two ovarian hormones, we review studies examining estrogen and progesterone separately in the following sections.

### *Estrogen decreases reactions to emotionally negative stimuli*

Animal studies indicate estrogen decreases reactions to emotionally negative stimuli. For example, exogenous estrogen administration decreases release of stress hormones at least when estrogen does not reach supra-physiological levels (Dayas, Xu, Buller, & Day, 2000; Young, Altemus, Parkison, & Shastry, 2001). Estrogen administration to ovariectomized female rats also increased time spent in open arms in the elevated plus maze (an aversive situation for a rat) and reduced duration of freezing after foot-shock (Frye & Wolf, 2004), thus reducing the intensity of anxious or depressive responses to aversive situations (for a review see Wolf & Frye, 2006).

Similar patterns were observed in studies in humans as well (e.g., Gasbarri et al., 2008). Higher levels of estrogen were associated with poorer performance in recognizing anger faces (Guapo et al., 2009). Estrogen therapy is also known to decrease depressive symptoms at least in perimenopausal females (Cohen et al., 2003; Soares, Almeida, Joffe, & Cohen, 2001). Furthermore, Goldstein et al. (2005) compared brain activity while viewing negative or neutral pictures during the early follicular (low estrogen and low progesterone) vs. late follicular phase (high estrogen and low progesterone). As shown in previous studies collapsing sex and menstrual cycle phases (e.g., Ochsner et al., 2004; Phan et al., 2002), females in both phases showed enhanced activity in emotion related regions, such as the amygdala and orbitofrontal cortex (OFC), when viewing negative pictures than neutral pictures. However, the activity of these areas was modulated by the menstrual cycle phases. That is, females showed greater activity in the amygdala and OFC to negative pictures during the early follicular phase than during the late follicular phase (see also Goldstein, Jerram, Abbs, Whitfield-Gabrieli, & Makris, 2010).

Thus, both animal and human studies suggest that reactions to negative stimuli are decreased by estrogen. Although different studies employed different tasks or measures (e.g., amygdala activity to negative pictures, facial emotion recognition), they have

observed consistent patterns, suggesting that estrogen has similar effects across different aspects of reactions to negative stimuli. However, this does not mean that estrogen inhibits any tasks involving negative stimuli. In fact, recent research has revealed the facilitative effects of estrogen on one type of learning involving negative stimuli – extinction of fear conditioning (Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad et al., 2010; Zeidan et al., forthcoming).

One possible factor contributing to the contradictory findings is the complexity of tasks being employed. While studies showing inhibitory effects of estrogen measured relatively simple reactions to negative stimuli (e.g., amygdala activity to negative pictures; facial emotion recognition), extinction learning requires multiple types of processing. For instance, recent research indicates that extinction of fear conditioning involves reward-related learning (Holtzman-Assif, Laurent, & Westbrook, 2010; Raczka et al., 2011). Thus, the facilitative effects of estrogen on extinction recall might be caused by the effects of estrogen on reward. Furthermore, hippocampal structure is changed by estrogen quite rapidly. For example, higher levels of estrogen result in greater synapse density of hippocampus within 24 hours in rats (Woolley & McEwen, 1993). Research in humans also revealed that the same women had increased hippocampal volume during the late-follicular phase than the premenstrual phase (Protopopescu et al., 2008). Since extinction of conditioning depends not only on emotion-related areas (e.g., OFC), but also on the hippocampus (Milad et al., 2007), structural changes in brain regions critical for extinction learning may also explain enhancing effects of estrogen on extinction. Taken together, it appears that estrogen decreases reactions to negative stimuli, but can have facilitative effects when tasks involve reward-related components or hippocampus-related processing.

#### *Progesterone enhances reactions to emotionally negative stimuli*

In contrast with estrogen's inhibitory effects on reactions to negative stimuli, past studies suggested that progesterone enhances reactions to negative stimuli at least in humans (e.g., Andreano, Arjomandi, & Cahill, 2008; Protopopescu et al., 2005). When females were tested at two timepoints with different level of progesterone, for example, they experienced more spontaneous intrusive recollections about unpleasant events when progesterone was high than when progesterone was low (Ferree & Cahill, 2009; Ferree, Kamat, & Cahill, forthcoming). Similarly, compared to the late follicular phase (high estrogen and low progesterone), females in the luteal phase (high estrogen and high progesterone) were more sensitive to facial cues signaling contagion and physical threat (Conway et al., 2007) and increased their heart rates more while watching negative videos (Ossewaarde et al., 2010). Furthermore, a neuroimaging study (Andreano & Cahill, 2010) revealed increased amygdala activity to negative pictures (relative to neutral pictures) when progesterone was high than when progesterone was low.

Human studies employing exogenous progesterone administration also confirmed the facilitative role of progesterone. For example, females in the follicular phase showed increased amygdala activity to angry and fearful faces when they were given progesterone compared with placebo (van Wingen et al., 2008). Progesterone administration also increased physiological reactions to a stress task both in males (Childs, Van Dam, & Wit, 2010b) and females (Roca et al., 2003). Furthermore, exogenous progesterone increased negative moods in women in the early follicular phase (Klatzkin, Leslie Morrow, Light, Pedersen, & Girdler, 2006; Soderpalm, Lindsey, Purdy, Hauger, & de Wit, 2004) as well



as in postmenopausal women (Andréen et al., 2009). Taken together, it appears that progesterone increases reactions to negative stimuli in humans.

However, animal studies provided contradictory findings (for a review see Wirth, 2011). That is, exogenous progesterone administration was revealed to decrease the intensity of anxious or depressive responses to aversive situations (e.g., elevated plus maze, foot-shock; Auger & Forbes-Lorman, 2008; Frye & Walf, 2004; Llana & Frye, 2009). Furthermore, some studies in humans also observed that progesterone administration weakened subjective reactions to negative stimuli (e.g., Childs et al., 2010b; de Wit, Schmitt, Purdy, & Hauger, 2001).

One possible reason for this inconsistency is that while increases in progesterone seen during normal menstrual cycles enhance reactions to negative stimuli (as we discussed above), concentrations of progesterone higher than the normal range might decrease emotional reactions and have calming effects (see Andréen et al., 2009 for a review). In fact, when progesterone was administered to post menopausal women, participants reported the highest negative mood scores with a moderate level of oral micronized progesterone (Andréen, Sundström-Poromaa, Bixo, Nyberg, & Bäckström, 2006). In contrast, both lower and higher concentrations of progesterone produced less negative moods (Andréen et al., 2006). Thus, it appears that the effects of progesterone follow an inverse-U function, rather than a linear correlation. Perhaps, if there is too much progesterone, progesterone no longer has facilitative effects and decreases reactions to negative stimuli (see also Andréen et al., 2005; Gomez, Saldivar-Gonzalez, Delgado, & Rodriguez, 2002). This might explain why studies with exogenous progesterone administration to animals and humans sometimes revealed inhibitory effects of progesterone on reactions to negative stimuli.

### *Summary*

Studies reviewed in this section indicate that estrogen and progesterone have opposing influences on reactions to emotionally negative stimuli. In other words, reactions to negative stimuli appear to be decreased by estrogen but enhanced by progesterone. These patterns were observed across different studies employing different types of tasks or measures (e.g., amygdala activity to negative pictures; stress hormones; facial emotion recognition). However, studies sometimes observed different patterns. Potential factors for these inconsistencies are an inverse quadratic function of progesterone's effects, reward-related components involved in tasks being employed, and structural changes of the brain across the menstrual cycle.

### **Effects of Ovarian Hormones on Reactions to Emotionally Positive Stimuli**

The amygdala, a key region for emotional processing, responds to emotionally arousing information, regardless of whether it is positive or negative (e.g., Anderson et al., 2003; Kensinger & Schacter, 2006; Sergerie, Chochol, & Armony, 2008). Thus, one might expect that estrogen and progesterone have similar influences on positive and negative stimuli. However, previous studies in humans provided mixed results regarding ovarian hormone effects on reactions to positive stimuli.

Consistent with facilitative effects of progesterone on reactions to negative stimuli, for example, progesterone administration increased positive emotional states in postmenopausal women (de Wit et al., 2001). Higher progesterone was also associated with a greater increase in cortisol after positive emotion induction in males (Wirth, Meier, Fredrickson,

& Schultheiss, 2007). However, opposite patterns have also been reported. That is, progesterone administration reduced amygdala activity to happy or neutral faces (van Wingen et al., 2007) and decreased positive emotional states, such as friendliness or confidence, in females in the early follicular phase (Klatzkin et al., 2006; de Wit et al., 2001). Results on estrogen were also mixed. Researchers sometimes observed increased activity in emotion-related areas to positive stimuli when estrogen was low than high (Zhu et al., 2010). However, other research provided evidence for facilitative effects of estrogen on reactions to positive stimuli (Amin, Epperson, Constable, & Canli, 2006; Gizewski et al., 2006).

One possible reason for this inconsistency is the role of reward. Although rewards and emotionally positive stimuli can be defined separately (as discussed above), they also overlap with each other. For example, positive but non-rewarding stimuli sometimes activate reward-related regions, such as striatum, in addition to the amygdala (Hamann & Mao, 2002). Recent research also revealed that viewing positive emotional stimuli can increase subsequent striatum activity to monetary rewards (Wittmann, Schiltz, Boehler, & Duzel, 2008). These results suggest that positive emotional stimuli not only evoke emotional arousal, but also prime reward-related processing.

This complex nature of positive stimuli might explain the mixed findings of estrogen and progesterone on reactions to positive stimuli. That is, estrogen might facilitate reward-related aspects of reactions to positive stimuli, but decrease their aspects related to emotional arousal. Similarly, progesterone might decrease reward-related aspects of reactions to positive stimuli, but have facilitative effects on their aspects related to emotional arousal. Thus, ovarian hormones might have opposing influences on the reward-related and arousal-related aspects of positive emotion, which could result in unclear effects of the ovarian hormones on reactions to positive stimuli.

### Questions for Future Research and Conclusions

In summary, the current paper suggests that estrogen and progesterone have opposing influences on both reactions to emotionally arousing negative stimuli and reactions to rewarding stimuli. In other words, reactions to negative stimuli seem to be decreased by estrogen, but enhanced by progesterone. In contrast, the opposite effects were observed in reactions to rewarding stimuli. That is, it appears that estrogen enhances reactions to rewards, while progesterone decreases reactions to rewards not only by itself, but also by countering the facilitative effects of estrogen. In addition to this overall pattern, the current paper also highlights several important questions for future studies.

The first question concerns the effects of the ovarian hormones on reactions to positive stimuli. As we pointed out in the previous section, past studies reported mixed findings on the effects of estrogen and progesterone on reactions to positive stimuli. Given a potential link between reward and positive emotion (e.g., Wittmann et al., 2008), reactions to positive stimuli might reflect not only emotional arousal-related processing, but also reward-related processing. Future studies should tease apart these two aspects of positive emotion to clarify how the ovarian hormones modulate reactions to positive stimuli.

A second question is which aspects of reward and emotion are affected by estrogen and progesterone. Reward is not a unitary concept and has been decomposed into two aspects (Berridge & Robinson, 2003; Berridge et al., 2009): a) hedonic consequences of consumption ('liking') and b) incentive salience (i.e., 'wanting'; craving). Studies reviewed in this paper demonstrated similar effects of estrogen and progesterone on these two aspects. That is, incentive salience (e.g., "want more") is enhanced by estrogen (e.g., Justice & de Wit, 2000b), but decreased by progesterone (Gray et al., 2010). Hedonic

consequences (e.g., “like drug”) is also enhanced by estrogen (e.g., Justice & De Wit, 2000a), but decreased by progesterone (e.g., Evans & Foltin, 2006). However, these two aspects often correlate with each other (e.g., Epstein et al., 2004). Thus, it is possible that the ovarian hormones influence only one of the aspects, and that the affected aspect modulates the other aspect, which results in similar patterns between them. Likewise, although previous research on negative emotion observed similar effects of the ovarian hormones across different aspects of emotional reactions (e.g., amygdala activity; stress hormone, subjective mood states), there might be some aspects that are more strongly modulated by ovarian hormones than others. Future studies need to clarify which aspects of emotional and reward reactions are modulated by the ovarian hormones, while considering detailed neurobiological mechanisms of the influences of estrogen and progesterone (e.g., Hudson & Stamp, 2011; Quinones-Jenab & Jenab, 2010).

Another question for future research is how ovarian hormones influence social behaviors or one’s personality. The construct of personality relies on the assumption that individuals can be characterized by qualities that are relatively invariant over time. However, many personality traits are related with emotion or rewards (e.g., trait anxiety, neuroticism, self-esteem, and reward sensitivity). Thus, the same woman might show cyclic variations in their emotion-related or reward-related personality tendencies. Similarly, the ovarian hormones might influence within-individual processes and social behaviors, such as emotion regulation, well-being, consumption behaviors, and attitudes toward other people, all of which are relevant to emotion or reward. Future studies need to address the effects of the ovarian hormones on those complex intra- and inter-personal processes, while combining traditional psychology research methods (e.g., personality assessment, behavioral experiment), with physiological measures (e.g., hormone assay) and neuroimaging methods. This multimethodological approach should provide better understanding of our behaviors in everyday life.

In conclusion, from the studies included in this review, it appears that the menstrual cycle and ovarian hormones modulate how people react to emotional and rewarding stimuli. Given the core importance of emotion and reward processing in our lives, such differences are important and further investigation is needed to better understand the mechanisms of the effects. These hormonal effects might explain why specific phases of the cycle are related to depressive symptoms (Farage, Osborn, & MacLean, 2008) or higher risks in addiction (Becker & Hu, 2008; Terner & de Wit, 2006). Thus, examining the effects of menstrual cycle or ovarian hormones may have theoretical implications in many fields, while providing practical suggestions on how to improve females’ well-being in real life.

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## **Short Biographies**

Michiko Sakaki received her PhD from the University of Tokyo and is an Assistant Research Professor of Gerontology at the University of Southern California. Her research focuses on the effects of emotion on cognition. Utilizing neuroimaging and behavioral methods, she addresses how emotion influences cognitive processing (e.g., memory, attention, problem solving) and how individual’s characteristics (e.g., age, sex) modulate

the emotional effects on cognition. She has authored and coauthored papers on these topics for “*Journal of Personality*”, “*Journal of Cognitive Neuroscience*”, “*Cognitive, Affective, & Behavioral Neuroscience*”, “*Social, Cognitive, Affective Neuroscience*” and “*Gerontology*.”

Mara Mather’s research focuses on how emotion and stress affect memory and decisions and how such influences differ depending on one’s age and gender. Her research elucidating the interaction of emotion, cognition, and aging has been recognized with the American Psychological Association Distinguished Scientific Award for Early Career Contribution to Psychology and the Springer Early Career Achievement Award in Research on Adult Development and Aging. She also received a National Institutes of Health K02 Career Development award and the Richard Kalish Innovative Publication Award from the Gerontological Society of America. She is Associate Professor of Gerontology and Psychology at the University of Southern California and holds an A.B. in psychology from Stanford University and a Ph.D. in cognitive psychology from Princeton University.

## Endnote

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