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Effects of menstrual cycle phase on electrocortical response to reward and depressive symptoms in women

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Abstract

The menstrual cycle impacts mood and neural response to reward—phenomena that may be related to natural fluctuations in ovarian hormones. Using a within-subject design, the present study examined ovarian hormones (i.e., estradiol and progesterone) and ERPs in response to feedback indicating gains and losses in both the follicular and luteal phases of the menstrual cycle. We examined whether hormone levels and variation in neural response to reward and loss across menstrual cycle phases were associated with depressive symptoms. Participants high in depressive symptoms showed a reduced reward positivity (RewP) to monetary gains during the luteal phase of the menstrual cycle as compared to the follicular phase, while those low in depressive symptoms showed no change in the RewP to monetary gains between phases. Thus, increased fluctuation in the neural response to gains (but not losses) across menstrual cycle phases was associated with greater depression symptoms. Overall, findings indicate that hormonal fluctuations associated with the menstrual cycle may relate to depressive symptoms by altering reward sensitivity. Furthermore, fluctuation in the neural response to rewards over the menstrual cycle may play an important role in the expression of depressive symptoms.

KEYWORDS

depression, ERPs, estradiol, menstrual cycle, progesterone, reward positivity

1 | INTRODUCTION

The menstrual cycle has long been associated with psychological changes: mood and neurocognitive processes are impacted, and females often experience increases in psychiatric symptoms that include depression and anxiety (Farage, Osborn, & Maclean, 2008; Kiesner, 2009). Specific hormones that vary across the menstrual cycle, including progesterone and estradiol, have been shown to impact emotion and cognition (Andreano & Cahill, 2010; Sakaki & Mather, 2012), and could therefore play a role in mood and cognitive variability across the menstrual cycle. Progesterone and estradiol have also been shown to impact neural and subjective measures of responsivity to reward (Dreher et al., 2007; Evans & Foltin, 2006; Evans, Haney, & Foltin, 2002; Ossewaarde et al., 2010; Sakaki & Mather, 2012), a construct that plays a central role in depression and risk for depression (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). Given these links, it stands to reason that reward function could be a mechanism by which ovarian hormones influence mood. Therefore, the current study utilized a within-subject design to examine the association between ovarian hormones, neural indices of reward sensitivity, and depressive symptoms at multiple points in the menstrual cycle.

The menstrual cycle is a biological phenomenon that can be divided into three phases that are characterized by distinct fluctuations in endogenous hormones (Farage et al., 2008).

The follicular phase begins with menstrual bleeding and typically lasts 13–14 days. The early part of the follicular phase is characterized by low levels of estrogen and progesterone, which cause the deterioration of the endometrium. The latter part of the follicular phase is characterized by a sharp increase in both estrogen and luteinizing hormone levels. The increase in luteinizing hormone leads into the 16- to 32-hr ovulatory phase, when estrogen levels plummet and an egg is released. The luteal phase begins after ovulation, lasts for about 14 days, and is characterized by a peak of progesterone and estrogen in the midluteal phase that is flanked by relatively decreased levels of both hormones in the early and late luteal phases. Natural variability in levels of estradiol and progesterone across the menstrual cycle are depicted in Figure 1. The menstrual cycle is also associated with psychological changes, such as increases in symptoms of depression and anxiety (Farage et al., 2008; Kiesner, 2009). More severe fluctuations in these psychological correlates have been referred to as premenstrual syndrome (PMS). While PMS is reported by about 75% of all premenopausal women, less than 10% of women experience severely debilitating PMS symptoms and are diagnosed with premenstrual dysphoric disorder (PMDD; Maharaj & Trevino, 2015).

Psychological changes relating to the menstrual cycle have been attributed to fluctuations in progesterone and estrogen. A growing number of studies have begun to examine the impact of hormonal fluctuation during the menstrual cycle on measures of emotional reactivity. Estrogen and progesterone both have receptors located in every organ of the body, as well as various regions of the brain linked to emotion and memory, including the amygdala, hypothalamus, and hippocampus (Jovanovic et al., 2004). Estradiol decreases reactions to negative emotional stimuli, and estrogen therapy has been shown to decrease depressive symptoms in some perimenopausal women (Cohen et al., 2003; Sakaki & Mather, 2012). On the other hand, progesterone has been shown to increase reactions to negative stimuli (Sakaki & Mather, 2012). Naturally high levels of progesterone in the midluteal phase have been related to heightened amygdala activity to negative stimuli as compared to the early follicular phase (Andreano & Cahill, 2010), and exogenous progesterone administration increased negative mood in women who were in the early follicular phase (Klatzkin, Morrow, Light, Pedersen, & Girdler, 2006). Thus, changes in emotional and cognitive processes across the menstrual cycle may be attributable to varying amounts and/or balances of estradiol and progesterone. Indeed, many studies have shown that most negative symptoms of PMS and PMDD, including emotional reactivity, occur during the luteal phase of the menstrual cycle—when estradiol and progesterone levels are both high (Dreher et al., 2007; Hoyer et al., 2013; Poromaa & Gingnell, 2014).

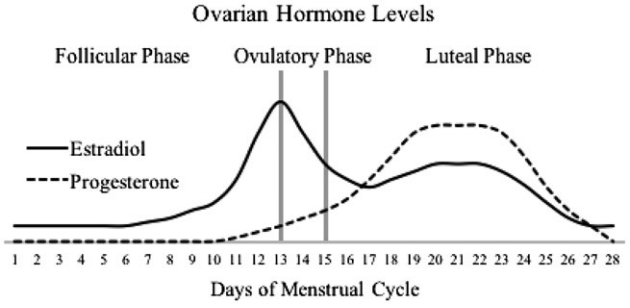

FIGURE 1 Schematic depicting the natural variability in the menstrual hormones estradiol and progesterone across the menstrual cycle

Recent studies of mood disorders—especially those examining depressive symptoms and anhedonia—have focused on how the brain responds to reward and how hormones that vary across the menstrual cycle impact reward sensitivity. For example, estrogen has been shown to enhance subjective and physiological responses to rewarding stimuli, whereas progesterone decreases sensitivity to rewarding stimuli and appears to suppress the positive impact of estrogen on response to reward (Sakaki & Mather, 2012). Consistent with these data, research indicates that women experience greater effects of mood-altering substances, such as cocaine, amphetamine, and nicotine, during the follicular compared to luteal phase (Sakaki & Mather, 2012). Further, administration of progesterone in women low in estradiol caused attenuation of subjective and physiological responsiveness to cocaine (Evans & Foltin, 2006; Evans et al., 2002). Therefore, the follicular phase may be characterized by increased responsiveness to reward due to increased estrogen levels, while the luteal phase may be associated with a blunted response to reward due to increased progesterone levels.

In terms of the relationship between menstrual phases and neural response to reward, fMRI studies have provided mixed findings. For instance, one fMRI study indicated increased neural activation in midbrain, striatum, and left frontopolar cortex to monetary rewards during the midfollicular relative to the midluteal phase (Dreher et al., 2007); however, another study demonstrated enhanced ventral striatal responses to reward anticipation in the premenstrual, or late luteal, phase as compared to the late follicular phase (Ossewaarde et al., 2010). This discrepancy may be due to different experimental paradigms (e.g., examination of neural activity to reward feedback vs. anticipation of reward), or could arise from differences in when reward was assessed within the menstrual phase (i.e., middle vs. late). Despite mixed fMRI findings with regard to reward responsivity in each phase, data such as these suggest that hormone-related variability in sensitivity to rewards across the menstrual cycle could underlie variation in mood (Sacher, Okon-Singer, & Villringer, 2013).

The current study examined this possibility by focusing on the neural response to rewards recorded with ERPs.

Approximately 300 ms after reward feedback, the ERP at frontocentral recording sites is characterized by a relative positivity; an apparent negativity is observed following feedback indicating loss (Hajcak, Moser, Holroyd, & Simons, 2007; Holroyd, Hajcak, & Larsen, 2006). The ERP response to reward is referred to as the reward positivity (RewP; Baker & Holroyd, 2011; Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Proudfit, 2015). According to Holroyd and colleagues, there is an N200 following both gain and loss feedback, which is suppressed by the overlapping RewP on reward trials (Holroyd et al., 2008; Proudfit, 2015). This view is similar to results from PCA-based analyses, which have consistently found that gain feedback elicit a relative positivity that is absent or suppressed following loss feedback (Foti & Hajcak, 2009; Foti, Weinberg, Dien, & Hajcak, 2011; Liu et al., 2014).

In research using ERPs, a smaller RewP has been associated with depression (Bress et al., 2013; Nelson et al., 2016; Proudfit, 2015). For instance, in a sample of never-depressed adolescent girls, a reduced RewP prospectively predicted first-onset depressive disorder and greater depressive symptoms 18 months later, even when controlling for depressive symptoms at initial testing and parental lifetime psychiatric history (Nelson et al., 2016). These findings suggest a link between reward insensitivity indexed by ERPs and risk for depression in women. However, there is a lack of studies examining the impact of menstrual cycle phases and ovarian hormones on ERP measures of reward processing, which may subsequently affect mood and related symptoms; that is, studies have not examined variability in reward sensitivity across the menstrual cycle in relation to depressive symptomatology.

The present study used a within-subject design to examine whether changes in ovarian hormones associated with menstrual cycle phases relate to neural indices of reward sensitivity and depressive symptoms. To this end, 43 undergraduate females completed a hormone assay for estradiol and progesterone, a depression symptom inventory, and an ERP monetary gambling task twice—once during their midfollicular phase and once during their midluteal phase—to examine within-subject changes in hormones and neural measures of reward processing, and their relationship to depressive symptoms. We hypothesized that the neural response to monetary gains would be increased during the midfollicular phase when estradiol and progesterone are low relative to the midluteal phase when progesterone is high and estradiol is moderate to high—and that the neural response to losses would be attenuated during the midfollicular phase relative to the midluteal phase. It was also hypothesized that increased depression symptoms would be associated with a reduced neural response to reward, greater levels of progesterone, and reduced levels of estradiol.

2 | METHOD

2.1 | Participants

Forty-three female undergraduates from Stony Brook University participated for course credit. The sample was college aged ($M = 20.70$ years, $SD = 3.28$) and ethnically diverse, including 51.1% Asian, 27.9% Caucasian, 14% Latino, and 7% Black. Demographic information can be found in Table 1. Participants were recruited from the introduction to psychology subject pool. Demographic information was obtained through an initial screening email, and eligibility for participation was determined through an online prescreen survey that assessed the use of hormonal/oral contraceptives, average menstrual cycle duration, date of onset of previous menses, and regularity of the menstrual cycle. The menstrual cycle length was defined as the number of days from the start of menses in one cycle to the start of menses in the next cycle. Inclusion criteria were age 18–35 years and regular menstrual cycle (average cycle length 28.65 days [$SD = 2.97$]; average length of menstruation 5.29 days [$SD = 0.95$]). Exclusion criteria were taking hormonal/oral birth control within the past 4 months, irregular menstruation, pregnancy or lactation within the past 12 months, or significant medical illness.

Information on the average cycle length and the date of onset of previous menses was used to schedule eligible participants for the initial assessment. Of the 43 participants, 23 (53.5%) were initially tested during the midfollicular phase (6 to 8 days following the start of menstruation) of their menstrual cycle, and 20 (46.5%)

TABLE 1 Demographics (top) and hormone levels and depression symptoms (bottom) across the different phases of the menstrual cycle

	M	*SD*		
Demographics				
Age (years)	20.70	3.28		
Education (years)	14.86	1.22		
Race				
Asian	51.1%			
Black	7%			
Caucasian	27.9%			
Latino	14%			
	Follicular phase		Luteal phase	
	M	*SD*	*M*	*SD*
Hormones (pg/mL)				
Estradiol	2.45	0.68	2.74	0.72
Progesterone	154.93	83.65	355.63	191.08
IDAS-II depression	42.00	10.83	41.86	12.28

Note. IDAS-II = Inventory of Depression and Anxiety Symptoms; *M* = mean; pg/mL = picograms per milliliter; *SD* = standard deviation.

were tested during the midluteal phase (6 to 8 days before the projected start of menstruation) of their cycle. For the second assessment, each participant was scheduled during the alternate phase of her cycle. Informed consent was obtained prior to participation, and the research protocol was approved by the Institutional Review Board at Stony Brook University.

2.2 | Measures

2.2.1 | Inventory of Depression and Anxiety Symptoms

The Inventory of Depression and Anxiety Symptoms (IDAS-II) is a 99-item self-report questionnaire that measures factor-analytically derived symptom dimensions of depression and anxiety (Watson et al., 2007). Each item measures symptoms over the past 2 weeks on a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*extremely*). The IDAS-II has good internal consistency, test-retest reliability, and convergent and discriminant validity with diagnoses and self-report measures (Watson et al., 2012). For the purposes of this study, depressive symptom scores were derived from the general depression subscale within the IDAS-II, which consists of 20 items.

2.3 | Procedure

Participants attended two laboratory visits: one during the mid-follicular phase and the other during the midluteal phase. There was an average of 2 weeks between visits ($M = 15.24$ days, $SD = 3.85$). All participants first provided written informed consent, and then completed self-report questionnaires. Participants then provided a salivary sample for hormone assay. All samples were assayed for salivary estradiol and progesterone using an enzyme immunoassay kit (Salimetrics, State College, PA). For estradiol assay, the test uses 100 ul of saliva, has a minimum detection limit of 0.1 pg/mL (range from 1–32 pg/mL), and average intra- and interassay variation coefficients were 7% and 6%, respectively. There is minimal cross-reactivity to estriol and estrone, and no detected cross-reactivity with progesterone. For progesterone assay, 50 µl of saliva were collected. There is a minimum detection limit of 5 pg/mL (range from 10–2,430) and average intra- and interassay coefficients of variation were 4% and 5.5%, respectively. There is minimal cross-reactivity to corticosterone and no detected cross-reactivity to estradiol. After collection of the salivary sample and EEG setup, participants completed the doors task (described below) while EEG was recorded.

The doors task was administered using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) and was similar to the version used in previous studies (Proudfit, 2015). The task consisted of 60 trials presented over three blocks of 20 trials. Each trial began with the presentation of two identical doors. Participants were instructed to select the left or right door by clicking the left or right mouse button, respectively. Participants were told that they could either win $0.50 or lose $0.25 on each trial. These values were chosen to equalize the subjective value of gains and losses (Tversky & Kahneman, 1981, 1992). The goal of the task was to guess which door hid the reward while attempting to earn as much money as possible. The image of the doors was presented until the participant made a selection. After stimulus offset, a fixation cross (+) was presented for 1,000 ms, and feedback was then presented on the screen for 2,000 ms. A gain was indicated by a green arrow pointing upward (↑), and a loss was indicated by a red arrow pointing downward (↓). The feedback stimulus was followed by a fixation cross (+) presented for 1,500 ms, immediately followed by the message, "Click for next round." This prompt remained on the screen until the participant responded with a button press to initiate the next trial. There was an equal number of gain and loss trials (30 each), such that participants had an equal likelihood of receiving gain and loss feedback throughout the task. Participants were explicitly informed that they would keep their earnings in the doors task.

2.4 | EEG recording and processing

Continuous EEG was recorded using an elastic cap with 34 electrode sites placed according to the 10/20 system. Electrooculogram (EOG) was recorded using four additional facial electrodes: two placed approximately 1 cm outside of the right and left eyes, and two placed approximately 1 cm above and below the right eye. All electrodes were sintered Ag/AgCl electrodes. Data were recorded using the Active Two BioSemi system (BioSemi, Amsterdam, Netherlands). The EEG was digitized with a sampling rate of 1,024 Hz using a low-pass fifth-order sinc filter with a half-power cutoff of 204.8 Hz. A common mode sense active electrode producing a monopolar (i.e., nondifferential) channel was used as recording reference. EEG data were analyzed using BrainVision Analyzer (Brain Products, Gilching, Germany). Data were referenced offline to the average of left and right mastoids and band-pass filtered (0.1 to 30 Hz, with a 12 dB/oct and 24 dB/oct roll-off, respectively).

Feedback-locked epochs were extracted with a duration of 1,000 ms, including a 200-ms prestimulus and 800-ms poststimulus interval; these segments were then corrected for eye movement artifacts using a regression-based approach (Gratton, Coles, & Donchin, 1983). Epochs containing a voltage greater than 50 µV between sample points, a voltage difference of 300 µV within a segment, or a maximum voltage difference of less than 0.50 µV within 100 ms intervals

were automatically rejected. Additional artifacts were identified and removed based on visual inspection. The 200-ms prestimulus interval was used as the baseline.

Feedback-locked ERPs were averaged separately for gains and losses in the midfollicular and midluteal phases. The number of trials per condition that remained after artifact rejection at the Cz electrode site were as follows: gain follicular ($M = 29.93$, $SD = 0.34$), gain luteal ($M = 29.93$, $SD = 0.34$), loss follicular ($M = 29.86$, $SD = 47$), and loss luteal ($M = 29.98$, $SD = 0.15$). The RewP to gains and losses in each menstrual phase was quantified using temporospatial principal component analysis (PCA), a factor analytic approach used to parse the ERP waveform into underlying constituent components (Dien, 2010a; Proudfit, 2015). PCA examines variance across electrode sites and time points, thereby using all of the data to discern latent components that underlie traditional ERP averages. Consistent with previous research utilizing PCA for computing evoked potentials (Dien, 2010b; Foti, Hajcak, & Dien, 2009), promax rotation was used in the temporal domain, and 16 factors were extracted based on the resulting scree plot. Covariance matrix and Kaiser normalization were used for this PCA (Dien, Beal, & Berg, 2005). The spatial distribution of these temporal factors was then analyzed with spatial PCA using infomax rotation. The covariance matrix was used for this PCA. Based on the averaged scree plot for all 16 temporal factors, two spatial factors were extracted, yielding 32 factor combinations. Nineteen factors accounted for more than 1% of the variance and were retained for further inspection (Kaiser, 1960). One factor was temporally and spatially analogous to the ERP of interest in the current study, evident as a positivity peaking at the Cz electrode site at 290 ms, which was potentiated to gains and reduced to losses. Thus, these factor scores were included in subsequent analyses.

2.5 | Data analysis

To determine whether we correctly indexed the follicular and luteal phases, two repeated measures analyses of variance (ANOVAs) were conducted on progesterone and estradiol levels with menstrual phase (follicular vs. luteal) entered as a within-subject factor. A paired samples *t* test was conducted to determine whether depression symptoms differed between menstrual phase. To examine relations between depression score, menstrual cycle phase, and neural response to gains and losses, a repeated measures analysis of covariance (ANCOVA) was conducted on the traditional and PCA-derived ERP responses with menstrual cycle phase (follicular vs. luteal) and trial outcome (gain vs. loss) entered as within-subject factors, and depression score entered as a between-subjects covariate.

3 | RESULTS

3.1 | Hormones

Participants had higher estradiol ($M = 2.76$, $SD = 0.73$) and progesterone ($M = 355.63$, $SD = 191.08$) levels during the luteal phase compared to the follicular phase (estradiol: $M = 2.44$, $SD = 0.68$; progesterone: $M = 153.67$, $SD = 84.25$, $F(1, 39) = 6.93$, $p = 0.01$, $\eta_p^2 = 0.15$; $F(1, 41) = 64.50$, $p < 0.001$, $\eta_p^2 = 0.61$, respectively). Descriptive statistics for hormones and depressive symptom scores are presented in Table 1.

3.2 | Depression symptoms

Depressive symptoms were highly correlated between menstrual phases, $r(43) = 0.66$, $p < 0.001$, and did not differ overall between follicular ($M = 42.00$, $SD = 10.82$) and luteal phases ($M = 41.86$, $SD = 12.28$); $F(1, 42) = 0.009$, $p = 0.93$, $\eta_p^2 = 0.001$. Depression scores were unrelated to hormone levels (all $ps > 0.05$). Thus, depression symptoms were averaged between follicular and luteal phases for all subsequent analyses.

3.3 | ERPs, menstrual phase, and depression symptoms

A 2 (Outcome) × 2 (Menstrual Phase) repeated measures ANCOVA with depression score as a between-subjects covariate revealed no significant main effects of menstrual phase, $F(1, 41) = 3.32$, $p = 0.08$, $\eta_p^2 = 0.08$, nor feedback outcome, $F(1, 41) = 1.91$, $p = 0.17$, $\eta_p^2 = 0.05$. However, there was a significant interaction between menstrual phase, trial outcome, and depression score, $F(1, 41) = 5.41$, $p = 0.03$, $\eta_p^2 = 0.12$.[1] Figure 2 depicts the traditional and PCA-based ERP waveforms for gain and loss feedback outcomes in the follicular and luteal menstrual phases. Scalp difference maps contrasting gains and losses in each menstrual phase are depicted in Figure 3.

To probe this three-way interaction, two post hoc repeated measures ANCOVAs were conducted. The first examined effects of menstrual phase and depression score on the neural response to gain trials. The second ANCOVA examined the effects of menstrual phase and depression score on the neural response to loss trials. These analyses showed a significant interaction between menstrual phase and depression scores for gain trials, $F(1, 41) = 7.72$, $p = 0.008$, $\eta_p^2 = 0.16$, but not for loss trials, $F(1, 41) = 0.84$, $p = 0.37$, $\eta_p^2 = 0.02$.

To illustrate these interactions, depression symptoms were dichotomized using a median split (median = 41.00), and the ERP response to gains and losses in the follicular and luteal phases were graphed for those with low versus high depression symptoms. As evident from Figure 4, individuals

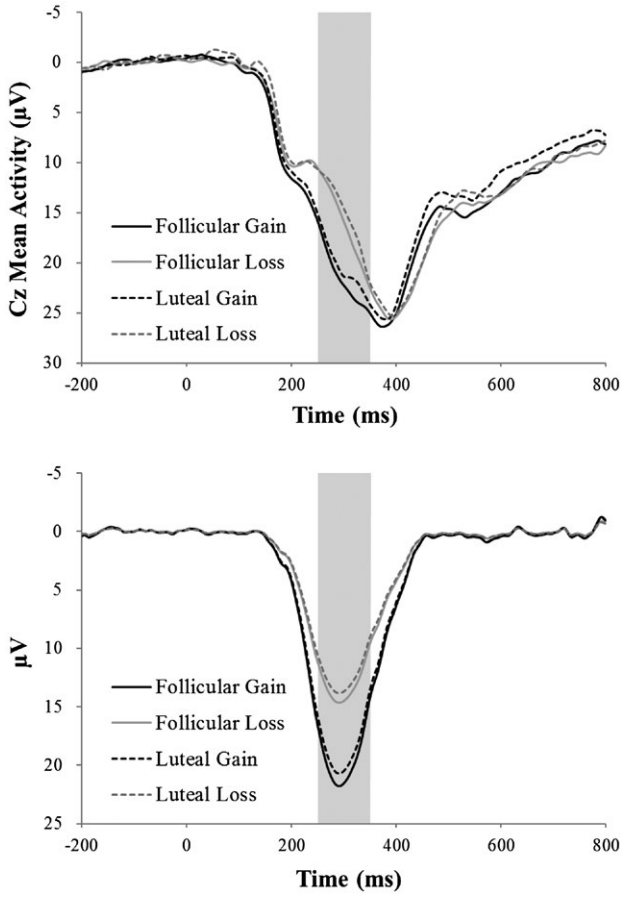

FIGURE 2 Feedback-locked raw ERPs (top) and PCA-derived ERPs (bottom) for gains and losses in the follicular and luteal phases. The ERP response is potentiated to gains compared to losses in both menstrual phases

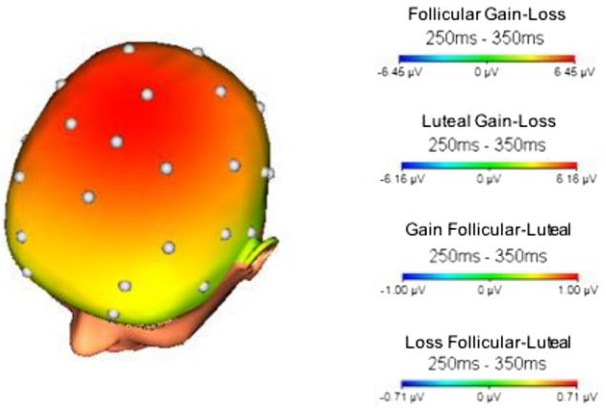

FIGURE 3 Topographic map for the temporospatial factor associated with the RewP (left). For each comparison, the scales presented give the microvolt range at the time of the maximum difference between conditions (right)

with high depression symptoms showed a reduced RewP to monetary gains in the luteal phase as compared to the follicular phase, while individuals with low depression symptoms showed minimal change in the ERP response to gains across menstrual phases.[2,3]

4 | DISCUSSION

The present study examined the impact of cyclic changes in ovarian hormones during the midfollicular versus midluteal phases of menstrual cycle on electrocortical measures in response to feedback indicating monetary gains and losses, and their relationship to depression symptoms. Results indicated that participants had higher levels of both estradiol and progesterone in the luteal phase as compared to the follicular phase. This finding is in line with previous work demonstrating that levels of progesterone and estradiol are both low in the early to midfollicular phase, and moderate to high in the midluteal phase (Farage et al., 2008).

The present study did not find a main effect of menstrual phase on RewP amplitude. This finding aligns with previous research that also failed to find differences in P300 amplitude as a function of menstrual phase (Fleck & Polich, 1988). However, results indicated that participants with high overall depression scores showed a reduced RewP to monetary gains in the luteal phase as compared to the follicular phase, whereas participants with low depression scores showed a similar RewP across menstrual phases. There was no relationship between depressive symptoms and changes in the neural response to loss. Thus, women with increased depressive symptoms had larger phase-related variation in neural response to reward. These results suggest that hormonal fluctuations associated with the menstrual cycle may impact neural response to reward—and that these cycle-related changes in neural response to reward may relate to depressive symptoms. While we did not find evidence for this mediation model, the current study may have not been adequately powered. Future studies should aim to test for mediation between similar variables with larger samples. Therefore, it could be the case that cycle-related variation in hormones between phases relates to depressive symptoms by inducing fluctuations in reward sensitivity. This may provide insight into mechanisms that cause women to be prone to mood disturbances in periods of high hormonal fluctuations, such as the premenstrual, postpartum, and menopausal periods.

Furthermore, participants high in depressive symptoms had a more positive ERP response to gain feedback during the follicular phase compared to the luteal phase. The direction of this finding is consistent with previous work—responsivity to reward stimuli is shown to be increased in the follicular phase due to presence of estradiol and lack of progesterone, whereas responsivity to reward stimuli is attenuated in the luteal phase, which is characterized by high progesterone and moderate to high estradiol (Dreher et al., 2007; Sakaki & Mather, 2012).

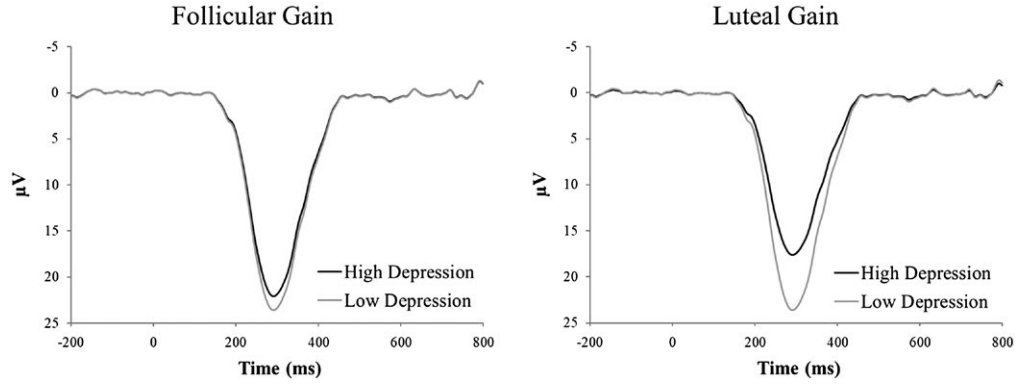

FIGURE 4 PCA-derived ERPs for monetary gains in the follicular (left) and luteal (right) phases in low and high depression groups. Individuals with high depression symptoms showed a reduced RewP to monetary gains in the luteal phase as compared to the follicular phase, while individuals with low depression symptoms showed minimal change in the ERP response to gains across menstrual phases

It is important to note that change in hormone levels between menstrual phases did not relate to change in RewP amplitude between phases. This could be due to a number of factors, such as our limited sample size, or limited variability in change in estradiol levels between phase ($M = -0.346$, $SD = 0.781$). Moreover, progesterone has been shown to counteract the effects of estradiol on mood and reward sensitivity (Sakaki & Mather, 2012), which could suggest that effects of estradiol may have been neutralized in the current study, which focused on the midluteal phase when progesterone was also high. Moreover, depressive symptoms did not show differences between follicular and luteal phases of the menstrual cycle. The IDAS-II assesses means levels of depressive symptoms over the past 2 weeks, which was the approximate duration between the two assessments. Thus, the IDAS may not have been sensitive to changes in depressive symptoms that fluctuate more rapidly.

Previous studies have found a reduced ERP response to rewards in those with higher risk for depression (Bress et al., 2013; Nelson et al., 2016; Proudfit, 2015). In the current study, a similar negative association between the ERP response to rewards and depressive symptoms was observed in the midluteal phase. The current results suggest that effects previously reported may depend partially on participant menstrual cycle phase at the time of testing. Future work in women of reproductive age may be able to account for more variance in the association between a reduced ERP response and depressive symptoms if menstrual phase or ovarian hormones are also examined.

While we interpret our results in the context of their relevance to reward sensitivity and depression, previous research investigating the RewP component (or, as it has been referred to previously, the feedback negativity, the feedback-related negativity, and the feedback error-related negativity) has suggested that the RewP is localized to the anterior cingulate cortex (ACC), and noted the role of the ACC in reinforcement learning, cognitive control, and motivation (Alexander & Brown, 2010; Holroyd & Yeung, 2012; Nieuwenhuis, Holroyd, Mol, & Coles, 2004). Specifically, the RewP is thought to reflect a reward prediction error signal originating in the ACC that codes whether outcomes are better or worse than expected, facilitating adaptive reinforcement learning and goal-directed behavior (Holroyd & Coles, 2002; Holroyd et al., 2008; Sambrook & Goslin, 2015; Walsh & Anderson, 2012). Within this framework, the current results suggest that level of depression may moderate the impact of menstrual cycle phase on reinforcement learning, which could potentially influence one's ability to engage in adaptive goal-directed behavior in response to feedback. Future studies might test this possibility by employing reinforcement learning paradigms such as the monetary incentive delay task or the probabilistic reward task (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). Employing these tasks would allow for the study of behavioral measures of reward sensitivity in relation to hormones and menstrual phase, as both paradigms have well-validated behavioral measures to assess reward sensitivity.

The present study had several limitations that warrant consideration. First, the sample was limited to college students and the results may not generalize to older or younger populations of women. Second, previous research suggests a role for the ACC in pain perception and regulation (Hutchinson, Davis, Lozano, Tasker, & Dostrovsky, 1999; Lenz et al., 1998; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Measures of menstrual-related and other pain at the time of testing were not collected in the current study. Thus, it may be possible that ACC perception and regulation of cycle-related and unrelated pain could have impacted ERP responses to monetary gain and loss in each of the two cycle phases differentially. Future studies should aim to record self-reported levels of pain for use in analysis. Third, the current sample was comprised of women not on hormonal contraceptives, who may be less likely to be sexually active. The current study did not collect data on sexual activity. Given prior research linking sexual

activity to greater psychological well-being (Ganong & Larson, 2011), future studies should consider samples that vary in levels of sexual activity or measure this variable. Additionally, although hormone measures were used to verify that assessments of early follicular and midluteal phases were correctly timed, the current study did not include other biological indicators of menstrual cycle phase. Accurate classification of menstrual cycle phases can be done through ovulation kits, which often involve urine sampling (Poromaa & Gingnell, 2014). Future studies may wish to employ multiple biological measures of menstrual phase to confirm accurate timing of assessments.

There are multiple possible future directions. First, the study should be extended to women from older age groups to determine whether these effects persist throughout adulthood. Second, following participants for multiple cycles or years would allow for a more fine-grained understanding of the intrasubject relationship between hormone levels and reward sensitivity—and how that variability relates to depression. Third, it might be important to examine hormones, ERPs, and depressive symptoms in the late follicular phase, which is characterized by high levels of estradiol unopposed by progesterone—a state that may have different effects on reward responsivity and mood (Sakaki & Mather, 2012). Fourth, future studies could utilize a self-report measure with greater temporal precision, such as ecological momentary assessment measures of emotion, to detect short-term variation in mood across menstrual phases. Finally, it would be worthwhile to carry out a similar study in adolescent girls. Adolescence is associated with increased rates and risk for depression, as well as the onset of menses. Having a better understanding of how hormonal changes impact mood through changes in neural response to reward could have implications for research on risk for the development of depression.

ENDNOTES

[1]In the traditional ERP data (non-PCA based), scored at the Cz electrode site between 250–350 ms, these effects replicated such that there were no significant main effects of menstrual phase, $F(1, 41) = 3.08$, $p = 0.08$, $\eta_p^2 = 0.07$, nor feedback outcome, $F(1, 41) = 0.64$, $p = 0.43$, $\eta_p^2 = 0.02$, but there was a significant three-way interaction between menstrual phase, feedback outcome, and depression score, $F(1, 41) = 4.56$, $p = 0.04$, $\eta_p^2 = 0.10$. Non-PCA based ERPs were scored at Cz because it is the site at which the PCA-derived RewP has been found to be maximal.

[2]Estradiol and progesterone levels were unrelated to traditional and PCA-derived RewP amplitude in the follicular and luteal phases (all *p*s>0.05).

[3]To examine whether the RewP to gain trials mediated a relationship between hormone levels and depression, we also tested two mediation models (one including estradiol and one including progesterone). Specifically, the models examined whether change in the RewP to gains between phase (i.e., follicular ERP to gains minus luteal ERP to gains, or ΔRewP) mediated a relationship between change in hormone level between phase (e.g., follicular progesterone minus luteal progesterone, or Δprogesterone) and depression score. For the mediation analyses, variables were entered into Model 4 of the PROCESS Macro for SPSS (Preacher & Hayes, 2004). In the analysis including progesterone, the results indicated that the indirect effect of Δprogesterone, mediated through ΔRewP, on depression score was not significant, $b = 0.001$ (95% CI: −0.007 to 0.008). In the analysis including estradiol, results indicated that the indirect effect of Δestradiol, mediated through ΔRewP, on depression score was also not significant, $b = -1.15$ (95% CI: −4.01 to 0.35).

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