Hormonal status effects on the electrophysiological correlates of performance monitoring in women

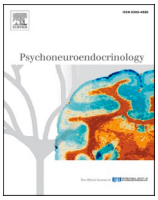
Jansen, M.; Does, A.J.W. van der; Rover, M. de; Bruijn, E.R.A. de; Hamstra, D.A.

Psychoneuroendocrinology 149 (2023) 106006

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Hormonal status effects on the electrophysiological correlates of performance monitoring in women

M. Jansen [a,b,*], A.J.W. Van der Does [a,b], M. De Rover [a,b], E.R.A. De Bruijn [a,b], D.A. Hamstra [a,b]

[a] Department of Clinical Psychology, Leiden University, the Netherlands
[b] Leiden Institute for Brain and Cognition (LIBC), Leiden, the Netherlands

ARTICLE INFO

Keywords:
Error-related negativity (ERN)
Error positivity (Pe)
Electrophysiological performance monitoring
Menstrual cycle
Ovarian hormones
Negative affect

ABSTRACT

Fluctuations in ovarian hormones are thought to play a role in the increased prevalence of mood and anxiety disorders in women. Error-related negativity (ERN) and error positivity (Pe) are two putative electrophysiological biomarkers for these internalizing disorders. We investigated whether female hormonal status, specifically menstrual cycle phase and oral contraceptive (OC) use, impact ERN and Pe. Additionally, we examined whether the relationship between the ERN and negative affect (NA) was moderated by hormonal status and tested whether the ERN mediated the relation between ovarian hormones and NA. Participants were healthy, pre-menopausal women who were naturally cycling (NC) or using OCs. Using a counterbalanced within-subject design, all participants performed a speeded-choice reaction-time task twice while undergoing electroencephalography measurements. NC women (N = 42) performed this task during the early follicular and midluteal phase (when estrogen and progesterone are both low and both high, respectively), while OC users (N = 42) performed the task during active OC use and during their pill-free week. Estradiol and progesterone levels were assessed in saliva. Comparing the two cycle phases within NC women revealed no differences in the (Δ)ERN, (Δ)Pe or NA. We did observe a negative relation between phase-related changes in the ΔERN and changes in NA. Mediation analysis additionally showed that phase-related changes in estradiol were indirectly and negatively related to NA through a reduction of ΔERN amplitudes. When comparing active OC users with NC women, we observed increased ΔPe- but not (Δ)ERN amplitudes in the former group. No evidence was found for moderating effects of menstrual cycle phase or OC use on the relation between the ERN and NA. These findings suggest that hormonal status may impact the neural correlates of performance monitoring and error sensitivity, and that this could be a potential mechanism through which ovarian hormones influence mood.

1. Introduction

During their reproductive years, women are twice as likely as men to be diagnosed with an internalizing disorder. The potential role of ovarian hormones has long been investigated (Altemus et al., 2014). Ovarian hormones have widespread effects on brain structure and function (Beltz and Moser, 2020). Receptors for estrogen and progesterone, the main ovarian hormones, are localized in various brain regions critical for emotion regulation and cognitive functioning, such as the amygdala, hypothalamus, cerebral cortex and hippocampus. These hormones interact with many neurochemical systems (Barth et al., 2015) and influence various emotional, cognitive, and neural processes (see e.g., Dubol et al., 2021; Hamstra, 2021; Toffoletto et al., 2014). Ovarian hormone levels importantly fluctuate during the female menstrual cycle, which is often divided in the follicular and luteal phase, each typically 14 days in length. The follicular phase begins with menses, where levels of estrogen and progesterone are low, and ends with a sharp rise in estrogen in the late follicular phase leading to ovulation. The following luteal phase is characterized by a peak of estrogen and progesterone in the midluteal phase, and relatively lower levels of these hormones in the early- and late luteal phase. Although findings are mixed, periods where estrogen is high have mostly been linked to positive mood states and to improved performance on emotion-related cognition, whereas progesterone and the (mid- and late) luteal phase of the menstrual cycle have been linked to negative mood, heightened emotional reactivity and poorer (emotion-related) cognitive performance (see e.g., reviews by Le et al., 2020; Sundström Poromaa, 2018; Sundström Poromaa and Gingnell, 2014). Importantly,

* Correspondence to: Department of Clinical Psychology, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, the Netherlands.
E-mail address: m.jansen@fsw.leidenuniv.nl (M. Jansen).

https://doi.org/10.1016/j.psyneuen.2022.106006
Received 12 September 2022; Received in revised form 11 November 2022; Accepted 13 December 2022
Available online 15 December 2022

the suppression of endogeneous hormones during oral contraceptive (OC) use has also been associated with a wide range of effects on social and emotional behavior, brain function, and cognitive performance including increased anxiety, emotional reactivity, and mood swings (Sundström Poromaa and Segebladh, 2012). Yet, the direction of OC effects seems to be rather inconsistent, with studies showing adverse, protective or no effects (see e.g., Brønnick et al., 2020; Hamstra, 2021; Lewis et al., 2019; Montoya and Bos, 2017; Pletzer and Kerschbaum, 2014; Toffoletto et al., 2014; Welling, 2013). Hence, although literature suggests that alterations in endogenous sex hormones across the menstrual cycle and during OC use may affect symptoms of internalizing disorders, the inconsistent effects warrant further research into the underlying mechanisms.

Importantly, internalizing disorders are associated with altered amplitudes of two event-related potential (ERP) components associated with error detection and performance monitoring (Lutz et al., 2021; Pasion and Barbosa, 2019; Riesel, 2019). These are the error-related negativity (ERN) and error positivity (Pe). The ERN is characterized by a negative frontocentral deflection occurring 50–100 ms after an incorrect response (Gehring et al., 1993; Falkenstein et al., 1991). The component is thought to result from dopamine-driven prediction errors generated in the anterior midcingulate cortex and has been linked to behavioral adjustments and learning (for a theoretical overview see Ullsperger et al., 2014b). The ERN has been suggested to reflect the integration of threat, pain and punishment information as it seems to be sensitive to affective and motivational factors (de Bruijn et al., 2020; Meyer, 2016; Proudfit et al., 2013; Riesel et al., 2012; Shackman et al., 2011). Interestingly, ERNs are enhanced in internalizing disorders but reduced in externalizing disorders (de Bruijn et al., 2006; Lutz et al., 2021; Lutz et al., 2021; Pasion and Barbosa, 2019). This may reflect an increased threat sensitivity and error aversion in internalizing populations (Weinberg et al., 2016) and the inability to inhibit or change disruptive and maladaptive behavior in externalizing disorders (Lutz et al., 2021; Pasion and Barbosa, 2019). The ERN is followed by the Pe, which is a positive component often divided in an early and a late part (Ullsperger et al., 2014a). Relative to the ERN, the functional significance of the Pe is more unclear. Some research suggests that the early Pe is closely linked to the automatic processing of errors and shares the same neural generators as the ERN while the late Pe is believed to be involved in the more conscious or affective processing of errors (Ullsperger et al., 2014a), and there is evidence that this component is altered in externalizing disorders as well (Brazil et al., 2009; Lutz et al., 2021). These findings have led to the suggestion that the ERN and Pe may represent candidate biomarkers for internalizing versus externalizing disorders (Lutz et al., 2021; Pasion and Barbosa, 2019; Riesel et al., 2019). However, before the ERN and Pe can be used as biomarkers, it is essential to establish the contextual factors that may modulate their amplitude.

Given the link between menstrual cycle phase and OC use and symptoms of internalizing disorders and the putative role of the ERN and Pe as biomarkers for internalizing disorders, assessing the potential impact of ovarian hormones on these components is of critical importance. A recent study found that ERNs had a significant positive association with checking symptoms in the luteal but not follicular phase (Mulligan et al., 2019), while another study found that OCs modulated the relation between the ERN and worrying, such that this relation was stronger in OC users (Louis et al., 2022). This may suggest that rather than impacting the ERN or internalizing symptoms directly, menstrual cycle phase and OC use may also modulate the relation between the ERN and internalizing symptoms. Mulligan et al. (2019) additionally found that the ERN mediated the relation between ovarian hormones and checking symptoms, which importantly indicates that increased performance monitoring as indexed by the ERN may represent a mechanistic pathway through which ovarian hormones influence symptoms of internalizing disorders.

Hence, the current study set out to investigate whether performance monitoring is modulated by ovarian hormones, specifically menstrual cycle phase and OC use. Using a within-subject design, we compared naturally-cycling (NC) women in the early follicular (day 2–6) and during the midluteal phase (3–10 days prior to onset of a new cycle), when estrogen and progesterone are both low and both high, respectively. Additionally, we compared NC women with users of the most commonly used monophasic, second-generation OCs, which contain the synthetic estrogen ethynylestradiol and the synthetic progesterone levonorgestrel (Lewis et al., 2019). In counterbalanced order, participants performed a speeded-choice test (Flanker task; Eriksen and Eriksen, 1974) and provided saliva samples to measure progesterone and estradiol levels. Both the midluteal phase and OC use have been associated with negative symptoms such as heightened anxiety, negative mood and emotional reactivity (Sundström Poromaa and Gingnell, 2014). Since these are factors associated with heightened performance monitoring, we hypothesized enhanced ERN and Pe amplitudes compared to the early follicular phase.

Additionally, given previous indications that the relation between the ERN and internalizing symptoms is dependent on menstrual cycle phase (Mulligan et al., 2019) and OC use (Louis et al., 2022), we also explored whether menstrual cycle phase and OC use moderated relation between the ERN and negative affect (NA). NA is a construct thought to characterize both depression and anxiety (Crawford and Henry, 2004), and we expected the relationship between the ERN and NA to be more pronounced in the midluteal phase and during OC use. Furthermore, based on evidence that the ERN mediated the relation between ovarian hormones and checking symptoms (Mulligan et al., 2019), we tested whether the ERN mediates the relation between ovarian hormones and NA in NC participants. Here, we expected progesterone levels to be positively- and estradiol to be negatively associated with NA.

2. Method

2.1. Participants

Data were collected from May 2016 until April 2017 at Leiden University. Healthy, Dutch speaking, right-handed female students of Northwestern European origin between the age of 18 and 35 were recruited for the study through advertisements on social media and the university campus. NC participants had to have a regular menstrual cycle between 25 and 35 days and not have used any OCs in the past three months. OC users were eligible if they used second generation monophasic OCs containing Ethinylestradiol (EE; 0.03 mg)/ Levonorgestrel (LNG; 0.15 mg) for at least three months and agreed to apply a pill-free week. Additional exclusion criteria were: physical or neurological illness, pregnancy; lactation; use of abortifacients in the past 3 months; current or past psychiatric illness as determined by the MINI International Neuropsychiatric Interview (Van Vliet and De Beurs, 2007); premenstrual syndrome as assessed by the Menstrual Distress Questionnaire (Moos, 1968); excessive alcohol use (>14 units per week); smoking; regular soft- or hard-drug use; and using prescribed medication. Participants completed the experiment for course credits or monetary compensation and provided written informed consent. The study was approved by the ethics committee of the Institute of Psychology at Leiden University (approval number: CEP16–0318/139).

2.2. Flanker task

Participants performed a letter version of the Flanker task (Eriksen and Eriksen, 1974) derived from previous work (de Rover et al., 2015). The goal of this task is to respond as fast as possible with a left or right button press according to the identity of the middle of a set of five letters presented on the screen, whereby surrounding letters could be either congruent (HHHHH and SSSSS) or incongruent (HHSHH and SSHSS). These four sets were presented in a randomized order across six blocks of 80 trials each. Each trial started with a white fixation cross presented on

a grey blackground for 500 ms. This was followed by the presentation of the stimulus for 100 ms, after which an empty grey screen was shown until a button was pressed. Verbal feedback was given in between blocks encouraging participants to either speed up of slow down their responses, in order to maintain an accuracy rate around 80%.

2.3. Negative affect

The Positive and Negative Affect Schedule (PANAS) was assessed to measure state affect or mood (Watson et al., 1988). This self-report questionnaire consists of a positive and negative subscale containing 10 items each. The current version ('right now') was used.

2.4. Other measures

The NEO Five-Factor Inventory (NEO-FFI) measures personality traits (Costa and McCrae, 1989) and the revised version of the Leiden Index of Depression Sensitivity (LEIDS-R) assesses cognitive reactivity to sad mood, a measure of cognitive susceptibility to depression (Solis et al., 2017).

2.5. Experimental procedure

Upon showing interest in the study, participants received an online screening questionnaire via Qualtrics assessing the inclusion criteria. If they met criteria for the study, a telephonic screening was carried out to asses the MINI and to schedule the two laboratory sessions. NC women were tested during the early follicular phase (day 2–6) and during the midluteal phase (3–10 days prior to onset of new cycle). OC users were tested during active use (day 8–14) and during their pill-free week (day 4–7). The order in which each phase was assessed was counterbalanced across participants. All sessions started between 8:30 AM and 5:30 PM. During the first session participants signed informed consent and completed the NEO-FFI and the LEIDS-R (see measures). In each session adherence to the inclusion criteria was checked first after which participants completed several tasks and questionnaires including the Flanker task and PANAS. At three different timepoints during the session saliva was collected (see hormonal assessment section). After the two lab sessions, participants sent a text message to the experimenter at the onset of their next cycle (or first day of new pill strip for OC users), to confirm that participants had been tested at the right moment using reverse day counting (Hampson, 2020).

2.6. Hormonal assessment

Progesterone, estradiol and estriol (to check for pregnancy) were measured in saliva. Participants were instructed to not eat, drink anything other than water or chew gum for 30 min before the start of each session. Participants rinsed their mouth with water and then spit 1 ml saliva into a sterile tube (SaliCap Sets; Innovation Beyond Limits, Hamburg, Germany) at three different time points with at least 30 min interval. Samples were immediately stored and kept frozen at − 20 °C until the day of assaying. The three samples were pooled and analyzed with highly sensitive luminescence assays of IBL at Ganzimmun Diagnostics AG. Reference values of free estradiol (E2) in saliva were: follicular phase 0.2–10.4 pg/ml; luteal phase 0.8–10.8 pg/ml. For free progesterone (P4) in saliva: follicular phase 28–82 pg/ml; luteal phase 127–445 pg/ml; OC: 18–51 pg/ml.

2.7. Electrophysiological recordings and pre-processing

The EEG signal was recorded from 15 Ag/AgCl scalp electrodes (F3, FZ, F4, CZ, CP1, CP2, P3, P1, PZ, P4, PO3, PO4, OZ) and from the left and right mastoids. Vertical and horizontal eye EOGs were recorded from electrodes above and below the right eye and at the outer canthi of the eyes, respectively. Electrodes were referenced to common mode sense (CMS) during data acquisition, and afterwards re-referenced to the average of both mastoids. Data were further processed and analyzed using Brain Vision Analyzer version 2 (Brain Products, Munich, Germany) using the preprocessing steps and settings as described in Jansen and de Bruijn (2020).

Based on previous research indicating that different quantification methods can impact the association between ERPs and individual differences (Klawohn et al., 2020), we used both a simple and difference (Δ) measure quantification for each ERP component. The simple ERN was quantified as peak-to-peak amplitude at electrode Cz for correct and incorrect trials separately by subtracting the most positive peak in the − 80–80 ms time window from the most negative peak in the 0–150 ms time window (cf. Jansen and de Bruijn, 2020). The ΔERN was calculated by substracting the waveforms for correct trials from the waveforms on error trials and then taking the most negative peak (Chong and Meyer, 2019; Klawohn et al., 2020) in the 0–150 ms time window. The early Pe was defined as the most positive peak in the 150–250 ms time window at electrode Cz, while the late Pe was defined as the mean activation in the 300–500 ms time window at electrode Pz (cf. de Bruijn et al., 2017; Jansen and de Bruijn, 2020). The early and late ΔPe were calculated by substracting the waveforms for correct trials from the waveforms on error trials and then quantified according to their respective definitions as described above. In line with earlier work (Jansen and de Bruijn, 2020; Riesel et al., 2017; Riesel et al., 2019) a time interval of 20 ms around each peak ERP measure was taken in order to reduce the influence of background EEG noise (Clayson et al., 2013).

2.8. Statistical analyses

Separate analyses were carried out to investigate the effects of menstrual cycle phase and OC use. Within NC participants, we compared the early follicular phase with the midluteal phase (model 1). Since hormonal levels did not significantly differ between active and inactive OC use (i.e., the pill-free week), we did not explore within-subject differences for OC users. Additionally, we examined between-subject differences by comparing NCs in their early follicular and midluteal phase with active OC users (model 2 and model 3, respectively), under the assumption that hormonal levels are most stable during the active intake of OCs. Model 1 always included the within-subject factor 'hormonal phase' (early follicular versus midluteal) while models 2 and 3 included the between-subject factor 'OC group' (users/non-users).

The presence of standard behavioral Flanker effects was investigated using repeated measures ANOVAs. Trials with too slow (>800 ms) or no responses were removed from the dataset (0.6% of all trials). The first analysis included the within-subject factors congruency (congruent vs incongruent) for reaction times to correct responses only, alongside the hormonal factors. The same factors were used to investigate the error rates. To investigate differences between erroneous and correct trials, reaction times were analyzed using the within-subject factors correctness (correct vs error). Since erroneous responses to congruent trials are rare, this analysis was performed on incongruent trials only. Post-error slowing, the phenomenon of slowing down after the commission of an error (PES; (Rabbitt, 1966), was quantified in accordance with Dutilh et al. (2012) and assessed using PES (pre-error vs post-error reaction time) as within-subject variable.

To investigate mean differences in ERP amplitudes between hormonal phases and between users and non-users of OCs, we conducted repeated measures ANOVAs with correctness as within-subject factor. In line with our previous work (e.g., de Bruijn et al., 2020; de Bruijn et al., 2017; Jansen and de Bruijn, 2020), we analysed incongruent trials only.

Difference ERPs (ΔERN, early ΔPe, late ΔPe) were analysed using either paired (model 1) or independent t-tests (models 2 and 3). In case of sphericity violation, Greenhouse-Geisser corrections were applied.

In line with previous work (Mulligan et al., 2019), we examined the association between the ΔERN and negative affect per hormonal phase separately as well as across phases using Pearson correlations. In case of

a significant phase-dependent relation between the ΔERN and negative affect, we additionally tested whether the ERN would act as a mediator between ovarian hormones and negative affect using model 4 (simple mediation) of the PROCESS macro for SPSS (Preacher and Hayes, 2004). Additionally, we used linear mixed models (LMMs) using the lme4 package (Bates et al., 2014) to formally test whether hormonal phase and OC status modulated the relation between negative affect and the ERN. In these models, the ERN was the outcome variable. Correctness, hormonal phase and OC group were deviation-coded (−0.5 vs 0.5) predictors, whereas negative affect was a grand mean-centered continuous predictor. The random-effects structure for each model was determined according to the procedure described in Bates et al. (2015). Each model included random intercepts for participants. The final phase model included independent random slopes for phase and correctness (ERN ~ negative affect*phase*correctness + (1 +phase+correctness|| ID), while the final OC status model included an independent slope for correctness (ERN ~ negative affect*OC group*correctness + (1 +correctness||ID). ANOVA tests and partial eta squared (ηp^2) estimates were provided using the anova_stats function from the sjstats package (Lüdecke and Lüdecke, 2019).

3. Results

3.1. Participant characteristics

A total of 107 women signed informed consent. After inclusion, 19 participants were excluded due to one of the following reasons: substance use (n = 6), drop-out (n = 3), change of hormonal status (n = 2), tested on wrong cycle day (n = 7), cycle length of more than 35 days (n = 1). After data collection, three participants were excluded because behavioral or EEG data for one of the sessions was missing due to technical reasons. One participant was excluded for having committed too many mistakes on the Flanker task (>45% for incongruent trials + >25% for congruent trials), leaving a final sample of 84 participants for analysis. Table 1 displays the background characteristics for the NC participants and OC users separately. No significant differences were found between the groups with regard to age, personality dimensions (NEO-FFI) or depression susceptibility (LEIDS-R).

3.2. Hormonal concentrations and mood states

Table 2 shows hormonal levels and mood states across the phases for each group separately. Hormonal assessment failed for one NC participant in the early follicular phase. As expected, progesterone and estradiol levels were significantly higher during the midluteal phase than during the early follicular phase, $F(1,40) = 25.93$, $p < .001$, $\eta p^2 = .39$ and $F(1,40) = 5.88$, $p = .02$, $\eta p^2 = .13$, respectively, while for OC users no difference was found between inactive and active OC use ($p = .69$ and $p = .70$, respectively). Additionally, both progesterone and estradiol were significantly higher in NC participants in the midluteal phase compared to active OC users, $t(82) = 6.28$, $p < .001$ and $t(82) = 5.09$, $p < .001$, respectively. Estradiol levels were also significantly higher for NC participants in the early follicular phase compared to active OC users, $t(81) = 2.08$, $p = .04$, while progesterone levels were not ($p = .19$). No significant differences in positive and negative affect as assessed by the PANAS were found between hormonal phases or OC groups (*ps* > 0.17 and >0.13, respectively).

Table 1
Background characteristics (means and SDs) separately for naturally cycling participants and oral contraceptive users.

		Naturally cycling participants	Oral contraceptive users	*p*-value
Session order (AB / BA), *N* per group		22 / 20	22 / 20	1.00
Age		21.83 (1.90)	22.14 (1.72)	0.436
NEO-FFI	*Agreeableness*	33.67 (3.59)	34.60 (4.02)	0.267
	Conscientiousness	40.50 (3.05)	40.64 (3.17)	0.834
	Extraversion	43.52 (6.06)	44.14 (4.81)	0.605
	Neuroticism	32.69 (6.68)	30.02 (6.53)	0.068
	Openness	33.62 (3.24)	34.00 (3.79)	0.622
LEIDS-R		39.05 (15.14)	37.83 (11.99)	0.685

Note. NEO-FFI = NEO Five-Factor Inventory; LEIDS-R = Leiden Index of Depression Sensitivity.

3.3. Behavioral data

Table 3 displays means and standard deviations for the behavioral data. All behavioral analyses showed the expected flanker effects (faster responses for congruent [vs incongruent] and error [vs correct] trials, post-error slowing, lower error rates for congruent [vs incongruent] trials), all *ps* < 0.001.

Analysis of behavioral performance did not reveal any significant effects of hormonal cycle phase or OC group (Fs < 2.86, ps >0.10), except for a significant between-subject effect indicating that active OC users had faster reaction times than NC participants in the midluteal phase ($F(1,82) = 4.47$, $p = .04$, $\eta p^2 = .05$; $F(1,82) = 4.67$, $p = .03$, $\eta p^2 = .05$, and $F(1,82) = 3.46$, $p = .07$, $\eta p^2 = .04$ for the analysis investigating the correctness, congruency and PES effect respectively).

3.4. ERP data

Fig. 1 and Table 3 shows the response-locked ERPs and mean amplitudes, respectively, of the ERN as well as the early- and late Pe for each hormonal phase and group. All models showed the expected main effects of correctness, all *ps* < 0.004, with more negative amplitudes for errors compared to correct responses.

3.4.1. ERP findings in naturally-cycling participants

3.4.1.1. Main ERP effects of menstrual cycle phase. Analysis of the ERN revealed no significant effects of hormonal cycle phase, as indicated by non-significant main and interaction effects of hormonal phase (main effect of phase: $F(1,41) = 0.34$, $p = .57$, $\eta p^2 = .01$, $p = .66$ for ΔERN; phase* correctness: $F(1,41) = 0.52$, $p = .47$, $\eta p^2 = .01$).

Similarly, effects of hormonal cycle phase were observed neither for the early Pe (main effect of phase, $F(1,41) = 0.07$, $p = .79$, $\eta p^2 = .00$, $p = .45$; phase*correctness, $F(1,41) = 0.06$, $p = .81$, $\eta p^2 = .00$) nor for the late Pe (main effect of phase: $F(1,41) = 0.17$, $p = .68$, $\eta p^2 = .00$, $p = .69$; phase*correctness: $F(1,41) = 0.16$, $p = .69$, $\eta p2 = 0.00$).

3.4.1.2. Examining phase-related associations between the ERN and negative affect. In line with previous work (Mulligan et al., 2019), we explored whether the associations between negative affect and the ΔERN would be dependent on menstrual cycle phase. We did not find a significant relation between negative affect in the early follicular phase and the ΔERN in the same phase ($r_{(42)} = 0.13$, $p = .41$), nor between negative affect and the ΔERN in the midluteal phase ($r_{(42)} = 0.02$, $p = .90$). To formally test for a moderation effect we additionally applied a linear mixed model (ERN ~ negative affect x phase x correctness). This model did not provide evidence for a moderating effect of phase on the association between negative affect and the ERN, as indicated by a non-significant interaction between phase, negative affect, and correctness ($F(1,46.64) = 1.32$, $p = .26$, $\eta p^2 = .01$).

Also in line with Mulligan et al. (2019), we furthermore examined the possibility that individual changes between phases in the ΔERN and negative affect would be associated with each other. Here, we observed a significant correlation between the change in negative affect between phases (midluteal – early follicular) and the ΔERN (midluteal – early follicular): $r_{(42)} = -.37$, $p =$[0.02 indicating that an increase in the size

Table 2
Hormonal levels (pg/ml) and positive and negative affect for each hormonal phase and group (means and SDs).

		Naturally cycling participants		Oral contraceptive users	
		Early follicular	Midluteal	Active OC-use	Inactive OC-use
Hormones	*Progesterone*	81.20 (75.46)	204.05 (134.75)	62.95 (48.57)	58.02 (67.60)
	Estradiol	3.00 (2.25)	3.87 (1.51)	2.17 (1.29)	2.07 (1.73)
PANAS	*Positive affect*	24.05 (5.71)	24.98 (5.18)	25.98 (5.80)	25.71 (5.77)
	Negative affect	13.48 (3.88)	12.79 (3.79)	12.43 (2.42)	11.98 (2.04)

Note. OC = Oral contraceptive; PANAS = Positive and Negative Affect Schedule.

Table 3
Behavioral and event-related potential data for each hormonal phase and group (means and SDs).

		Naturally cycling participants		Oral contraceptive users	
		Early follicular	Midluteal	Active OC-use	Inactive OC-use
Reaction times (ms)	*Congruent correct*	356 (34)	357 (28)	344 (26)	338 (23)
	Incongruent correct	374 (40)	377 (35)	362 (33)	377 (35)
	Incongruent error	309 (34)	314 (34)	301 (29)	292 (27)
	Pre-error	348 (27)	352 (27)	340 (27)	332 (25)
	Post-error	385 (51)	381 (38)	368 (41)	358 (34)
Error rates (%)	*Congruent*	8.50 (4.20)	8.79 (4.43)	9.68 (5.10)	10.63 (5.30)
	Incongruent	15.64 (6.27)	16.20 (7.13)	17.08 (7.13)	17.66 (6.87)
ERN at Cz (μV)	*Correct*	-2.46 (1.97)	-2.45 (1.81)	-3.40 (2.48)	-2.97 (2.25)
	Error	-8.32 (4.49)	-8.81 (4.96)	-9.72 (5.66)	-8.96 (4.96)
Early Pe at Cz (μV)	*Correct*	3.03 (3.41)	3.15 (4.16)	1.92 (3.28)	2.71 (3.66)
	Error	4.87 (5.98)	5.18 (7.41)	6.23 (5.89)	6.04 (7.28)
Late Pe at Pz (μV)	*Correct*	-0.96 (3.42)	-1.36 (3.25)	-2.62 (4.20)	-1.63 (3.96)
	Error	1.10 (3.78)	1.10 (4.17)	1.81 (4.52)	1.40 (4.30)
Δ ERN at Cz (μV)		-7.32 (5.14)	-7.65 (5.26)	-6.93 (4.25)	-7.46 (4.78)
Δ Early Pe at Cz (μV)		3.43 (5.57)	4.21 (6.83)	6.86 (6.76)	5.53 (7.18)
Δ Late Pe at Pz (μV)		2.07 (4.55)	2.46 (4.46)	4.43 (6.15)	3.03 (5.31)

Note. ERN = Error-related negativity;Pe = Error positivity; OC = Oral contraceptive.

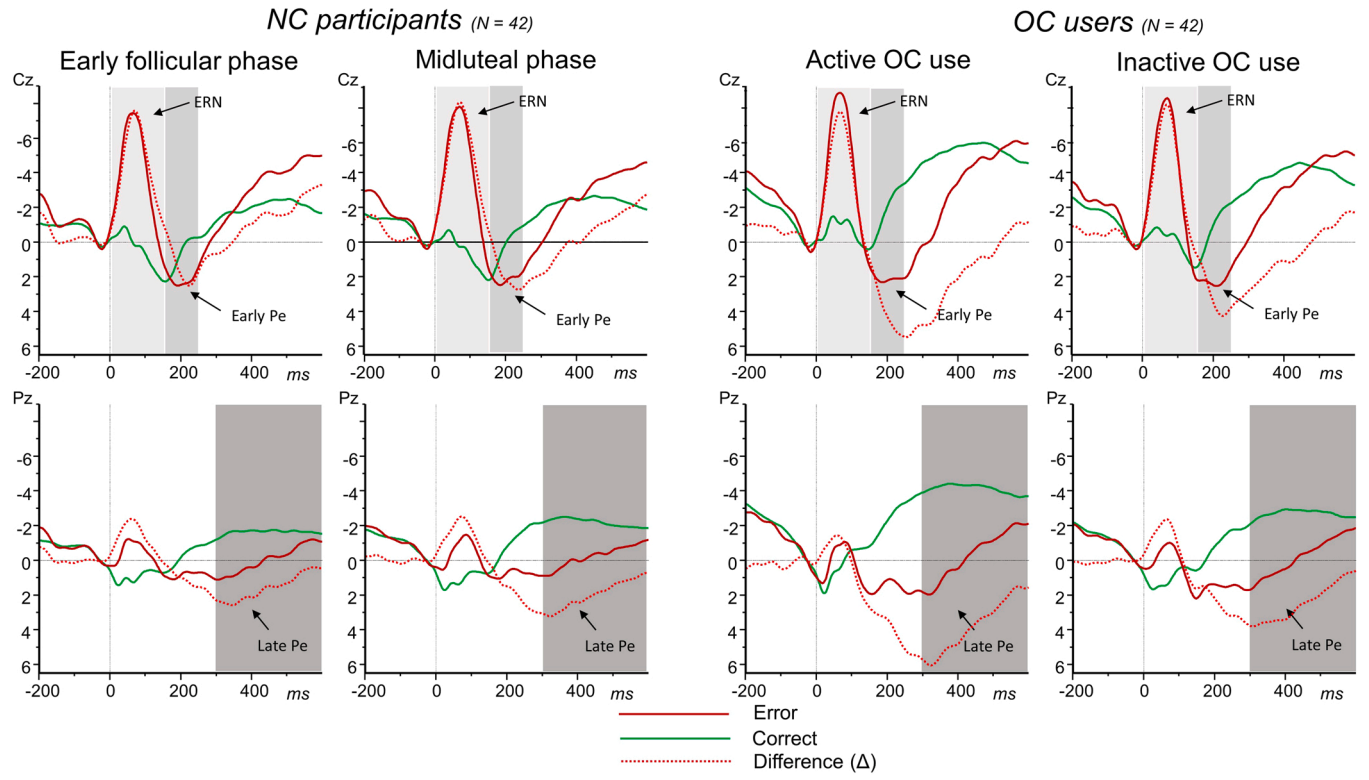


Fig. 1. Response-locked grand averages at electrode Cz and Pz (μV) for each hormonal phase and group. The figure displays the error-related negativity (ERN) and the early- and late error positivity (Pe) for naturally cycling (NC) participants in their early follicular and midluteal phase (left panel), and for oral contraceptive (OC) users during their active and inactive OC use (right panel). Grey blocks indicate the time windows employed for the quantification of each component at the relevant electrodes. Note that an additional baseline correction (−50 to 0 ms) was applied for visual representation only.

of the ΔERN (i.e., a more negative ΔERN) from the early follicular to the midluteal phase was associated with an increase in negative affect, and vice versa. See Fig. 2 for a depiction of this correlation. The association remained significant after removing one outlying value on negative affect ($r_{(41)} = -.36$, p =[0.02.

3.4.1.3. Examining the ERN as a mediator between hormones and negative affect. Given the above association between phase-related changes in the ΔERN and negative affect, we additionally explored a mediation model whereby we tested whether the ΔERN would mediate the relation between changes in hormonal levels and negative affect across phases, in line with previous studies (Mulligan et al., 2019; Mulligan et al., 2018). We first tested whether changes in the ΔERN across phases would mediate the relation between changes in *progesterone* and negative affect. Except for the path from ΔERN to negative affect ($b = -.25$, *SE* ==0.10 $t(38) = -2.52$, p =[0.02 95% CI [− .46, −[0.05, none of the paths reached significance, all *p*s > 0.15.

Next, we tested the pathway from *estradiol* to negative affect via the ΔERN. The direct pathway (c') from estradiol to negative affect was not significant, b= −−0.07 *SE* =[0.23 $t(38) = --0.32$ p =[0.75 95% CI [− .53,0.39. However, the a-path from estradiol to the ΔERN was significant, b =[0.81 *SE* =[0.30 $t(39) = 2.72$, p =[0.01 95% CI [.21, 1.41], and so was the b-pathway from the ΔERN to negative affect, b = −−0.24 *SE* =[0.11 $t(38) = -2.15$, p =[0.04 95% CI [− .47. −[0.01. Additionally, there was a significant indirect effect (ab) of estradiol on negative affect through the ΔERN, effect = −−0.20 *SE* =[0.12 95% CI [−[0.48 −[0.04, indicating that increases in estradiol levels from the early follicular to midluteal phase were associated with a decrease in negative affect via ΔERN amplitudes (note that the ΔERN is scored as a negative component meaning that the positive relation between estradiol and the ΔERN indicate that increases in estradiol are associated with a reduction in amplitudes of the ΔERN). Fig. 3 displays the mediation model for this effect. This indirect effect remained significant when excluding outliers (z-score > 3) on estradiol (N = 2) and negative affect (N = 1), effect = −−0.20 *SE* =[0.14 95% CI [−[0.54 −[0.002.

3.4.2. ERP effects of oral contraceptive status

3.4.2.1. Main ERP effects of oral contraceptive status. Analysis of the ERN revealed no significant main or interaction effects of OC use when comparing active OC users with NC participants in either the early follicular phase (main effect of OC use: $F(1,82) = 2.90$, p =[0.09 $\eta p^2 = .03$, $p = .70$ for ΔERN; OC use*correctness: $F(1,82) = .20$, p =[0.65 $\eta p^2 = .00$) or the midluteal phase (main effect of OC use: $F(1,82) = 1.75$, $p = .19$, $\eta p^2 = .02$, $p = .49$ for ΔERN; OC use*correctness: $F(1,82) = .00$, p =[0.97 $\eta p^2 = .00$).

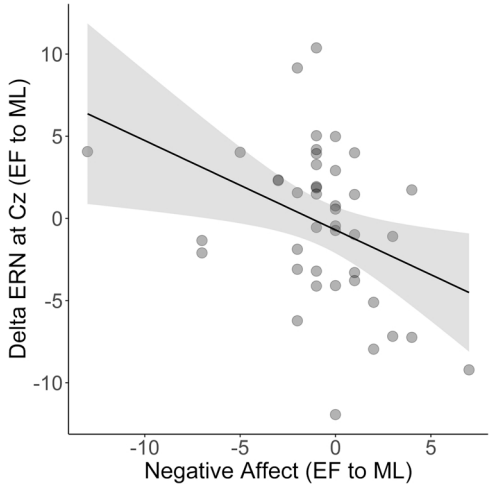


Fig. 2. Scatterplot depicting the negative association between the phase-related change in error-related negativity (μV) and the change in negative affect. The scatterplot shows that having higher (i.e., more negative) error-related negativity (ΔERN) amplitudes from the early follicular (EF) phase to midluteal (ml) phase was associated with more self-reported negative affect and vice versa, $r_{(42)}$= −.37, p =[0.02 Note that this association remained significant after removing an outlying value (z-score >3) on negative affect ($r_{(41)} = -.36$, p =[0.02.

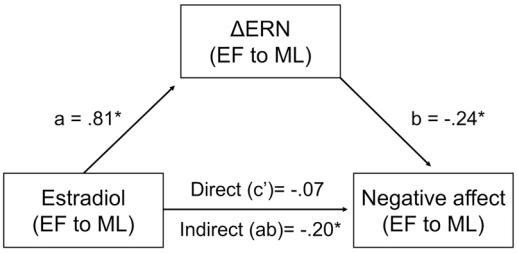


Fig. 3. Schematic overview of the mediation model demonstrating a significant indirect association between estradiol and negative affect through the ΔERN. The figure depicts the significant indirect effect (ab) of estradiol on negative affect through the ΔERN, effect = −−0.20 SE =[0.12 95% CI [−[0.48 −[0.04, indicating that increases in estradiol levels from the early follicular to midluteal phase were associated with a decrease in negative affect via ΔERN amplitudes (note that the ΔERN is scored as a negative component meaning that the positive relation between estradiol and the ΔERN indicate that increases in estradiol are associated with a reduction in amplitudes of the ΔERN). Note that this indirect effect remained significant when excluding outliers (z-score >3) on estradiol ($N = 2$) and negative affect ($N = 1$), effect = −−0.20 SE =[0.14 95% CI [−[0.54 −[0.002. The figure also shows the significant a-path from estradiol to the ΔERN (b ==0.81 SE ==0.30 t(39) = 2.72, p =[0.01 95% CI [.21, 1.41]), the significant b-pathway from the ΔERN to negative affect (b = −−0.24 SE ==0.11 t(38) = −2.15, p =[0.04 95% CI [− .47. −[0.01), and the non-significant direct pathway (c') from estradiol to negative affect (b = −−0.07 SE ==0.23 t(38) = −−0.32 p =[0.75 95% CI [− .53,0.39).

Analysis of the early Pe also revealed no main effect of OC use, $F(1,82) = .02$, p =[0.89 $\eta p^2 = .00$ and $F(1,82) = .10$, p =[0.76 $\eta p^2 = .01$. However, a significant interaction was observed between OC use and correctness when comparing active OC users with NCs in both their early follicular and midluteal phase ($F(1,82) = 4.99$, $p = .03$, $\eta p^2 = .06$ and $F(1,82) = 3.99$, $p = .05$, $\eta p^2 = .05$, respectively). Post-hoc comparisons did not reveal any significant effects, but inspection of the means indicated that the interaction is explained by the fact that OC users had more positive mean amplitudes on error trials and more negative amplitudes on correct trials compared to NC participants in both the early follicular and midluteal phase, resulting in a larger amplitude difference between errors and correct trials. In line with this, analysis of the early ΔPe showed higher difference amplitudes for active OC users ($M = 6.86$, $SE = 1.04$) compared to NC participants in the early follicular phase ($M = 3.43$, *SE* =.86), $t(82) = -2.53$, p =[0.01 whereas the early ΔPe difference between active OC users and NC participants in the midluteal phase did not reach significance, $t(82) = -1.79$, $p = .08$. Likewise, analysis of the late Pe revealed no significant between-subject effect of OC use when comparing active OC users with the early follicular phase ($F(1,82) = .56$, p =[0.46 $\eta p^2 = .01$) nor the midluteal phase ($F(1,82) = .17$, p =[0.68 $\eta p^2 = .00$, $p = .10$). However, a significant interaction between correctness and OC use was observed when comparing OC users to non-users in their early follicular phase: $F(1,82) = 3.99$, $p = .05$, $\eta p^2 = .05$. Post-hoc comparisons indicated that OC users had significantly more negative amplitudes on correct trials compared to NC participants in the the early follicular phase ($p = .05$). Analysis of the late ΔPe likewise revealed a significant effect of OC use, $t(82) = -2.00$, $p = .05$, showing larger difference amplitudes for OC users. The same comparison between active OC users and NC participants in the midluteal phase did not reach significance (OC use*-correctness, $F(1,82) = 2.81$, $p = .10$, $\eta p^2 = .03$, $p = .10$ for main effect of late ΔPe).

3.4.2.2. Examining OC-dependent associations between the ERN and negative affect. Based on a previously reported modulating effect of OC status on relation between the ERN and worrying (Louis et al., 2022), we additionally explored whether the relation between the ERN and negative affect was dependent on OC status. As was the case for the NC participants, there was no significant relation between the ERN and negative affect in OC users, neither during active OC use ($r_{(42)}= -.07$, $p =[0.67$, nor during inactive use ($r_{(42)}= -.08$, $p =[0.64$. We additionally applied a linear mixed model (ERN ~ negative affect x OC status x correctness), taking into account both sessions for each group, which also did not provide evidence for a moderating effect of OC status on the association between negative affect and the ERN, as indicated by a non-significant interaction between OC status, negative affect, and correctness ($F(1187.60) = 1.96$, $p = .16$, $\eta p^2 = .01$).

4. Discussion

The current study examined the effect of hormonal status, specifically menstrual cycle phase and oral contraceptive (OC) use, on two putative, electrophysiological biomarkers for internalizing disorders; the error-related negativity (ERN) and error positivity (Pe). We also examined whether the relationship between the ERN and negative affect (NA) was moderated by menstrual cycle phase and OC use and investigated if the ERN could play a mediating role in the relation between ovarian hormones and NA. We confirmed that estradiol and progesterone levels were higher in the midluteal compared to early follicular phase, whereas no difference in hormonal levels were found between active and inactive OC use. We did not observe any overall within-subject differences in performance monitoring (PM) between the early follicular and midluteal phase for naturally cycling (NC) participants, nor did we find evidence for a moderating effect of cycle phase on the relation between the ERN and NA. However, correlational analyses did reveal an association between phase-related changes in the ΔERN and NA: if the ΔERN increased from the early follicular to midluteal phase, so did NA, and vice versa. Mediation analysis additionally showed a negative indirect effect of between-phase changes in estradiol on NA via the ΔERN. Furthermore, when comparing (active) OC users with NC participants, we found no differences in ERN amplitudes or NA, nor did we find evidence for a moderating effect of OC use on the relation between the ERN and NA. However, active OC users did show larger ΔPe amplitudes compared to NC participants in the early follicular phase and faster reaction times compared to NC participants in the midluteal phase.

4.1. Findings in naturally-cycling women

Importantly, we did not find any evidence for an overal difference in PM when comparing the early follicular and midluteal phase. Although this is in contrast with our hypothesis of heightened PM during the midluteal phase, it is consistent with a previous study that did not find an overall difference in ERN amplitudes between the follicular and luteal phase of the menstrual cycle (Mulligan et al., 2019). Likewise, we did not find overall differences in NA between cycle phases. This contrasts with literature reporting mood fluctuations across the menstrual cycle (Sundström Poromaa and Gingnell, 2014). However, two recent studies did not find differences in mean NA across the menstrual cycle in healthy, premenopausal women either (Hengartner et al., 2017; Weigard et al., 2021), suggesting that there may not be a direct association between menstrual cycle phase and self-reported NA.Given the evidence for substantial inter-individual differences in the effects of- or sensitivity to hormonal cycle effects and ovarian hormones (see e.g., Hamstra, 2021), it may not be unsurprising to find non-significant group-level phase effects on PM and NA. The existence of conditions such as premenstrual syndrome (PMS) and premenstrual dysphoric disorder (Hofmeister and Bodden, 2016) indicates that specific subgroups may be more sensitive to hormonal fluctuations during the menstrual cycle, and there are many biological or psychological factors that could modulate the effects of ovarian hormones. For example, previous work has indicated that effects of estrogen on cognitive performance are dependent on individual differences in baseline dopamine functioning (e.g., Jacobs and D'Esposito, 2011), highlighting the need for future research to explore potential modulators of cycle effects. Furthermore, we tested participants at two specific points in the menstrual cycle, where estrogen and progesterone were either both low or both high. There is evidence to suggest that progesterone and estrogen may have opposing influences on emotional responses (see e.g., Sakaki and Mather, 2012), which indicates that their separate effects may have been cancelled out during the midluteal phase. Relatedly, it has been suggested that the most negative emotional symptoms, and hence potentially heightened PM, may be found in the late luteal phase, when progesterone levels are declining rather than at its peak (Sundström Poromaa, 2018). Additionally, the co-presence of high progesterone levels in the midluteal phase prevented us from assessing isolated effects of estrogen. This highlights the need to investigate PM at additional time points in the menstrual cycle, such as periods where only estrogen is high (i.e., the pre-ovulatory phase) or progesterone levels declining (i.e., the late luteal phase), to enable making more definite statements about menstrual cycle phase effects on PM.

The fact that we found no significant difference in ERN or Pe amplitudes between the two cycle phases could give the impression that the ERN and Pe are predominantly trait-like markers that are relatively stable across the menstrual cycle. However, when considering the intra-subject consistency or test-retest reliability of the ERPs for NC participants, correlations between phases only ranged between.46 and.59, with amplitudes of the late Pe and late ΔPe even showing no significant correlations.[1] Notably, these correlations are somewhat lower than the moderate to strong correlations observed in previous studies investigating test-retest reliability over comparable time intervals in mixed-sex samples (Lin et al., 2020). The existence of such substantial intra-individual variation may explain why we failed to find significant phase differences, and stresses the importance of improving our understanding of the circumstances under which these ERPs are modulated. For the ERN and Pe to be considered biomarkers of internalizing disorders, they first need to be reliably measured. Furthermore, they need to be associated with internalizing symptoms. Yet, we did not observe a significant relation between the ERN and NA in either hormonal phase. The fact that we find low to moderate test-retest reliability of these components and the absence of a relation with NA hence calls into question the validity of these ERPs as markers of internalizing disorders. However, enhanced ERNs have also been proposed to be more specific to anxiety or obsessive-compulsive symptoms than to depressive symptoms or internalizing symptoms in general (Pasion and Barbosa, 2019), which may perhaps explain the absence of a significant relation with NA. Hence, future research should look further into the specificity of the ERN as a biomarker.

Though we did not find any evidence that cycle phase moderated the relation between the ERN and NA, as observed in previous work investigating checking symptoms (Mulligan et al., 2019), we did find a negative association between individual changes in the ΔERN from the midluteal and early follicular phase and changes in NA. Specifically, when NC participants had larger (i.e., more negative) amplitudes of the ΔERN in the midluteal compared to early follicular phase, they also tended to show more NA, and vice versa. This association suggests that the ERN may be sensitive to state-related fluctuations in mood, or conversely, that changes in internal PM processes influence mood states, and fit with previous research showing that affective factors can modulate ERN amplitudes (e.g., de Bruijn et al., 2020; Jansen and de

[1] Correlations between phases were as follows: ERN: r=.535, $p < .001$; ΔERN: $r = .587$, $p <.001$; Early Pe: $r =.467$; $p =.002$, Early ΔPe: $r = .456$; $p = .002$; Late Pe: $r = .128$, $p = .421$; Late ΔPe: $r = -.015$, $p = .925$.

Bruijn, 2020; Proudfit et al., 2013; Riesel et al., 2012). Mediation analysis additionally showed a significant, negative indirect effect of estradiol on NA, via the ΔERN, indicating that phase-related increases in estradiol levels were indirectly associated with a reduction in NA via a reduction in amplitudes of the ΔERN. This is in line with recent reports of positive or protective mood effects of estrogen (Graham et al., 2017; Rehbein et al., 2021), and could indicate that one potential mechanism through which estradiol exerts such effects may be the alteration of the neurocognitive mechanisms underlying PM, or the neural sensitivity to errors, which may also be closely linked to the heightened interpersonal sensitivity that many individuals with PMS experience (Hofmeister and Bodden, 2016). Our finding fits with previous work suggesting that the ERN mediates effects of ovarian hormones on symptoms of internalizing disorders (Mulligan et al., 2019). However, it should be noted that this previous study found a mediating role (in the opposite direction) of the ΔERN for progesterone rather than estradiol, which may be explained by differences in the type of symptoms (checking symptoms versus NA) and the fact that their model concerned levels measured during the luteal phase rather than a measurement of the change between phases. Also, it should be emphasized that the associations that we observed cannot be considered as a pure estrogen effect, since our study assessed hormonal levels at times where estrogen and progesterone were either both low or both high, meaning that the separate effects of estrogen and progesterone cannot be disentangled.

4.2. Effects of oral contraceptive status

We did not observe general group differences in NA or ERN amplitudes between users of OCs and NC participants, which may not be surprising given the inconsistent effects of OCs reported in the literature (e.g., Brønnick et al., 2020; Hamstra, 2021; Lewis et al., 2019; Montoya and Bos, 2017; Pletzer and Kerschbaum, 2014; Toffoletto et al., 2014; Welling, 2013). Neither did we find evidence for a modulating effect of OC use on the relation between the ERN and NA, in contrast to previous findings of a modulating OC effect on the relation between the ERN and worrying (Louis et al., 2022). In fact, there were no significant correlations between the ERN and NA, neither for NC participants nor for OC users, which may hint at a lack of specificity of the ERN for more depression-related symptoms (Pasion and Barbosa, 2019), as discussed previously.

With regard to the Pe, however, we did find indications for enhanced ΔPe amplitudes in users of OCs. This effect was seen for both the early and late Pe and was significant only when comparing active OC users with NC participants in their early follicular phase, though the same pattern was observed at trend-level when comparing OC users with NC participants in the midluteal phase. It is important to note that the group differences are small, which is in line with the mixed literature and the presumably large individual variation in the emotional and cognitive effects of OC use (Lewis et al., 2019). Additionally, while the groups were comparable with regard to age, personality dimensions, and depression scores, there may be many other pre-existing differences in characteristics between OC users and NC participants that could potentially influence PM correlates (see e.g., Oinonen et al., 2008) and thus explain our results. To truly disentangle effects of OC use, randomized controlled trials (RCTs) and prospective studies are necessary.

Still, the current findings indicate that there may be generic differences in the electrophysiological correlates of PM and error processing between OC users and NC participants. The fact that a similar pattern was observed when comparing active OC users with the early follicular and midluteal phase suggests that the group differences in the ΔPe amplitudes cannot simply be explained by a difference in endogenous sex hormonal levels, as these levels are actually most comparable between active OC use and the early follicular phase, and suggests that findings are more likely to reflect a general effect of OC use. Importantly, a recent prospective cohort study indicates that OC use during adolescence increases women's likelihood to develop depression in early adulthood (Anderl et al., 2022). As the Pe is thought to reflect the awareness or affective response to errors (Ullsperger et al., 2014a), increased Pe amplitudes may speculatively reflect a generic underlying cognitive vulnerability to depression in OC users.

Delta score ERPs are sometimes thought to reflect more 'pure' measures as error-related activation is isolated by substracting it from a baseline (correct-related activation) (Meyer, Lerner, De Los Reyes, Laird, and Hajcak, 2017). However, the fact that the correct-related waveform seems to be altered in various states and traits in its own right (Kaczkurkin, 2013; Larson et al., 2016; Simons, 2010), may call into question to what extent this waveform represents a valid and stable baseline for the error positivity to sit on. Indeed, inspection of the grand averages and mean amplitudes indicates that the difference between groups is primarily driven by alterations in the correct-related amplitudes, with the amplitude difference on correct trials between active OC use and NC participants in the early follicular phase reaching significance for the late Pe, suggesting that findings may not be error-specific. Nevertheless, while PM research has primarily focused on the ERN, our findings highlights the need for future research to also take into account possible hormonal influences of the Pe.Behaviorally, reaction times were also slightly faster for OC users compared to NC participants in their midluteal phase, despite there being no difference in accuracy rates. Interestingly, faster reaction times in OC users has been reported before in tasks involving emotion-related cognitive performance such as the facial emotion recognition task (Hamstra et al., 2015; Hamstra et al., 2017). Future studies should find out whether this could reflect a genuine effect of OC use.

4.3. Strengths and limitations

The current study had its strengths and limitations. We used a within-subject design to compare menstrual cycle phases, which has important power benefits over cross-sectional designs. Additionally, we made use of strict exclusion criteria and only included OC users with the monophasic, second-generation pill, which is the first-choice birth control in the Netherlands with 1.2 million users (SFK, 2018).[2] Our results cannot be generalized to other age groups, nor users of OCs with a different pill composition. Given that age is positively associated with the amount of endogenous sex hormones (Hampson, 2020), it is essential to investigate other age groups as well. Likewise, investigating other OC compounds is important as different types and brands of OCs vary in their formulations and consequently, their biological effects. Furthermore, NC participants visited the lab at a time where their estradiol and progesterone levels where either both high or both low, which allowed us to assess potential changes in PM during the two main phases of the menstrual cycle, whereby we made use of reverse day counting to ensure that assessment took place in the correct cycle phase and confirmed this using saliva samples. However, despite its ecological validity, this design did not permit us to disentangle the individual role of each hormone in PM. To investigate this, future studies should include the (pre-)ovulatory phase as well, when estradiol is high but progesterone is low, which requires the inclusion of additional biological measures, such as urine samples to assess the surge of luteinizing hormone (Sundström Poromaa and Gingnell, 2014). Alternatively, pharmacological manipulations of ovarian hormones with for example a gonadotropin releasing hormone agonist could be used (Frokjaer, 2020). Furthermore, the early follicular phase is characterized by menses, which means that observed effects of hormonal status may in part be explained by the physical discomforts that usually accompany this period. Lastly, even though visual inspection of the grand averages shows very comparable waveforms between the phases, it is possible that effects of menstrual cycle phase were smaller than this study was powered to identify. A sensitivity power

[2] Stichting Farmaceutische kengetallen (2018). https://www.sfk.nl/publicaties/PW/2018/minder-vrouwen-aan-anticonceptie

analysis suggests that the current sample size allowed us to detect medium (f =.=0.22ith a power of 80%), but not small effect sizes. Naturally, power was even smaller for the between-subject comparisons. Given the inconclusive and mixed literature on menstrual cycle phase and OC use effects, and the general concerns with the reliability and reproducibility of studies in this field (Hamstra, 2021; Sundström Poromaa, 2018; Warren et al., 2014), especially our between-subject findings should be interpreted with caution and warrant replication in larger sample sizes and using RCTs.

4.4. Conclusion

In summary, our study found no evidence for an overall difference in PM or NA between NC women in the early follicular versus midluteal phase of the menstrual cycle. We did observe a negative association between individual changes in the ΔERN between the midluteal and early follicular phase and changes in NA, suggesting that the ERN may be sensitive to state-like fluctuations in mood. Mediation analysis additionally showed a negative indirect effect of phase-related changes in estradiol on NA via the ΔERN, suggesting that between-phase fluctuations in estradiol may indirectly impact NA by altering PM activity.

Additionally, comparing OC users with non-users revealed no difference in ERN amplitudes, but increased ΔPe amplitudes in the former group. This could potentially indicate that the use of monophasic, second-generation OCs specifically alters the later- and presumably more affective processing of errors, rather than earlier- and more automatic PM processes (as reflected in the ERN). While our results require replication, our findings suggest that ovarian hormones may impact the neural mechanisms underlying PM and error sensitivity, and that this could be a potential mechanism through which ovarian hormones influence mood. Hence, our findings highlight the need for future research on PM to take hormonal status into account.

Funding

Myrthe Jansen was in part supported by personal grants from the Netherlands Organization for Scientific Research (NWO; VIDI grant nr. 452–12-005) and the Westerdijk Talent Scheme awarded to E. R. A. de Bruijn.

CRediT authorship contribution statement

Myrthe Jansen: Formal analysis, Investigation, Visualization, Writing – original draft. **Willem van der Does:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Mischa de Rover:** Software, Writing – review & editing. **Ellen de Bruijn:** Formal analysis, Supervision, Writing – review & editing. **Danielle Hamstra:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

Danielle Hamstra, the driving force behind this research, sadly passed away very unexpectedly in July 2022. During her PhD, which she successfully defended less than one year prior, she devoted herself to the study of the effects of changes in female hormonal levels on depression-related cognitive-emotional processes. With her research, Danielle was able to shed some light onto the complex interplay between female hormones and genetic differences in one's vulnerability to depression. Danielle also was a great advocate for the need for everyday research and clinical practice to take into account female hormonal influences such as menstrual cycle phase and oral contraceptive use. To promote this message, she developed a habit of asking every researcher she came across whether they had registered the menstrual cycle phase or hormonal contraceptive use and type of their female participants. We would like to dedicate our paper to this inspiring colleague who will be greatly missed, and we hope that with this paper we can help convey her message. We would like to thank Imme van der Bent, Stephanie Bauduin, Laila Franke, Nick Heres and Saskia Borg for their help in collecting the data for this study.

References

Altemus, M., Sarvaiya, N., Epperson, C.N., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35 (3), 320–330.
Anderl, C., de Wit, A.E., Giltay, E.J., Oldehinkel, A.J., Chen, F.S., 2022. Association between adolescent oral contraceptive use and future major depressive disorder: a prospective cohort study. J. Child Psychol. Psychiatry 63 (3), 333–341.
Barth, C., Villringer, A., Sacher, J., 2015. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front. Neurosci. 9, 37.
Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. arXiv preprint arXiv:1406.5823.
Bates, D., Kliegl, R., Vasishth, S., & Baayen, H. (2015). Parsimonious mixed models. arXiv preprint arXiv:1506.04967.
Beltz, A.M., Moser, J.S., 2020. Ovarian hormones: a long overlooked but critical contributor to cognitive brain structures and function. Annals of the New York Academy of Sciences 1464 (1), 156–180.
Brazil, I.A., de Bruijn, E.R., Bulten, B.H., von Borries, A.K.L., van Lankveld, J.J., Buitelaar, J.K., Verkes, R.J., 2009. Early and late components of error monitoring in violent offenders with psychopathy. Biol. Psychiatry 65 (2), 137–143.
Brønnick, M.K., Økland, I., Graugaard, C., Brønnick, K.K., 2020. The effects of hormonal contraceptives on the brain: a systematic review of neuroimaging studies. Front. Psychol. 11 (2813) https://doi.org/10.3389/fpsyg.2020.556577.
Chong, L.J., Meyer, A., 2019. Understanding the link between anxiety and a neural marker of anxiety (the error-related negativity) in 5 to 7 year-old children. Dev. Neuropsychol. 44 (1), 71–87.
Clayson, P.E., Baldwin, S.A., Larson, M.J., 2013. How does noise affect amplitude and latency measurement of event-related potentials (ERPs)? A methodological critique and simulation study. Psychophysiology 50 (2), 174–186.
Costa, P., & McCrae, R. (1989). NEO five-factor inventory (NEO-FFI). Odessa, FL: Psychological Assessment Resources, 3.
Crawford, J.R., Henry, J.D., 2004. The Positive and Negative Affect Schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. Br. J. Clin. Psychol. 43 (3), 245–265.
de Bruijn, E.R., Ruissen, M.I., Radke, S., 2017. Electrophysiological correlates of oxytocin-induced enhancement of social performance monitoring. Soc. Cogn. Affect. Neurosci. 12 (10), 1668–1677.
de Bruijn, E.R., Jansen, M., Overgaauw, S., 2020. Enhanced error-related brain activations for mistakes that harm others: ERP evidence from a novel social performance-monitoring paradigm. NeuroImage 204, 116238.
de Bruijn, E.R., Grootens, K.P., Verkes, R.J., Buchholz, V., Hummelen, J.W., Hulstijn, W., 2006. Neural correlates of impulsive responding in borderline personality disorder: ERP evidence for reduced action monitoring. J. Psychiatr. Res. 40 (5), 428–437.
de Rover, M., Brown, S.B., Band, G.P., Giltay, E.J., van Noorden, M.S., van der Wee, N.J., Nieuwenhuis, S., 2015. Beta receptor-mediated modulation of the oddball P3 but not error-related ERP components in humans. Psychopharmacology 232 (17), 3161–3172.
Dubol, M., Epperson, C.N., Sacher, J., Pletzer, B., Derntl, B., Lanzenberger, R., Comasco, E., 2021. Neuroimaging the menstrual cycle: a multimodal systematic review. Front. Neuroendocrinol. 60, 100878.
Dutilh, G., Van Ravenzwaaij, D., Nieuwenhuis, S., Van der Maas, H.L., Forstmann, B.U., Wagenmakers, E.-J., 2012. How to measure post-error slowing: a confound and a simple solution. J. Math. Psychol. 56 (3), 208–216.
Eriksen, B.A., Eriksen, C.W., 1974. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept. Psychophys. 16 (1), 143–149.
Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. Electroencephalography and clinical neurophysiology, 78(6), 447-455: Falkenstein, M. (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. Psychophysiological brain research.
Frokjaer, V.G., 2020. Pharmacological sex hormone manipulation as a risk model for depression. J. Neurosci. Res. 98 (7), 1283–1292.
Gehring, W.J., Goss, B., Coles, M.G.H., Meyer, D.E., Donchin, E., 1993. A neural system for error detection and compensation. https://journals.sagepub.com/doi/abs/10.1111/j.1467-9280.1993.tb00586.x Psychol. Sci., 4(6), 385-390. https://doi.org/10.1111/j.1467-9280.1993.tb00586.x.
Graham, B.M., Ash, C., Den, M.L., 2017. High endogenous estradiol is associated with enhanced cognitive emotion regulation of physiological conditioned fear responses in women. Psychoneuroendocrinology 80, 7–14.
Hampson, E., 2020. A brief guide to the menstrual cycle and oral contraceptive use for researchers in behavioral endocrinology. Horm. Behav. 119, 104655.
Hamstra, D., De Kloet, E., Van Hemert, A., De Rijk, R., Van der Does, A., 2015. Mineralocorticoid receptor haplotype, oral contraceptives and emotional information processing. Neuroscience 286, 412–422.

Hamstra, D.A., 2021. *Mood and the pill*. Doctoral dissertation, Leiden University.
Hamstra, D.A., de Kloet, E.R., Quataert, I., Jansen, M., Van der Does, W., 2017. Mineralocorticoid receptor haplotype, estradiol, progesterone and emotional information processing. Psychoneuroendocrinology 76, 162–173.
Hengartner, M.P., Kruger, T.H., Geraedts, K., Tronci, E., Mancini, T., Ille, F., Leeners, B., 2017. Negative affect is unrelated to fluctuations in hormone levels across the menstrual cycle: Evidence from a multisite observational study across two successive cycles. Journal of psychosomatic research 99, 21–27.
Hofmeister, S., Bodden, S., 2016. Premenstrual syndrome and premenstrual dysphoric disorder. Am. Fam. Physician 94 (3), 236–240.
Jacobs, E., D'Esposito, M., 2011. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. J. Neurosci. 31 (14), 5286–5293.
Jansen, M., de Bruijn, E., 2020. Mistakes that matter: an event-related potential study on obsessive-compulsive symptoms and social performance monitoring in different responsibility contexts. Cogn., Affect., Behav. Neurosci. 20 (4), 684–697.
Kaczkurkin, A.N., 2013. The effect of manipulating task difficulty on error-related negativity in individuals with obsessive-compulsive symptoms. Biol. Psychol. 93 (1), 122–131.
Klawohn, J., Meyer, A., Weinberg, A., Hajcak, G., 2020. Methodological choices in event-related potential (ERP) research and their impact on internal consistency reliability and individual differences: an examination of the error-related negativity (ERN) and anxiety. J. Abnorm. Psychol. 129 (1), 29.
Larson, M.J., Clayson, P.E., Keith, C.M., Hunt, I.J., Hedges, D.W., Nielsen, B.L., Call, V.R., 2016. Cognitive control adjustments in healthy older and younger adults: conflict adaptation, the error-related negativity (ERN), and evidence of generalized decline with age. Biol. Psychol. 115, 50–63.
Le, J., Thomas, N., Gurvich, C., 2020. Cognition, the menstrual cycle, and premenstrual disorders: a review. Brain Sci. 10 (4), 198.
Lewis, C.A., Kimmig, A.-C.S., Zsido, R.G., Jank, A., Derntl, B., Sacher, J., 2019. Effects of hormonal contraceptives on mood: a focus on emotion recognition and reactivity, reward processing, and stress response. Curr. Psychiatry Rep. 21 (11), 1–15.
Lin, M.H., Davies, P.L., Stephens, J., Gavin, W.J., 2020. Test–retest reliability of electroencephalographic measures of performance monitoring in children and adults. Developmental neuropsychology 45 (6), 341–366.
Louis, C.C., Kneip, C., Moran, T.P., Beltz, A.M., Klump, K.L., Moser, J.S., 2022. Hormonal contraceptive use moderates the association between worry and error-related brain activity. Int. J. Psychophysiol. 171, 48–54.
Lüdecke, D., & Lüdecke, M.D. (2019). Package 'sjstats'. Statistical functions for Regression Models, Version 0.17, 3.
Lutz, M.C., Kok, R., Franken, I.H., 2021. Event-related potential (ERP) measures of error processing as biomarkers of externalizing disorders: a narrative review. Int. J. Psychophysiol.
Lutz, M.C., Kok, R., Verveer, I., Malbec, M., Koot, S., van Lier, P.A., Franken, I.H., 2021. Diminished error-related negativity and error positivity in children and adults with externalizing problems and disorders: a meta-analysis on error processing. J. Psychiatry Neurosci. 46 (6), E615–E627.
Meyer, A., 2016. Developing psychiatric biomarkers: a review focusing on the error-related negativity as a biomarker for anxiety. Curr. Treat. Options Psychiatry 3 (4), 356–364.
Meyer, A., Lerner, M.D., De Los Reyes, A., Laird, R.D., Hajcak, G., 2017. Considering ERP difference scores as individual difference measures: issues with subtraction and alternative approaches. Psychophysiology 54 (1), 114–122.
Montoya, E.R., Bos, P.A., 2017. How oral contraceptives impact social-emotional behavior and brain function. Trends Cogn. Sci. 21 (2), 125–136.
Moos, R.H., 1968. The development of a menstrual distress questionnaire. Psychosom. Med. 30 (6), 853–867.
Mulligan, E.M., Hajcak, G., Klawohn, J., Nelson, B., Meyer, A., 2019. Effects of menstrual cycle phase on associations between the error-related negativity and checking symptoms in women. Psychoneuroendocrinology 103, 233–240.
Mulligan, E.M., Nelson, B.D., Infantolino, Z.P., Luking, K.R., Sharma, R., Hajcak, G., 2018. Effects of menstrual cycle phase on electrocortical response to reward and depressive symptoms in women. Psychophysiology 55 (12), e13268.
Oinonen, K.A., Jarva, J.A., Mazmanian, D., 2008. Pre-existing Hormonal Differences between Oral Contraceptive Users and Nonusers? Evidence from Digit Ratio, Age of Menarche, and Sociosexual Orientation. Progress in biological psychology research. Nova Science Publisher, Hauppauge, NY.
Pasion, R., Barbosa, F., 2019. ERN as a transdiagnostic marker of the internalizing-externalizing spectrum: a dissociable meta-analytic effect. Neurosci. Biobehav. Rev. 103, 133–149.
Pletzer, B.A., Kerschbaum, H.H., 2014. 50 years of hormonal contraception—time to find out, what it does to our brain. Front. Neurosci. 8, 256.
Preacher, K.J., Hayes, A.F., 2004. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav. Res. Methods, Instrum., Comput. 36 (4), 717–731.
Proudfit, G., Inzlicht, M., Mennin, D., 2013. Anxiety and error monitoring: the importance of motivation and emotion. Front. Hum. Neurosci., 7(636). https://doi.org/10.3389/fnhum.2013.00636.
Rabbitt, P.A., 1966. Errors and error correction in choice-response tasks. J. Exp. Psychol. 71 (2), 264.
Rehbein, E., Kogler, L., Hornung, J., Morawetz, C., Bayer, J., Krylova, M., Derntl, B., 2021. Estradiol administration modulates neural emotion regulation. Psychoneuroendocrinology 134, 105425.
Riesel, A., 2019. The erring brain: error-related negativity as an endophenotype for OCD—A review and meta-analysis. Psychophysiology 56 (4), e13348.
Riesel, A., Goldhahn, S., Kathmann, N., 2017. Hyperactive performance monitoring as a transdiagnostic marker: Results from health anxiety in comparison to obsessive–compulsive disorder. Neuropsychologia 96, 1–8.
Riesel, A., Weinberg, A., Endrass, T., Kathmann, N., Hajcak, G., 2012. Punishment has a lasting impact on error-related brain activity. Psychophysiology 49 (2), 239–247.
Riesel, A., Klawohn, J., Grützmann, R., Kaufmann, C., Heinzel, S., Bey, K., Kathmann, N., 2019. Error-related brain activity as a transdiagnostic endophenotype for obsessive-compulsive disorder, anxiety and substance use disorder. Psychol. Med. 49 (7), 1207–1217.
Sakaki, M., Mather, M., 2012. How reward and emotional stimuli induce different reactions across the menstrual cycle. Soc. Personal. Psychol. Compass 6 (1), 1–17.
Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12 (3), 154–167.
Simons, R.F., 2010. The way of our errors: theme and variations. Psychophysiology 47 (1), 1–14.
Solis, E., Antypa, N., Conijn, J.M., Kelderman, H., Van der Does, W., 2017. Psychometric properties of the Leiden Index of Depression Sensitivity (LEIDS). Psychol. Assess. 29 (2), 158.
Sundström Poromaa, I., Segebladh, B., 2012. Adverse mood symptoms with oral contraceptives. Acta Obstet. Et. Gynecol. Scand. 91 (4), 420–427.
Sundström Poromaa, I., Gingnell, M., 2014. Menstrual cycle influence on cognitive function and emotion processing—from a reproductive perspective. . Front. Neurosci. 8 (380) https://doi.org/10.3389/fnins.2014.00380.
Sundström Poromaa, I, 2018. The menstrual cycle influences emotion but has limited effect on cognitive function. Vitam. Horm. 107, 349–376.
Toffoletto, S., Lanzenberger, R., Gingnell, M., Sundstrom-Poromaa, I., Comasco, E., 2014. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: a systematic review. Psychoneuroendocrinology 50, 28–52. https://doi.org/10.1016/j.psyneuen.2014.07.025.
Ullsperger, M., Danielmeier, C., Jocham, G., 2014b. Neurophysiology of performance monitoring and adaptive behavior. Physiol. Rev. 94 (1), 35–79.
Ullsperger, M., Fischer, A.G., Nigbur, R., Endrass, T., 2014a. Neural mechanisms and temporal dynamics of performance monitoring. Trends Cogn. Sci. 18 (5), 259–267.
Van Vliet, I., De Beurs, E., 2007. The MINI-InteRnational Neuropsychiatric Interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders. Tijdschr. voor Psychiatr. 49 (6), 393–397.
Warren, A.M., Gurvich, C., Worsley, R., Kulkarni, J., 2014. A systematic review of the impact of oral contraceptives on cognition. Contraception 90 (2), 111–116.
Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Personal. Soc. Psychol. 54 (6), 1063.
Weigard, A., Loviska, A.M., Beltz, A.M., 2021. Little evidence for sex or ovarian hormone influences on affective variability. Scientific reports 11 (1), 1–12.
Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein, D.N., Hajcak, G., 2016. Error-related negativity (ERN) and sustained threat: conceptual framework and empirical evaluation in an adolescent sample. Psychophysiology 53 (3), 372–385.
Welling, L.L.M., 2013. Psychobehavioral effects of hormonal contraceptive use. Evolut. Psychol. 11 (3), 147470491301100315 https://doi.org/10.1177/147470491301100315.