Effect of Menstrual Cycle and Spontaneous Eye Blink Rate on Performance Monitoring in Naturally Cycling Adult Females

Bode, Shareen Sophie

Effect of Menstrual Cycle and Spontaneous Eye Blink Rate on Performance Monitoring in Naturally Cycling Adult Females

S.S. Bode
Master Clinical Psychology
Supervisor: Jansen, M. (MSc)
Institute of Psychology
Universiteit Leiden
Date: 02-03-2022

Abstract

The effect of hormones on mood and cognition has been widely recognized yet often ignored in neurocognitive research. The error-related negativity, an event-related potential supposed to index performance monitoring, is thought to be driven by dopamine and has been shown to be amplified by anxiety and reduced by mood. The current study utilized a within-subject design to examine the association between menstrual cycle phase, spontaneous eye blink rate (as putative marker of dopamine) and the error-related negativity. 42 normal-cycling females performed a Flanker task during the early follicular phase, which is characterized by low levels of estrogen and progesterone and during the mid-luteal phase, which is characterized by high levels of estrogen and progesterone. It was hypothesized that females with a lower eye blink rate have a larger error-related negativity in the mid-luteal phase compared to the early follicular phase and females with a higher eye blink rate have a larger error-related negativity in the early follicular phase compared to the mid-luteal phase. Results showed no main or interaction effect of cycle phase and eye blink rate on the ERN. However, there was an interaction of cycle phase and eye blink rate on reaction times and a link between eye blink rate and estrogen in the mid-luteal phase. These findings point to a link between ovarian hormonal fluctuations and dopaminergic functioning and might aid future research in understanding the influence of the menstrual cycle on women's mental and emotional health.

Keywords: performance monitoring, error-related negativity, menstrual cycle, spontaneous eye blink rate, Eriksen flanker task

The monitoring of one's own performance is essential in order to learn from mistakes and to adapt one's actions accordingly (Olvet & Hajcak, 2008; Ullsperger, Danielmeier, & Jocham, 2014). The ability to monitor action outcomes and to act upon them is called performance monitoring (PM). PM is commonly indexed by the error-related negativity (ERN), which is a negative deflection in the event-related potential (ERP) that peaks approximately 50 ms after the commission of an error. It is thought to reflect early error-processing activity of the anterior cingulate cortex (ACC; Olvet & Hajcak, 2008), a brain region that is said to process information about pain, threat, and punishment to facilitate behavior change (Shackman et al., 2011). According to the reinforcement learning theory by Holroyd and Coles (2002), the ERN results from a dopamine disinhibition of the ACC when

outcomes are evaluated as worse than expected. In line with this, it has been proposed to function as a sign to increase cognitive control and behavior adjustment in response to error commission (Weinberg et al., 2016). To investigate the ERN, the *Eriksen flanker task* (Eriksen, 1995) is an often used speeded-choice reaction time paradigm where participants must respond to target stimuli while simultaneously ignoring interfering stimuli (the flankers).

The ERN has been shown to differ among several psychiatric disorders that may be characterized by a differential sensitivity to threat. For example, individuals with clinical anxiety have a bias towards negative information and display higher error sensitivity compared to individuals with no anxiety (Tobias & Ito, 2021). Several studies show an enhanced ERN signaling in individuals with anxiety disorders such as obsessive-compulsive disorder, generalized anxiety disorder and social anxiety disorder (Meyer, 2016; Riesel et al., 2019). Moreover, Meyer (2016) found that checking behavior - the tendency to engage in self-monitoring of one's own behavior to reduce anxiety - was the anxiety symptom mostly linked to the ERN, which appears similar to the concept of PM. In contrast, depressive symptoms have been linked to decreased ERN amplitudes and may even attenuate the effect of anxiety on the ERN (Weinberg et al., 2016). Indeed, this is in line with the notion that individuals with depression have a blunted response to threatening information (Dillon et al., 2014). Interestingly, the ERN has been proposed as a potential biomarker for clinical anxiety (Michael et al., 2021) and several psychiatric disorders that may be characterized by a sensitivity to threat, such as obsessive-compulsive disorder (Meyer, Nelson, Perlman, Klein, & Kotov, 2018; Riesel, 2019). Thus, the ability to monitor one's own actions seems to be related to anxiety-specific symptoms and mood, and the direction may be caused by a differential threat evaluation.

The link between the ERN and affective disorders raises the question whether ovarian hormones might also assert an effect on these neural monitoring processes as it has long been recognized that fluctuations in ovarian hormones are associated with changes in affective and cognitive functioning. A recent review article by Green and Graham (2022) showed that symptom severity in several anxiety disorders may be modulated by the menstrual cycle, with symptom exacerbation most evident just before and after ovulation. Several double-blind randomized-controlled studies have shown that the administration of transdermal estradiol (with and without progesterone) can prevent the development of clinically significant depressive symptoms and reduce those in women with depressive disorders (Gordon et al.,

2018; Schmidt et al., 2015). There is also research indicating that women in their premenstrual and menstrual phase have a higher risk of attempting suicide as lower estrogen levels were associated with more suicidal behavior (Owens & Eisenlohr-Moul, 2018; Sublette, 2020). Moreover, studies by Beltz and Moser (2020) and Girard et al. (2017) found cycle-related changes in prefrontal brain regions related to cognitive control. In addition, ERP and fMRI research suggests that higher ovarian hormones positively impact a wide range of neurocognitive functions such as working memory, response inhibition or visuo-spatial skills (Hidalgo-Lopez & Pletzer, 2021; Wang et al., 2020; Brötzner, Klimesch, & Kerschbaum, 2015, respectively). Given these links, it could be assumed that ovarian hormones and the neural correlate of PM might also be related, as they both show associations with a wide range of psychiatric symptoms and possibly affect similar prefrontal brain regions.

In naturally cycling healthy females, the menstrual cycle occurs in a monthly rhythm and lasts about 28 days. It can be divided into the follicular phase and luteal phase, which are each characterized by distinct hormonal fluctuations. The early follicular (EF) phase begins with menses and is characterized by low levels of estrogen and progesterone, followed by a rise in estrogen in the mid-follicular phase that peaks shortly before ovulation. The luteal phase begins with ovulation and is characterized by a gradual increase in estrogen and progesterone to the mid-luteal (ML) phase, followed by a decline in both hormones in the late luteal phase (for illustration see Green, 2022). Fluctuations in these hormones have been linked to alterations in mood (Gordon et al., 2018; Wharton, Gleason, Sandra, Carlsson, & Asthana, 2012) and research on the influence of the menstrual cycle is emerging.

However, only one study by Mulligan, Hajcak, Klawohn, Nelson and Meyer (2019) has yet investigated the effect of ovarian hormones on the ERN. They utilized a within-subject design to examine cycle-dependent changes in the ERN during an arrowhead version of the flanker's task. Against their hypothesis, they did not find a significantly larger ERN in the luteal phase compared to the follicular phase. However, they did find that a larger ERN was associated with greater checking symptoms in the luteal phase of the menstrual cycle, which is in line with findings by Meyer (2016) who found checking behavior to be linked to the ERN. Overall, their results suggest that hormonal fluctuations may impact the severity of symptoms by modulating neural mechanisms associated with PM. Moreover, there is fMRI research indicating cycle-related changes in the activation of the dorsal ACC (Diekhof & Ratnayake, 2016). Given that the ERN is supposed to result from a dopamine disinhibition of

the ACC (Ullsperger et al., 2014; Weinberg et al., 2016), this finding could indicate a possible impact of the menstrual cycle on PM processes.

One possible reason for the lack of findings by Mulligan et al. (2019) could be that they did not account for the moderating role of dopamine in the relationship between ovarian hormones and cognitive processes. Research indicates that cognitive functioning is modulated by dopamine in an inverted U-shaped manner, with too low or too high levels as impedimental (Cools & D'Esposito, 2011). Estrogen has been shown to compensate for low dopamine as it modulates dopamine release- and receptor binding (Barth, Villringer, & Sacher, 2015; Yoest, Quigley, & Becker, 2018) and, on the other side, aggravates cognitive functioning with already high dopamine (Jacobs & D'Esposito, 2011). In fact, there is a coherent mass of behavioral research indicating that the effect of hormones on cognition depends on baseline dopamine. For example, a study by Hidalgo-Lopez and Pletzer (2017) found that women with lower baseline dopamine (indirectly measured with eye blink rate) had a faster reaction time performance on the Stroop task in the luteal as compared to the EF phase and pre-ovulation, and women with higher dopamine had a slower performance in the luteal phase compared to the other phases. Similar results have been found by Jacobs and D'Esposito (2011) who showed that estrogen had an enhancing effect on females' performance on a working memory task, and the direction of this effect was dependent on baseline dopamine (measured with COMT enzymatic activity). In addition to these behavioral findings, there is also research indicating that the ERN is affected by dopamine-related genes and that dopamine agonists enlarge and dopamine antagonists reduce the ERN (De Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004; Jocham & Ullsperger, 2009). Moreover, there are studies indicating that the ACC plays a role in dopaminergic functioning (Diekhof & Ratnayake, 2016; Steullet, Cabungcal, Cuénod, & Do, 2014), which seems intuitive as the ERN is supposed to be a dopamine-driven signal (Ullsperger et al., 2014). Altogether these findings might indicate a role of dopamine in the relationship between ovarian hormones and neural monitoring processes.

One indirect way to measure dopamine is the recording of spontaneous eye blink rates (EBR), which refers to the brief closure of both eyelids without any stimulation and volition (Maffei & Angrilli, 2018). There is research indicating that the frequency of the EBR depends on dopaminergic activity, with higher EBR predicting higher dopamine. For example, Groman et al. (2014) found that the EBR is significantly correlated to striatal D2-like receptor

density. Moreover, a review article by Jongkees and Colzato (2016) showed that the EBR can be used to reliably predict individual differences in dopamine-related cognitive performance. Other dopamine measurements such as the measurement of the striatal dopamine synthesis capacity with a position emission tomography scan are quite exhaustive and difficult to implement (Jongkees & Colzato, 2016). Caution is warranted as there are also studies indicating a lack of association between the EBR and other measurements of dopamine (Sescousse et al., 2018). Still, a coherent mass of research indicates that the EBR might serve as an easily accessible and non-invasive behavioral index of baseline striatum dopamine (Maffei & Angrilli, 2018).

It is important to note that most studies on hormones investigated estrogen and progesterone separately while ignoring the menstrual phases themselves. In fact, most findings on the relationship between ovarian hormones and cognition are based on estrogenic activity (Jacobs & D'Esposito, 2011; Schmidt et al., 2015), whereas the impact of progesterone is less clear, and some research indicates opposite effects of estradiol, a modulation of estrogenic actions or similar effects of both hormones together (Baudry & Aguirre, 2013; Brötzner et al., 2015; Singhal et al., 2016). However, in reality, hormones do not occur in absence of each other and seem to have a great impact on each other instead (Hidalgo-Lopez & Pletzer, 2017; Yoest et al., 2018). Thus, from an ecological viewpoint, it is essential to investigate the menstrual phases and not the hormones separately. For example, a comparison of the EF phase to the ML phase might be useful to investigate interactional effects of estrogen and progesterone as both are low during the EF phase and high during the ML phase. In addition, most research on the relation between hormones and cognition rely on self-reports and behavioral measures, whereas biological measures such as electroencephalography (EEG) are more objective and could give rise to the underlying brain mechanisms.

To investigate this, the present study aimed at identifying the effect of the menstrual cycle on electrophysiological measures of PM in naturally cycling females. In addition, it was investigated whether the EBR plays a role in this as behavioral research indicates that the effect of ovarian hormones on cognition depends on dopaminergic functioning (Hidalgo-Lopez & Pletzer, 2017; Jacobs & D'Esposito, 2011). To this end, 42 females performed the Flanker task twice during their menstrual cycle - once during the EF phase and once during the ML phase - to examine changes in the ERN. Based on previous research it was

hypothesized that females with lower EBR have a larger (i.e., more negative) ERN in the ML phase compared to the EF phase and females with higher EBR have a larger ERN in the EF phase compared to the ML phase. On an exploratory level, it was also investigated whether cyclical changes in both estrogen and progesterone relate to the ERN to see whether data supports previous hormone research.

Method

Design

This study is a sub-project of a larger research project, in which the role of female hormonal status and MR haplotypes on neural correlates of emotional information processing was examined. The current study has a within-subject counterbalanced design. Participants were tested during the EF phase (day 2-6), which is characterized by low levels of estrogen and progesterone and during the ML phase (day 18-25), which is characterized by high levels of estrogen and progesterone. The study has been approved by the Medical Ethics Committee (METC) and the Ethics Committee Psychology (CEP) with the approval number CEP16-0318/139.

Participants

Recruitment took place via advertisement at sites at the campus of the Leiden University. If participants were interested, they received further information via email to attend the online intake procedure in Qualtrics. In order to confirm their eligibility for participation and to set up dates for the two sessions, they were subsequently contacted via telephone or email. Participants were fluent in Dutch, right-handed and of North -Western European ancestry. Participants were reimbursed after confirmation of their next cycle onset (first day of menses) with a monetary reward (50€) for participation.

There were several exclusion criteria in this study: Participants with a diagnosis of ADHD, dyslexia, autism spectrum disorders, or with any neurological disorder (e.g., epilepsy) could not participate in this study. Participants who were pregnant, lactating or made use of abortion pills in the past 3 months were also excluded from participation. The current use of medication that is likely to interfere with the study (e.g., benzodiazepines, antidepressants, St. John's worth, ADHD medication) or with female hormonal levels (e.g., corticosteroids)

constituted another exclusion criteria. Participants who used alcohol more than 14 units per week or more than 4 units on any day during the week prior to the study or during the study period were also excluded. Participants who were regular smoker during the past year or made use of any nicotine products during the past week as well as a history of regular (more than once per month for three or more months) use of soft/hard drugs or any use during past months were also excluded. Moreover, participants who were left-handed or wore contact lenses during the experiment were excluded (glasses were allowed).

One participant was excluded from all analyses as there were missing behavioral and questionnaire data due to technical errors. Another participant was excluded from the hormonal manipulation check and correlation analyses due to missing hormone data. Hence, the final sample consisted of 42 naturally cycling healthy females aged 18-26 (M = 21.83, SD = 1.90).

Measures

To measure PM, participants performed a Flanker paradigm that is derived from the study of De Rover et al. (2015). This paradigm consisted of four sets of five horizontally arranged letters, that were either congruent ("HHHHH"; "SSSSS") or incongruent ("HHSHH"; "SSHSS"). Participants were instructed to respond as fast as possible with a left- or right button press corresponding with mapping of the center letter ('H' is mapped to the left button and 'S' to the right one), while ignoring the other letters (the flankers). There were six blocks of 80 trials each (1730ms) with a random distribution of 20 trials of each of the four possible stimulus arrays in each block. Participants received verbal feedback (after each block) to speed up or down in order to maintain an accuracy level of around 80%. While performing the Flanker task, cortical activation was monitored with EEG.

To assess the EBR, a resting state paradigm was used that is derived from a study by Putman (Putman, 2011). It consisted of eight blocks of one minute where participants were instructed to open or close their eyes in alternation with each block. In the open-eyes blocks, they were instructed to stare at a blank screen with a black cross while baseline EEG was recorded. For the current study, only the four open-eyes segments (4 seconds of each) were used for calculation of the EBR. Moreover, as we were interested in baseline dopamine, we only made use of EBR data from the EF phase as the EBR from the ML phase could have been impacted by high levels of ovarian hormones.

Estradiol and progesterone levels were obtained via collection of saliva at three time points during each session. Saliva was assessed by Medivere GmbH, and the hormone concentrations were averaged to gain one value for each session. Mood state on the two constructs of positive and negative affect (dimensions of emotional experience) were assessed with the 20-item state version of the Positive and Negative Affectivity Scales (PANAS; Watson, Clark, & Tellegen, 1988) after each saliva extraction. The five domains of personality (agreeableness, extraversion, conscientiousness, neuroticism, and openness to experience) were assessed with the 60-item version of the NEO-Five Factor Inventory (NEO-FFI; Hoekstra, Ormel, & de Fruyt, 1996). Vulnerability for depression was assessed with the 34-item revised edition of the Leiden Index of Depression Sensitivity (LEIDS-R; Van der Does, 2002).

Procedure

The two sessions took place in the same manner except that in the first session participants were given full explanation of the study, signed an informed consent, and filled out the NEO-FFI and LEIDS-R questionnaires. At the beginning of every session, they were also asked whether they still met the in- and exclusion criteria. During both sessions EEG was installed, and cortical activation was being monitored while the EBR was assessed, and the Flanker task was performed. Ovarian hormones were assessed at three time points: right at the beginning of the session, after EEG installation and after the experimental task. In total, participants spend approximately two hours per session in the lab, including the other experimental tasks and psychological tests that were part of the larger research project but are not relevant for this study. Participants were fully debriefed about the actual purpose of the study after completion of the second session.

Electrophysiological recordings and data processing

EEG 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. Horizontal and vertical eye electrooculograms (EOG) were recorded from electrodes placed on the outer canthi of the two eyes and from electrodes above and below the right eye. Eye blinks were defined as a change of voltage of 100 μV in a time interval of 500 ms. The data was digitized with a sampling rate of 512 Hz using a high-pass filter at 0.01 Hz. Cz was referenced to common mode sense

during data acquisition, and then re-referenced to the average of both mastoids. Data were processed and analyzed using the second version of the Brain Vision Analyzer (Brain Products, Munich, Germany). Cz was filtered with a high-pass filter of 0.02 Hz and a time constant of 8 seconds. Subsequently, a low-pass filter of 20 Hz (order 8) and a notch filter of 50 Hz was applied on all channels except the EOG. Before ocular correction, a lenient artifact rejection was performed using the following settings: maximum voltage step: 50 Hz, maximum amplitude difference: 300 μVin 200-ms interval, minimal and maximum amplitude: −250 and 250 μV, lowest activity in interval: 0.5 μV in 100 ms interval. Afterwards, eye movements were corrected with the automatic independent component analysis for ocular correction as provided in the Brain Vision Analyzer and checked afterwards. If for individual cases the automatic ocular independent component analysis correction proved unsatisfactory, the semiautomatic procedure was performed to remove EOG and cardiac artifacts.

Epochs with other artifacts were also discarded according to the following settings: maximum allowed voltage step: 50 Hz, maximum allowed amplitude difference: 100 μVin 200-ms interval, minimal and maximum allowed amplitude: −75 μVand 75 μV. Response-locked ERP were averaged separately based on correctness and time-locked ERP to response onset, from 200 ms before to 600 ms after the response. These ERP were then baseline corrected relative to a pre-response duration of 200 ms. The ERN amplitude was calculated using a peak-to-peak measure by subtracting the most positive peak (−80 to 80 ms) from the most negative peak (0 to 150 ms) at electrode Cz. Peak amplitudes were determined with a time interval of 20 ms surrounding each peak to reduce the influence of background EEG noise (see Jansen & de Bruijn, 2020).

Statistical analyses

To investigate possible differences between the low and high EBR groups, an independent-samples *t*-test was conducted with age, the total and individual personality scores of the NEO-FFI, the total score of the LEIDS-R and the negative and positive affect scores within both menstrual phases of the PANAS as dependent variables and the EBR (low | high) as between-subject factor.

To investigate standard behavioral Flanker effects, we made use of repeated measures ANOVAs. In the first analysis, we used cycle phase (EF | ML) and congruency (congruent |

incongruent) as within-subject factors and EBR (low | high) as between-subject factor to analyze reaction times to correct responses only. These factors were also used in a second analysis to investigate the error rates (in %). In the third analysis, we investigated differences between erroneous and correct trials with the within-subject factors cycle phase (EF | ML) and correctness (correct | incorrect) and the between-subject factor EBR (low | high) for reaction times to incongruent trials only.

For the ERN analysis, a repeated measures ANOVA was performed with cycle phase (EF | ML) and correctness (correct | incorrect) as within-subject factors, EBR (low | high) as between-subject factor and ERN amplitude as continuous DV. The factor correctness (correct | incorrect) was included in order to investigate whether amplitudes are indeed more negative for erroneous compared to correct responses. To create low and high EBR groups, a median split was used to divide groups equally. We expected a significant interaction effect between cycle phase, correctness and EBR on the ERN. To correct for multiple testing, we made use of Bonferroni correction and a significance threshold set at 0.05.

In addition, a paired-samples *t*-test was performed as a manipulation check to see whether both hormones are indeed higher in the ML phase than in the EF phase. Correlation analyses were conducted on an exploratory basis to see whether changes in hormonal levels correlate to changes in the ERN. For that we created difference scores for the ERN between phases for estrogen (ML - EF) and progesterone (ML - EF). We also included both hormones separately within both phases and the EBR from the total sample. Effect sizes were based on categorizations by Cohen (1988), with the following ranges: r < 0.1 = very small, r >= 0.1 and < 0.3 = small, r >= 0.3 and < 0.5 = moderate and r >= 0.5 = large.

The program JASP was used to run Bayesian mixed models in order to assess the strength of evidence for the null and alternative hypotheses. A Bayes factor (*BF*) value usually ranges from 0.01 to 100, where a BF <0.33 suggests that the null model is three times more favored than the alternative model, whereas a *BF* >3 is in favor of the alternative model, given the data. The inclusion Bayes factor (BF_{incl}) is a BF that compares a model with a specific factor with a model without that factor, in order to provide evidence for the data to include this specific factor (Hinne, Gronau, van den Bergh, & Wagenmakers, 2020). The classification system by Lee and Wagenmakers (Lee & Wagenmakers, 2014) provides a series of interpretative labels for a range of *BF* values that are either in favor of the null or alternative hypothesis, namely “anecdotal” for *BF* >.33 or <3, “moderate” for *BF* between .1

and .33 or 3 and 10, “strong” for *BF* between .03 and .1 or 10 and 30, “very strong” for *BF* between .01 and .03 or 30 and 100, and “extreme” for *BF* <.01 or >100 (for illustration see Quintana & Williams, 2018). Moreover, data sensitivity might also be inferred from a *BF*, indicating whether the sample size was sufficient to support one hypothesis over another. *BFs* between .33 and 3 may indicate that the sample size was too small, whereas *BFs* <.33 or >3 suggest that the sample size was sufficient to provide evidence for either the null or alternative hypotheses (Dienes, 2014).

Results

Questionnaires

There were no significant differences between participants scoring low and high on EBR regarding age, NEO-FFI, LEIDS-R and PANAS (see Table 1). This indicates that any potential differences between the EBR groups cannot be explained by differences in these group characteristics.

Hormones

To see whether the manipulation was effective, and that assessment took place at the right time, we performed a paired-samples *t*-test as a manipulation check to see whether estrogen and progesterone are higher in the ML phase than in the EF phase. Results showed that estrogen was indeed higher in the ML phase ($M = 3.90$, $SD = 1.52$) compared to the EF phase ($M = 3.00$, $SD = 2.25$), $t\,(40) = 2.424$, $p = .020$. The same was found for progesterone in the ML phase ($M = 202.51$, $SD = 136.05$) compared to the EF phase ($M = 81.20$, $SD = 75.46$), $t\,(40) = 5.093$, $p < .001$. This indicates that the manipulation was effective and expected effects could be ascribed to hormonal fluctuations in the menstrual cycle.

Behavioral Results

As expected, the analysis on correct responses showed a significant main effect of Congruency, $F(1,40) = 156.875$, $p < .001$, $\eta^2 = .797$, with slower reaction times to incongruent (376 ms) compared to congruent (357 ms) trials. There was also a significant interaction effect of congruency and EBR, $F(1,40) = 5.885$, $p = .020$, $\eta^2 = .128$. This interaction appears to be explained by the fact that the difference between congruent and

incongruent trials was larger for those in the high EBR group compared to the low EBR group, leading to a larger difference between EBR groups for the incongruent trials. However, post-hoc tests showed that there was no significant difference between the low (M = 353) and high (M = 361) group in the congruent trials (p = .324), and also not between the low (M = 368) and high (M = 384) group in the incongruent trials (p = .129). In addition, there was also a significant interaction effect of cycle phase and EBR, $F(1,40) = 4.533$, $p = .039$, $\eta^2 = .102$. This interaction appears to be explained by the fact that the low EBR group showed an increase in reaction times from the EF phase to the ML phase whereas the high EBR group showed a decrease, with post-hoc tests showing a trend difference in reaction times between the low (M = 355) and high (M = 376) EBR group during the EF phase (p = .054), but not for the low (M = 366) and high (M = 369) group during the ML phase (p = .779), and also a trend difference in reaction times between the EF phase and ML phase in the low EBR group (p = .081), but not in the high group (p = .223).

As expected, the analysis on incongruent trials showed a significant main effect of Correctness, $F(1,40) = 371.560$, $p < .001$, $\eta^2 = .903$, with slower reaction times to correct trials (376 ms) compared to erroneous trials (312 ms). No other main or interaction effect reached significance (all ps > .093, all Fs < 2.955). In line with the standard behavioral Flanker effects, the error-rate analysis showed the expected significant main effect of congruency, $F(1,40) = 134.974$, $p < .001$, $\eta^2 = .771$, with more errors for incongruent (15.9 %) compared to congruent trials (8.6 %), indicating the presence of an interference effect. No other significant main or interaction effects were observed (all ps > .249, all Fs < 1.367).

ERN Analyses

Figure 1 displays the mean ERN for the EF phase and ML phase as well as for the EBR groups. A Repeated Measures ANOVA was conducted to explore the interaction of cycle phase, EBR and correctness on the ERN. The analysis revealed a significant main effect of correctness, $F(1,40) = 100.201$, $p < .001$, $\eta^2 = .715$, with ERN amplitudes being larger (i.e., more negative) for erroneous (M = -8.565, SE = 0.648) compared to correct (M = -2.454, SE = 0.251) responses. There was no significant main effect of cycle phase, $F(1,40) = 0.288$, p = .595, $\eta^2 = .007$, or EBR, $F(1,40) = 0.000$, $p = .994$, $\eta^2 = .000$. There was also no significant interaction effect of cycle phase and correctness, $F(1,40) = 0.532$, $p = .470$, $\eta^2 = .013$, and no significant interaction effect of EBR and correctness, $F(1,40) = 0.000$, $p = .983$, $\eta^2 = .000$. In

addition, the interaction of cycle phase, EBR and correctness was also non-significant, $F(1,40) = 0.099$, $p = .755$, $\eta^2 = .002$. Bayesian mixed models indicate extremely strong evidence that data can best be explained by the factor correctness ($BF_{incl} = 1.025e + 23$), whereas cycle phase ($BF_{incl} = .185$), the interaction of cycle phase and correctness ($BF_{incl} = .296$), EBR and correctness ($BF_{incl} = .222$) and the interaction cycle phase, EBR and correctness ($BF_{incl} = .168$) provide moderate evidence in favor of the null hypothesis.

Correlations

There were no significant cycle-dependent correlations between the ERN, estrogen and progesterone. However, there was a moderate negative correlation between the EBR in the total group and estrogen in the ML phase, $r(39) = -.34$, $p = .028$, with the EBR decreasing as the estrogen increases. There was also a moderate negative correlation between the EBR in the total group and the difference in estrogen between the menstrual phases, $r(39) = -.35$, $p = .025$, with the EBR decreasing the larger the difference scores. Progesterone was not associated with the EBR (see Table 2).

Table 1

Group characteristics of total sample and participants scoring low and high on EBR

		Total (N = 42)	Low EBR (n = 22)	High EBR (n = 20)	
		M (SD)	*M (SD)*	*M (SD)*	*p* value
Age		21.83 (1.90)	21.77 (1.57)	21.90 (2.25)	.831
NEO-FFI	Total	184.00 (9.36)	182.36 (9.12)	185.80 (9.52)	.239
	Agreeableness	33.67 (3.59)	33.41 (3.03)	33.95 (4.17)	.631
	Conscientiousness	40.50 (3.05)	40.73 (2.69)	40.25 (3.45)	.618
	Extraversion	43.52 (6.06)	43.59 (6.58)	43.45 (5.61)	.941
	Neuroticism	32.69 (6.68)	31.05 (7.12)	34.50 (5.81)	.094
	Openness	33.62 (3.24)	33.59 (2.82)	33.65 (3.72)	.954
LEIDS-R		39.05 (15.14)	38.00 (14.87)	40.20 (15.74)	.644
PANAS	Negative Affect EF	13.48 (3.88)	13.41 (3.83)	13.55 (4.05)	.908
	Negative Affect ML	12.79 (3.79)	13.23 (4.96)	12.30 (1.84)	.435
	Positive Affect EF	24.05 (5.71)	24.32 (6.61)	23.75 (4.67)	.752
	Positive Affect ML	24.98 (5.18)	25.55 (6.05)	24.35 (4.10)	.462

Note. EBR = Spontaneous eye blink rate; NEO-FFI = NEO-Five Factor Inventory; LEIDS-R = Leiden Index of Depression Sensitivity; PANAS = Positive and Negative Affectivity Scales; EF = Early follicular phase; ML = Mid-luteal Phase

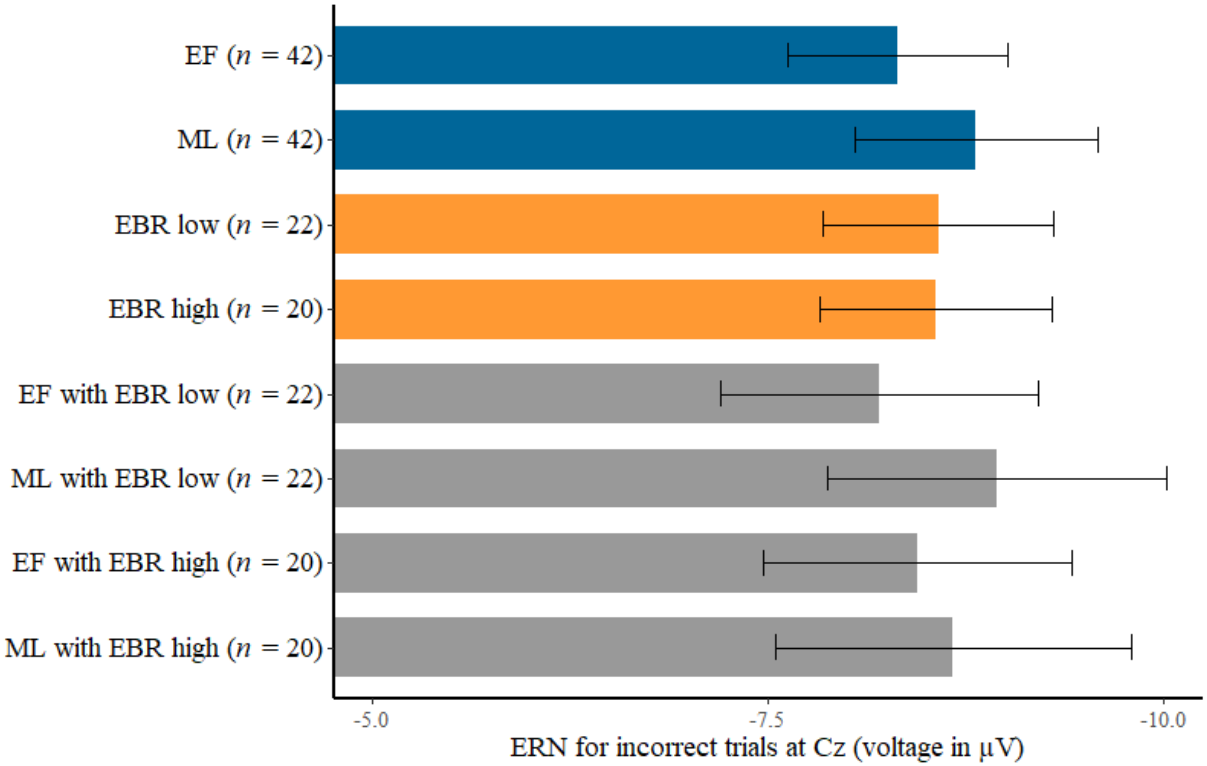

Figure 1

Bar chart depicting the ERN for the EF phase and ML phase (blue) and for the low and high EBR groups (orange) as well as for the EF phase and ML phase with low and high EBR (grey). Values are means, with error bars depicting standard errors.

Table 2

Descriptive Statistics and Correlation Coefficients for EBR, Estrogen, Progesterone and the Difference Scores of Estrogen, Progesterone and ERN (n = 41)

Variable	*M*	*SD*	1.	2.	3.	4.	5.	6.	7.
1. EBR	239.02	128.34							
2. E2 EF	3.00	2.25	.136						
3. E2 ML	3.90	1.52	-.343*	.262					
4. P4 EF	81.20	75.46	.026	.161	.196				
5. P4 ML	202.51	136.05	-.082	.094	.194	.045			
6. E2 ML-EF	0.89	2.36	-.351*	-.783**	.395*	-.027	.035		
7. P4 ML-EF	121.32	152.54	-.086	.004	.076	-.454**	.869**	.045	
8. ERN ML-EF	-0.51	4.63	.029	-.032	.104	.017	.141	.098	.117

Note. *$p < .05$. **$p < .01$. EBR = Eye blink rate in total group; E2 – Estrogen; P4 – Progesterone; EF = Early follicular phase; ML = Mid-luteal phase; ERN = Error-related negativity

Discussion

The present study is the first to explore the interactional effects of menstrual cycle and EBR on electrophysiological measures of PM in naturally cycling females. It was hypothesized that females with a lower EBR have a larger ERN in the ML phase compared to the EF phase and females with higher EBR have a larger ERN in the EF phase compared to the ML phase. Against the hypothesis, there was no main or interaction effect of cycle phase and EBR on the ERN. In fact, Bayesian analyses indicate moderate evidence against an interaction effect. Moreover, phasic changes in the ERN did not correlate with changes in either estrogen or progesterone. However, there was an interaction effect of cycle phase and EBR on reaction times, with reaction times becoming slower from the EF to the ML phase in the low EBR group and faster in the high EBR group, with post-hoc tests supporting only the effect in the low EBR group. Also, within the EF phase, the low EBR group had faster reaction times compared to the high EBR group. Furthermore, lower EBR was associated with higher estrogen in the ML phase, but not with progesterone.

That the menstrual cycle and the EBR did not have an effect on the ERN is contrary to research indicating a modulatory role of estrogen on dopaminergic activity (Barth et al., 2015; Jacobs & D'Esposito, 2011; Yoest et al., 2018). The higher estrogen levels in the ML phase did not seem to compensate for lower dopamine and also did not aggravate performance with higher dopamine. It also contradicts the findings by Hidalgo-Lopez and Pletzer (2017) and Jacobs and D'Esposito (2011), whose participants showed an enhanced performance when high in ovarian hormones and low in dopamine as well as low in ovarian hormones with high dopamine levels. Moreover, the non-significant main effect of EBR on the ERN is not in line with research indicating that the ERN is sensitive to changes in dopamine (Ullsperger et al., 2014) and the assumption that the ERN originates from a dopamine disinhibition of the ACC (Holroyd & Coles, 2002; Weinberg et al., 2016). However, the non-significant main effect of cycle phase on the ERN is in line with Mulligan et al. (2019), as they also found no effect of cycle phase on the ERN.

These results are unlikely to be explained by missing hormonal fluctuations or flaws in the application of the EEG or the behavioral task. Participants showed higher levels of both estradiol and progesterone in the ML phase as compared to the EF phase. This is in line with previous hormone work (Hidalgo-Lopez & Pletzer, 2021; Mulligan et al., 2019) and indicates

that measurements were taken at appropriate times and participants were indeed naturally cycling. Moreover, we did find the standard behavioral Flanker interference effects, which is in line with previous research (Jansen & de Bruijn, 2020) and indicates that participants sufficiently deployed inhibitory control to suppress non-target stimuli (Tiego, Testa, Bellgrove, Pantelis, & Whittle, 2018). The interference effect was also evident on a neural level as there were larger ERN amplitudes for errors compared to correct responses and for incongruent compared to congruent stimuli, which indicates that EEG measurements were taken properly. In addition, Bayesian analyses indicate that the sample size was large enough to produce possible effects (Dienes, 2014).

One possible reason why there was no interaction effect of cycle phase and EBR on the ERN could be that the EBR did not sufficiently indexed baseline dopamine levels. The EBR is a potential indirect measurement of dopaminergic activity and does not exactly equate baseline dopamine levels. Although research does point to its reliable use as an index of baseline dopamine (Maffei & Angrilli, 2018), there are also some studies that do not support the link between the EBR and dopaminergic activity (Sescousse et al., 2018). This might also provide a possible explanation why Jacobs and D'Esposito (2011) did find an interaction between cycle phase and baseline dopamine (measured with COMT enzymatic activity), while Hidalgo-Lopez and Pletzer (2017) did not show this interaction on the same task using the EBR as a dopamine measurement. Moreover, as a median split was used to distinguish low and high EBR, it is unclear whether participants in the low EBR group indeed had low baseline dopamine levels or ones that fall more into the medium range, thereby being closer to the optimal range of dopamine (Cools & D'Esposito, 2011). Thus, it is possible that the EBR was not sensitive enough to reliably measure baseline dopamine.

Furthermore, it is important to emphasize the differences in the experimental tasks used to investigate the relations between ovarian hormones and dopaminergic activity. The two studies showing an interaction of cycle phase and EBR (Hidalgo-Lopez & Pletzer, 2017; Jacobs & D'Esposito, 2011) utilized the Stroop task and the verbal n-back task, which can be compared to the Flanker task as they measure similar cognitive abilities. In particular, all tasks are supposed to measure response inhibition control and selective attention as participants have to inhibit (distracting) stimuli and focus their attention on the targets. However, the verbal n-back task seems more cognitive demanding as it varies in task load and additionally requires participants to continuously update their targets (Scharinger, Soutschek,

Schubert, & Gerjets, 2015). The color Stroop task can further be differentiated from the Flanker task as the first one requires participants to retrieve colors whereas the latter focuses on letters. In fact, Hidalgo-Lopez & Pletzer (2017) did only find an interaction in the color condition of the Stroop task, and not in the word condition. The authors concluded that this difference may be explained by the theory that the color condition elicits more response competition and requires more cognitive control than the word condition, as the reading of words is more practiced and automatic than the reading of colors. Even though the Flanker task requires participants to attend to single letters instead of reading words, these findings point out that it is possible that already small differences in the experimental design could be responsible for missing effects.

Another possible reason why there was no cycle effect on the ERN could be that hormonal concentrations were not large enough to produce the expected effects. The menstrual cycle consists of several phases and while estrogen and progesterone levels in the ML phase are both high, the highest estrogen levels are evident just before ovulation. This phase is usually termed pre-ovulatory or late follicular phase and consists of peak estrogen and low progesterone levels. Jacobs and D'Esposito's (2011) finding of an interaction between estrogen and dopamine on working memory performance was based on a comparison of the early- and late follicular phase. Likewise, findings by Diekhof et al. (2016) on cycle-related changes in the activation of the dorsal ACC were based on a comparison of ovarian hormones between the late follicular and luteal phase. Thus, it could be that estrogen levels in the ML phase were not high enough to sufficiently modulate dopamine activity for an impact on cognition as suggested by previous research (Barth et al., 2015; Jacobs & D'Esposito, 2011; Yoest et al., 2018). However, it should also be noted that findings by Hidalgo-Lopez and Pletzer (2017) on the interaction between cycle phase and dopamine were observed for a comparison of the early follicular phase and luteal phase, and no difference was made with the pre-ovulatory phase.

Moreover, the effect of progesterone on cognition is rather unclear and some studies have suggested an attenuating effect on estrogenic activity. For example, a review article by Baudry and Aguirre (2013) showed that progesterone has antagonistic effects on estrogenic actions. In addition, a study by Singhal et al. (2016) found progesterone to antagonize estrogen signaling at a cellular level, while showing similar effects by itself. While these interactions are not fully understood yet, it might be possible that high levels of progesterone

in the ML phase diminish or modulate the effect of estrogen on dopaminergic activity. This modulation would be less evident in the pre-ovulatory phase, as the peak estrogen levels are accompanied by low progesterone levels. This could also provide a possible explanation for the non-significant results by Mulligan et al. (2019), who compared the mid-follicular phase with the ML phase.

Even though there was no effect on the ERN, results did show an interaction of cycle phase and EBR on reaction times. Participants in the low EBR group reacted faster in the EF phase than in the ML phase, while those in the high group showed the opposite pattern. This direction was unexpected, as research on the estrogen-dopamine link indicates that higher estrogen levels facilitate performance with low dopamine and hinders it with high dopamine (Barth et al., 2015; Jacobs & D'Esposito, 2011; Yoest et al., 2018). Interestingly, the main effects of cycle phase and EBR did not reached significance, indicating that only their interaction affected reaction times. These findings are in line with Hidalgo-Lopez and Pletzer (2017), as they also found no main but interaction effects of cycle phase and EBR on reaction time performance in the color Stroop task. However, their interaction was in the opposite direction and did support the expected effect of estrogen on dopamine. A comparison of the study by Hidalgo-Lopez and Pletzer (2017) to the current study indicates that they only differed in their experimental task, which might further emphasize the important role of the task and the specific underlying cognitive processes being addressed.

Moreover, in the EF phase, participants in the low EBR group had faster reaction times than the high group, indicating a better behavioral performance the lower the hormonal and dopamine levels. This finding contradicts research that consistently indicates enhanced cognitive performances with higher dopamine levels (Cools & D'Esposito, 2011; Pekcec et al., 2018). However, the inverted U-shaped function of dopamine and cognition also indicates that optimal dopamine levels exist, and it could be that dopamine levels in the high EBR group were too high and detrimental to performance. Likewise, dopamine levels in the low EBR group might have been closer to the optimal range and therefore resulted in a faster performance (Cools & D'Esposito, 2011). Moreover, these results should be interpreted with caution as the behavioral performance outcomes do not have a high validity due to their manipulation (instructions to speed up or down for the right amount of errors).

Interestingly, lower EBR in the EF phase was associated with higher levels of estrogen in the ML phase. Although this association is not tied to any performance measures and no

causality can be inferred, it does point into the expected direction that estrogen compensates for lower baseline dopamine. The fact that the EBR was only associated with estrogen and not with progesterone provides further support for the theory that estrogen has a distinct relationship with dopamine and that the link to progesterone is less clear (Baudry & Aguirre, 2013; Yoest et al., 2018). Although the literature on the validity of the EBR as a measurement of dopamine is mixed, these findings do indicate that there is a link between estrogen and the EBR as an indirect measurement of dopaminergic functions.

Several limitations should be considered. First, the absence of differences between the EF and ML phase is difficult to interpret as both estradiol and progesterone are higher during the ML phase and possible effects could be either through increased levels of estradiol, progesterone, both hormones, or neither. Future studies should therefore include the pre-ovulatory phase as its high estrogen and low progesterone levels might help discern effects of estrogen when being compared to the EF phase, and also allows for inferences of both hormones when compared with both the EF and ML phase. The inclusion of at least three menstrual phases, especially the pre-ovulation phase, has also been emphasized by a recent review article by Bernal and Paolieri (2022) on studies comparing the effect of menstrual phases. Thus, a comparison of at least three menstrual phases helps to disentangle combinatory effects and allows more room for causal inferences.

Second, the EBR as a measurement of baseline dopamine should be taken into account as no objective cut-off was used to distinguish between low and high levels. Future studies might incorporate more valid and direct measurements of baseline dopamine, such as the COMT enzymatic activity (see Jacobs & D'Esposito, 2011). However, it should also be noted that the EBR as an indirect dopamine measurement was a strength of this study, as it is a fast, inexpensive and non-invasive measurement tool (Maffei & Angrilli, 2018). Other strengths of the study were the inclusion of the menstrual phases instead of each hormone separately. This inclusion contributes to a high ecological validity as the hormones do not occur separately from each other within the menstrual cycle. Also, the homogeneity of the sample was useful for the sensitivity to and interpretability of possible effects. However, this comes at the cost of the generalizability as the sample might not be a realistic representation of the majority of adult females.

In conclusion, this study did not show an effect of the menstrual cycle and the EBR on the ERN in naturally cycling adult females. Although the hypotheses were not confirmed,

there were still some noteworthy findings that might shed more light into the complex interplay of ovarian hormones and cognitive functioning. Only the interaction of the menstrual cycle and the EBR, and not their main effects, did affect reaction times, which might indicate a link between ovarian hormones and dopamine. Moreover, the association between the EBR and estrogen in the ML phase might support previous research on the estrogen-DA link. Given that the neural index of PM is related to mood and supposed to be a biomarker for several psychopathologies, future studies could investigate whether the menstrual cycle differentially affects the ERN of individuals with mood disorders compared to healthy controls. A better understanding of the impact of ovarian hormonal fluctuations on cognitive functioning might emerge to be useful in studying risks for psychiatric disorders and their pharmacological treatment. Investigating the neural underpinnings of cycle-induced affective changes might also have implications for the use of contraceptive pills and their impact on women's physical and emotional health.

References

Barth, C., Villringer, A., & Sacher, J. (2015). Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Frontiers in Neuroscience, 9*, 1-20. doi:10.3389/fnins.2015.00037

Baudry, M., Bi, X., & Aguirre, C. (2013). Progesterone–estrogen interactions in synaptic plasticity and neuroprotection. *Neuroscience, 239*, 280-294. doi:10.1016/j.neuroscience.2012.10.051

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. doi:10.1111/nyas.14255

Bernal, A., & Paolieri, D. (2022). The influence of estradiol and progesterone on neurocognition during three phases of the menstrual cycle: modulating factors. *Behavioural Brain Research, 417*, 1-12. doi:10.1016/j.bbr.2021.113593

Brötzner, C. P., Klimesch, W., & Kerschbaum, H. H. (2015). Progesterone-associated increase in ERP amplitude correlates with an improvement in performance in a spatial attention paradigm. *Brain Research, 1595*, 74–83. doi:10.1016/j.brainres.2014.11.004

Cohen, J. 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd Ed. New York: Routledge.

Cools, R., & D'Esposito, M. (2011). Inverted-U–Shaped Dopamine Actions on Human Working Memory and Cognitive Control. *Biological Psychiatry, 69*(12), e113-e125. doi:10.1016/j.biopsych.2011.03.028

De Bruijn, E. R. A., Hulstijn, W., Verkes, R. J., Ruigt, G. S. F., & Sabbe, B. G. C. (2004). Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology, 177*(1-2), 151–160. doi:10.1007/s00213-004-1915-6

De Rover, M., Brown, S. B. R. E., Band, G. P., Giltay, E. J., van Noorden, M. S., van der Wee, N. J. A., & Nieuwenhuis, S. (2015). Beta receptor-mediated modulation of the oddball P3 but not error-related ERP components in humans. *Psychopharmacology*, *232*(17), 3161–3172. doi:10.1007/s00213-015-3966-2

Diekhof, E. K., & Ratnayake, M. (2016). Menstrual cycle phase modulates reward sensitivity and performance monitoring in young women: preliminary fMRI evidence. *Neuropsychologia, 84*, 70-80. doi:10.1016/j.neuropsychologia.2015.10.016

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in psychology, 5*, 1-17. doi:10.3389/fpsyg.2014.00781

Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and pleasure: An RDOC-inspired examination of threat responses and reward processing in anxiety and depression. *Depression and anxiety, 31*(3), 233-249. doi:10.1002/da.22202

Eriksen, C. W. (1995). The flankers task and response competition: A useful tool for investigating a variety of cognitive problems. *Visual Cognition, 2*(2-3), 101-118. doi:10.1080/13506289508401726

Girard, R., Météreau, E., Thomas, J., Pugeat, M., Qu, C., & Dreher, J. C. (2017). Hormone therapy at early post-menopause increases cognitive control-related prefrontal activity. *Scientific reports, 7*(1), 1-11. doi:10.1038/srep44917

Gordon, J. L., Rubinow, D. R., Eisenlohr-Moul, T. A., Xia, K., Schmidt, P. J., & Girdler, S. S. (2018). Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA psychiatry, 75*(2), 149-157. doi:10.1001/jamapsychiatry.2017.3998

Green, S. A., & Graham, B. M. (2022). Symptom fluctuation over the menstrual cycle in anxiety disorders, PTSD, and OCD: a systematic review. *Archives of Women's Mental Health, 25*, 71-85. doi:10.1007/s00737-021-01187-4

Groman, S. M., James, A. S., Seu, E., Tran, S., Clark, T. A., Harpster, S. N., ... & Jentsch, J. D. (2014). In the blink of an eye: relating positive-feedback sensitivity to striatal dopamine D2-like receptors through blink rate. *Journal of Neuroscience, 34*(43), 14443-14454. doi:10.1523/JNEUROSCI.3037-14.2014

Hidalgo-Lopez, E., & Pletzer, B. (2017). Interactive Effects of Dopamine Baseline Levels and Cycle Phase on Executive Functions: The Role of Progesterone. *Frontiers in Neuroscience, 11*, 1-14. doi:10.3389/fnins.2017.00403

Hidalgo-Lopez, E., & Pletzer, B. (2021). Fronto-striatal changes along the menstrual cycle during working memory: Effect of sex hormones on activation and connectivity patterns. *Psychoneuroendocrinology, 125*, 1-12. doi:10.1016/j.psyneuen.2020.105108

Hinne, M., Gronau, Q. F., van den Bergh, D., & Wagenmakers, E. J. (2020). A conceptual introduction to Bayesian model averaging. *Advances in Methods and Practices in Psychological Science, 3*(2), 200-215. doi:10.1177/2515245919898657

Hoekstra, H. A., Ormel, J., & De Fruyt, F. (1996). *Handleiding NEO persoonlijkheids-vragenlijsten NEO-PI-R en NEO-FFI*. Lisse: Swets Test Services.

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological review, 109*(4), 679–709. doi:10.1037/0033-295X.109.4.679

Jacobs, E., & D'Esposito, M. (2011). Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *Journal of Neuroscience, 31*(14), 5286-5293. doi:10.1523/JNEUROSCI.6394-10.2011

Jansen, M., & de Bruijn, E. R. A. (2020). Mistakes that matter: An event-related potential study on obsessive-compulsive symptoms and social performance monitoring in *different responsibility contexts. Cognitive, Affective, & Behavioral Neuroscience, 20*(4), 684-697. doi:10.3758/s13415-020-00796-3

Jocham, G., & Ullsperger, M. (2009). Neuropharmacology of performance monitoring. *Neuroscience & Biobehavioral Reviews, 33*(1), 48-60. doi:10.1016/j.neubiorev.2008.08.011

Jongkees, B. J., & Colzato, L. S. (2016). Spontaneous eye blink rate as predictor of dopamine-related cognitive function - A review. *Neuroscience & Biobehavioral Reviews, 71*, 58-82. doi:10.1016/j.neubiorev.2016.08.020

Lee, M. D., & Wagenmakers, E. J. (2014). *Bayesian cognitive modeling: A practical course*. New York, NY: Cambridge university press

Maffei, A., & Angrilli, A. (2018). Spontaneous eye blink rate: An index of dopaminergic component of sustained attention and fatigue. *International Journal of Psychophysiology, 123*, 58–63. doi:10.1016/j.ijpsycho.2017.11.009

Meyer, A. (2016). Developing psychiatric biomarkers: A review focusing on the error-related negativity as a biomarker for anxiety. *Current Treatment Options in Psychiatry, 3*(4), 356–364. doi:10.1007/s40501-016-0094-5

Meyer, A., Nelson, B., Perlman, G., Klein, D. N., & Kotov, R. (2018). A neural biomarker, the error-related negativity, predicts the first onset of generalized anxiety disorder in a large sample of adolescent females. *Journal of Child Psychology and Psychiatry*, *59*(11), 1162-1170. doi:10.1111/jcpp.12922

Michael, J. A., Wang, M., Kaur, M., Fitzgerald, P. B., Fitzgibbon, B. M., & Hoy, K. E. (2021). EEG correlates of attentional control in anxiety disorders: A systematic review of error-related negativity and correct-response negativity findings. *Journal of Affective Disorders, 291*, 140-153. doi:10.1016/j.jad.2021.04.049

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. doi:10.1016/j.psyneuen.2019.01.027

Olvet, D., & Hajcak, G. (2008). The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clinical Psychology Review, 28*(8), 1343–1354. doi:10.1016/j.cpr.2008.07.003

Owens, S. A., & Eisenlohr-Moul, T. (2018). Suicide risk and the menstrual cycle: a review of candidate RDoC mechanisms. *Current psychiatry reports, 20*(11), 1-11. doi:10.1007/s11920-018-0962-3

Pekcec, A., Schülert, N., Stierstorfer, B., Deiana, S., Dorner-Ciossek, C., & Rosenbrock, H. (2018). Targeting the dopamine D1 receptor or its downstream signalling by inhibiting

phosphodiesterase-1 improves cognitive performance. *British journal of pharmacology, 175*(14), 3021-3033. doi:10.1111/bph.14350

Putman, P. (2011). Resting state EEG delta–beta coherence in relation to anxiety, behavioral inhibition, and selective attentional processing of threatening stimuli. *International Journal of Psychophysiology, 80*(1), 63–68. doi:10.1016/j.ijpsycho.2011.01.011

Quintana, D. S., & Williams, D. R. (2018). Bayesian alternatives for common null-hypothesis significance tests in psychiatry: a non-technical guide using JASP. *BMC psychiatry*, *18*(1), 1-8. doi:10.1186/s12888-018-1761-4

Riesel, A. (2019). The erring brain: Error-related negativity as an endophenotype for OCD - A review and meta-analysis. *Psychophysiology, 56*, 1-22. doi:10.1111/psyp.13348

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. *Psychological medicine, 49*(7), 1207-1217. doi:10.1017/S0033291719000199

Scharinger, C., Soutschek, A., Schubert, T., & Gerjets, P. (2015). When flanker meets the n-back: What EEG and pupil dilation data reveal about the interplay between the two central-executive working memory functions inhibition and updating. *Psychophysiology, 52*(10), 1293-1304. doi:10.1111/psyp.12500

Schmidt, P. J., Dor, R. B., Martinez, P. E., Guerrieri, G. M., Harsh, V. L., Thompson, K., ... & Rubinow, D. R. (2015). Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. *JAMA psychiatry, 72*(7), 714-726. doi:10.1001/jamapsychiatry.2015.0111

Sescousse, G., Ligneul, R., van Holst, R. J., Janssen, L. K., de Boer, F., Janssen, M., ... & Cools, R. (2018). Spontaneous eye blink rate and dopamine synthesis capacity: preliminary evidence for an absence of positive correlation. *European Journal of Neuroscience, 47*(9), 1081-1086. doi:10.1111/ejn.13895

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. *Nature Reviews Neuroscience, 12*(3), 154-167. doi:10.1038/nrn2994

Singhal, H., Greene, M. E., Tarulli, G., Zarnke, A. L., Bourgo, R. J., Laine, M., ... & Greene, G. L. (2016). Genomic agonism and phenotypic antagonism between estrogen and

progesterone receptors in breast cancer. *Science Advances, 2*(6), 1-14. doi:10.1126/sciadv.1501924

Steullet, P., Cabungcal, J. H., Cuénod, M., & Do, K. Q. (2014). Fast oscillatory activity in the anterior cingulate cortex: dopaminergic modulation and effect of perineuronal net loss. *Frontiers in cellular neuroscience*, *8*, 1-10. doi:10.3389/fncel.2014.00244

Sublette, M. E. (2020). Lipids and Suicide Risk. In E. Baca-Garcia (Eds.), *Behavioral Neurobiology of Suicide and Self Harm* (pp. 155-177). doi:10.1007/7854_2020_163

Tiego, J., Testa, R., Bellgrove, M. A., Pantelis, C., & Whittle, S. (2018). A hierarchical model of inhibitory control. *Frontiers in psychology, 9*, 1-25. doi:10.3389/fpsyg.2018.01339

Tobias, M. R., & Ito, T. A. (2021). Anxiety increases sensitivity to errors and negative feedback over time. *Biological Psychology, 162*, 1-15. doi:10.1016/j.biopsycho.2021.108092

Ullsperger, M., Danielmeier, C., & Jocham, G. (2014). Neurophysiology of performance monitoring and adaptive behavior. *Physiological Reviews, 94*(1), 35–79. doi:10.1152/physrev.00041.2012

Ullsperger, M., Fischer, A. G., Nigbur, R., & Endrass, T. (2014). Neural mechanisms and temporal dynamics of performance monitoring. *Trends in cognitive sciences, 18*(5), 259-267. doi:10.1016/j.tics.2014.02.009

Van der Does, A.J.W. (2002). Cognitive reactivity to sad mood: structure and validity of a new measure. *Behavioral Research Therapy, 40*, 105-120. doi:10.1016/S0005-7967(00)00111-X

Wagenmakers, E. J., Love, J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., ... & Morey, R. D. (2018). Bayesian inference for psychology. Part II: Example applications with JASP. *Psychonomic bulletin & review, 25*(1), 58-76. doi:10.3758/s13423-017-1323-7

Wang, J. X., Zhuang, J. Y., Fu, L., Lei, Q., Fan, M., & Zhang, W. (2020). How ovarian hormones influence the behavioral activation and inhibition system through the dopamine pathway. *PLOS ONE, 15*(8), 1-17. doi:10.1371/journal.pone.0237032

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology, 54*(6), 1063-1070. doi:10.1037/0022-3514.54.6.1063

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. doi:10.1111/psyp.12538

Wharton, W., E Gleason, C., Sandra, O., M Carlsson, C., & Asthana, S. (2012). Neurobiological underpinnings of the estrogen-mood relationship. *Current psychiatry reviews, 8*(3), 247-256. doi:10.2174/157340012800792957

Yoest, K. E., Quigley, J. A., & Becker, J. B. (2018). Rapid effects of ovarian hormones in dorsal striatum and nucleus accumbens. *Hormones and Behavior, 104*, 119–129. doi:10.1016/j.yhbeh.2018.04.002