

Mid-luteal phase progesterone effects on vigilance tasks are modulated by women's chronotype

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ABSTRACT

Background: In this study we assessed the effects of progesterone on vigilance tasks that require sustained attention. In contrast to previous research, we differentiated two components of vigilance: the exogenous component, involved in monotonous and tedious tasks such as the Psychomotor Vigilance Task (PVT); and the endogenous component, involved in tasks that require cognitive control such as the Sustained Attention to Response Task (SART).

Methods: A sample of 32 female participants differing in extreme chronotypes were tested at their optimal and non-optimal time-of-day, as secretion of sex hormones follows biological rhythms. Ovulation tests that measure the presence of luteinizing hormone (LH) in urine were used to minimize methodological errors. Women of Morning-type or Evening-type chronotypes completed 4 experimental sessions of the two attentional tasks when they were in their follicular (low progesterone level) and mid-luteal (high progesterone level) phases, both in the morning (8:00 AM) and the evening (8:30 PM).

Results: Compared with the follicular phase, performance in the mid-luteal phase improved in the Morning-type participants and worsened in the Evening-type participants. This pattern of results was observed only when testing occurred at the optimal time-of-day and with both the PVT and the SART tasks.

Conclusion: These results suggest that the simultaneous presence of both progesterone and cortisol at 8:00 AM may explain the benefit observed in Morning-type females. In contrast, the low concentration of cortisol along with the reduced benefit of mid-luteal phase progesterone in the evening may account for the worsening in performance observed in Evening-type females.

1. Introduction

Cognitive performance involves many different processes associated to specific psychological functions, and the efficiency of such processes may depend on variations in the pre-existing state of the organisms (see Colzato et al., 2020). Here we will focus on how the level of some sexual hormones usually observed along the menstrual cycle, concretely progesterone, influence women's performance when they perform some vigilance tasks that require sustained attention.

Progesterone is crucial in the implantation of the fertilized ovocyte and its receptors are distributed among areas such as amygdala, hippocampus, hypothalamus, thalamus and frontal cortex (Kato et al., 1994; Guerra-Araiza et al., 2000, 2002, 2003). In these regions, progesterone binds to receptor membrane component-1 (PGRMC1) (Intlekofer and Petersen, 2011). Once bound to its receptor, it induces

rapid non-genomic changes. Metabolization of progesterone produces neuroactive steroids such as pregnanolone and allopregnanolone, which in turn stimulate GABA receptors, related to the excitation/inhibition balance of brain regions (Inghilleri et al., 2004; Smith et al., 2002) and thus to the modulation of cognitive function (Sundström Poromaa and Gingnell, 2014). However, the influence of sexual hormones on attentional tasks is particularly sparse (Pletzer et al., 2017). Moreover, it must be taken into account that attention is not a unitary concept and several attentional functions have already been dissociated at both the behavioral and neural levels (Posner and Petersen, 1990).

Importantly, most attentional functions seem to be fostered in the mid-luteal phase, when the progesterone level is at its peak and cortical inhibition is at its maximum. For example, enhancement has been observed in tasks that require spatial attention (Brötzner et al., 2015), decision-making (Solis-Ortiz et al., 2004), inhibition (Lord and Taylor,

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1991), vigilance (Vidafar et al., 2018), and conflict resolution (Cohen et al., 2019). All of these attention-based processes require the ability to maintain attention on task over time, an ability that has been termed sustained attention or vigilance (Davies and Parasuraman, 1982). From a neuroanatomical point of view, vigilant attention comprises a network of right-lateralized cortical areas involving the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), and the right inferior parietal lobe (Sturm and Willmes, 2001; see Robertson and O'Connell, 2010, for a review). There is some consensus regarding the effects of progesterone on sustained attention tasks, suggesting a possible facilitatory effect on any task that directly involves the prefrontal cortex (Solís-Ortiz et al., 2004), where, as previously mentioned, there are many progesterone receptors that modulate activity of that particular brain region. Some researchers have shown an improvement in performance when the tasks were performed during the luteal phase (e.g., Solís-Ortiz and Corsi-Cabrera, 2008), while others showed such improvement in the follicular phase, when the level of progesterone is low (e.g., Matthews and Ryan, 1994; Pletzer et al., 2017). Both theoretical views on vigilant attention and procedural differences between studies may underlie these discrepancies.

Regarding the concept of vigilance, there are two mechanisms that could be involved when people have to maintain attention on the task over time. The activation of these mechanisms depends on the cognitive demands required by the task at hand. When the cognitive demands are low and the task is rather monotonous and tedious, an *arousal vigilance* state would be activated to maintain attention for the duration of the task. In contrast, when the nature of the task is more difficult and involves high-level cognitive resources, a type of *executive vigilance* is then activated (Luna et al., 2018; Martínez-Pérez et al., 2020, 2021). To our knowledge, this distinction regarding the components of vigilance has not been taken into account when researchers have investigated the effects of the menstrual cycle on attentional tasks.

Regarding procedural differences in determining the phase throughout the menstrual cycle, there is broad agreement that cycle phases are determined as a function of some hormones of interest. However, there is no specific agreed protocol for assessing menstrual cycle influences on cognition and, therefore, any comparison between the results of different studies is rather problematic (Pletzer et al., 2017; Sundström Poromaa and Gingnell, 2014). In this regard, the way these hormones are measured has to be distinguished. For example, the amount of hormones can be determined directly by capturing the peak of luteinizing hormone (LH) through ovulation testing, or indirectly as when estimating the early follicular phase, characterized by low sex hormone levels, without necessarily measuring them. The use of a marker beyond the menstrual cycle recording itself is highly recommended (e.g., Becker et al., 2005).

Finally, there are other important variables that modulate women's performance in relation to the menstrual cycle that are often not taken into account. It is well known that hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes interact. For example, a stress-induced increase in glucocorticoids secretion leads to hypothalamic suppression of GnRH-secreting neurons, which suppresses reproduction (Kirby et al., 2009). Likewise, the interplay between the axes has been used to explain concepts of social dominance or competitiveness (DHH: dual hormone hypothesis) in relation to both testosterone (Mehta and Josephs, 2010) and estradiol (Tackett et al., 2015). Importantly, progesterone exerts hyperactivation effects on the HPA axis (Henderson, 2018), culminating in cortisol secretion (Goldstein et al., 2005; Keller-Wood, 1998; Roca et al., 2003). Thus, an interaction between the day of the menstrual cycle when the level of progesterone increases (i.e., the mid-luteal phase) can directly impact cortisol levels, which also increase in the early morning. The interaction between these two substances would also influence participants' performance. Another variable relates to the time-of-day when hormone assessment is performed (Cohen et al., 2019). The secretion of female sex hormones follows biological rhythms (Becker et al., 2005) and links

the menstrual cycle to circadian rhythmicity. Circadian rhythms include a set of variables that vary according to a 24-hour daily cycle. This endogenous biological clock works in synchrony with external signals to determine individuals' time preferences for daily activities and sleep. These preferences allow individuals to be classified into Morning-types, Evening-types, or Neither-types, which is the definition of chronotype (Levandovski et al., 2013; Schmidt et al., 2007). The chronotype paradigm is frequently used for studying the influence of circadian rhythms on higher order cognitive processes (Schmidt et al., 2007). Given the interaction between the HPA and HPG axes, the use of the chronotype paradigm could be useful to study the modulation of the menstrual cycle by circadian rhythms. In addition, it also takes into account the time-of-day when the assessment is performed. Previous research on the cognitive domain has found differences in performance depending on the time of testing according to the chronotype of the participants. Thus, Morning-types perform more efficiently during the early hours of the day, while their performance decreases in the afternoon. On the contrary, Evening-types have their optimal time in the afternoon, while their worst performance occurs in the morning. Neither-types refer to individuals who do not develop any marked time preference for either performance or rest (Schmidt et al., 2007). The interaction between chronotype and time of testing determines the synchrony effect (May and Hasher, 1998). The synchrony effect has previously been reported in tasks that require sustained attention, and Morning-types tend to be less affected by the time of testing than Evening-types (Mongrain et al., 2008; Adan et al., 2012).

In the present study, a sample of female participants performed two sustained attention tasks that differed in the vigilance component involved. The tests took place at their optimal and non-optimal time-of-day according to their chronotype. Recent studies (e.g., Lara et al., 2014; Martínez-Pérez et al., 2020, 2021, 2022) have found the Psychomotor Vigilance Task (PVT; Dinges and Powell, 1985) to be an adequate test of arousal vigilance, whereas the Sustained Attention to Response Task (SART; Robertson et al., 1997) is an adequate test of executive vigilance. The main aim of the present study was to determine whether performance in these vigilance tasks was differently affected by progesterone level across different phases of the menstrual cycle, as a function of women's chronotype and time of testing. Two indices were used to estimate phase: an indirect index (menstruation) for the follicular phase; and a direct index, luteinizing hormone (LH) using ovulation tests for the mid-luteal phase. Given that progesterone has been shown to increase attentional capacity (Brötzner et al., 2015; Cohen et al., 2019; Lord and Taylor, 1991; Solís-Ortiz et al., 2004; Solís-Ortiz and Corsi-Cabrera, 2008; Vidafar et al., 2018), we hypothesize that it will act as an alertness activator. Thus, performance is expected to be optimized in the mid-luteal phase compared to the follicular phase. However, it is possible that this performance-enhancing effect may be modulated by chronotype and time of testing, since as we mentioned above progesterone and cortisol secretion, as well as how they interact to affect cognitive performance, will depend on the timing of the test, differentially affecting Morning-type and Evening-type participants.

2. Methods

2.1. Participants

Thirty-two female undergraduate students from the University of Murcia (M age = 19.75, SD age = 1.57) participated in our experiment for course credit. Recruitment of participants was as follows. First, we made a selection of participants from an available database of previous chronotype studies. From this database we selected 83 potential female participants with extreme chronotypes (42 Morning-types; 41 Evening-types) classified according to the reduced Spanish version of the Horne and Östberg's Morningness-Eveningness Questionnaire (rMEQ) developed by Adan and Almirall (1990) and whose scores ranged from 4 (definitely Evening-types) to 25 (definitely Morning-types). Participants

who scored between 17 and 25 ($M = 18.4$) formed the Morning-type group, and those who scored between 4 and 11 ($M = 8.6$) formed the Evening-type group.

Fifty-six potential participants who attended the meeting, where the requirements for participation were explained, filled out a questionnaire that included data on their last three menstrual periods (dates, regularity and total duration) and contraceptive use. All those on contraceptive treatment were excluded and all those with natural menstrual cycles between 28 and 32 days and with a certain regularity were invited to participate. Based on these criteria, only 27 women were selected. Subsequently, we made a second call for participants following the same procedure described above and selected a total of eight additional participants, four Morning-types and four Evening-types. The COVID-19 pandemic forced us to interrupt the experimental sessions, so only 6 participants completed the experiment before lockdown. The study continued after the confinement and we interviewed another 46 potential participants. Based on their scores on the rMEQ questionnaire and menstrual cycle regularity, the sample consisted of 32 women, 16 Morning-types and 16 Evening-types. However, data from one of the Morning-type participants at optimal and non-optimal time-of-day just during the mid-luteal phase could not be collected because she tested positive for coronavirus and dropped out of the study. Consequently, the final sample consisted of 31 participants.

A post-hoc power (1- β) analysis was performed using G*Power to detect a medium effect size of $f = .25$ at $\alpha = .05$, with a final sample of 31 participants, two groups, four assessments per participant, and given a repeated measures correlation of $r = .5$. The resulting statistical power was .91.

All participants reported the absence of mental or physical illness, as well as being under psychological or pharmacological treatment at the time of testing. They also declared having normal or corrected-to-normal vision and not suffering from any chronic disease. Written informed consent was obtained from all participants.

2.2. Tasks

Participants were tested individually in sound-attenuated booths. The two tasks were programmed in E-Prime 3 (Psychology Software Tools; Schneider et al., 2012). The visual stimuli were presented on a 22" TFT monitor with a screen resolution of 1920×1080 pixels. A Chronos® device with five buttons was used to collect responses. In the PVT, each trial began with a random interval of between 2 and 10 s in which the computer screen remained black. Then, a red circle (50 pixels in diameter) appeared in the center of the screen and participants had to press, as quickly as possible, the center button of the response box with the index finger of their dominant hand. Once the response was made, the screen went blank and a new trial began. All participants were instructed to respond as quickly as possible in all conditions. In the SART, a go/no-go paradigm, individuals' ability to retain a response to an infrequent target digit is assessed. Digits from 1 to 9 were presented and participants were required to respond by pressing the center button of the response box with the index finger of their dominant hand, except when the target digit "3" appeared (Robertson et al., 1997). Each of the 9 digits was displayed 25 times for 250 ms, so that the total number of stimuli presented was 225. After the presentation of each digit, a mask appeared for 900 ms. The mask consisted of a circle with a diagonal cross in the center. Both the digits and the mask appeared in the center of the screen in white on a black background. In addition, the digits were presented in 5 different fonts: 48, 72, 94, 100 and 120 points. The interval between the digits was 1150 ms. Participants were asked to respond as quickly as possible trying not to make mistakes.

2.3. Procedure

Participants completed a total of 4 experimental sessions. Regarding the menstrual cycle, they came to the laboratory during the early

follicular phase (1–3 days of the cycle) and during the mid-luteal phase (approximately on the 21st day of the cycle). In addition, the experimental sessions for both phases were scheduled at 8:00 AM and 8:30 PM. Accordingly, each participant was examined 4 times, during the early follicular phase in the morning; in the early follicular phase in the afternoon; in the mid-luteal phase in the morning; and in the mid-luteal phase in the afternoon. During the experimental sessions, participants completed the two attentional tasks. They first performed the PVT, and then the SART. The order in which participants performed the attentional tasks was counterbalanced for menstrual cycle phase (follicular, mid-luteal) and the time-of-day (morning, evening), resulting in 4 experimental conditions: (1) follicular phase/morning first – mid-luteal phase/afternoon after; (2) follicular phase/afternoon first – mid-luteal phase/morning after; (3) mid-luteal phase/morning first – follicular phase/afternoon after; (4) mid-luteal phase/afternoon first – follicular phase/morning after. Eight participants from both chronotypes were initially randomly assigned to each experimental condition.

Participants contacted the experimenter by e-mail on the same day as the onset of menstruation. The tests then proceeded as follows. For the follicular phase, participants came to the laboratory between days 1 and 3 of the cycle and completed the first two experimental sessions. Based on the onset and duration of menstruation, the probable day of ovulation was estimated and corroborated with DIAGNOS Ovulation (LH) Test Strips (Manufacturer: Cuckool, ref.: 74t5486gg-jj 197) which have a measurement accuracy of 99%. The main advantage of this test is that it detects the presence of LH in urine and thus the presence of ovulation. It allows researchers to more accurately define the phase of the woman's cycle and thus to determine the days on which cognitive assessment should be performed.

Ovulation tests were carried out between 12:00 and 13:00 h on the scheduled day, following the manufacturer's instructions. Once in the laboratory, participants were given a bottle to collect urine for analysis. A positive result meant that ovulation should occur within 24–48 h. The mid-luteal phase was expected to occur about 6–7 days after the time interval when ovulation was supposed to have occurred, so participants were invited to come to the laboratory on those days. It is known that the mid-luteal phase is stable and that its duration is approximately 14 days (Lenton et al., 1984). Thus, it is possible to confirm that the participant was in that phase once the exact day on which she started menstruating again was known. Accordingly, we asked participants to inform us about the onset of their next menstruation to confirm that the evaluation had occurred in their mid-luteal phase. In case the ovulation test was negative, the test was continued to be administered during the following days until a positive result was obtained. As Sundström Poromaa and Gingnell (2014) point out, a single administration of the test is not sufficient to determine the phase of a woman's menstrual cycle.

Once the participant was summoned, she had to come to the laboratory either in the morning and then in the afternoon, or in the afternoon and then in morning of the following day, depending on the experimental condition to which she had been assigned. This procedure allowed us to assess participants at their optimal and non-optimal time-of-day according to their chronotype. Participants were asked not to drink coffee or other stimulants at least 2 h before the start of the experimental tasks. They were also asked to try to get between 6 and 9 h of sleep the night before. All participants complied with these requirements.

2.4. Statistical analysis

Data were pre-processed with R software, (R Core Team, 2017) and analyzed with JASP .9.2 (JASP Team, 2019). Also, outliers were considered to be all reaction times (RTs) that after logarithmic transformation were separated by more than four semi-interquartile ranges from the median value. We adopted a statistical significance level of $\alpha = .05$ for all statistical analyses. Data were entered into three-ways mixed 2 (chronotype) $\times$ 2 (phase) $\times$ 2 (time-of-day) ANOVAs, separate for each

task. In the PVT, transformed means of RTs were considered the dependent variable. In the SART, the dependent variables were transformed means of RTs and accuracy on go trials, and percentage of non-responses on no-go trials. When an interaction probed statistically significant, further simple main effects were carried out through either paired (between-participants factor) or unpaired (within-participants factor) *Student's t* tests, because none of such analyses required the comparison of more than two groups/conditions.

3. Results

The results of the two attentional tasks in the different experimental conditions are shown in Table 1.

3.1. Menstrual cycle statistics

All participants reported having regular natural menstrual cycles ($M = 28.02$, $SD = 1.29$). In addition, the duration of their three menstrual cycles prior to the experiment was recorded ($M = 28.68$, $SD = 2$). The difference between the reported and recorded duration was not statistically significant, $t(29) = 1.36$, $p = .19$. The correlation between the two scores was statistically significant ($r = .58$, $p < .01$). As mentioned above, women were examined in two phases of their menstrual cycle: early follicular phase and mid-luteal phase. The mean cycle days for data collection in the early follicular phase was 3.06 ($SD = 1.32$). The mean cycle days for data collection in the mid-luteal phase was 20.43 ($SD = 2.80$). The date predicted by a positive ovulation test result was, on average, around day 13.47 ($SD = 2.85$) of the cycle. The mean number of days elapsed between the mid-luteal phase and the next menstruation was 7.83 days on average ($SD = 1.83$), confirming that the tests were performed at the appropriate time.

3.2. Psychomotor Vigilance Task (PVT)

The first trial of each session was considered as practice and subsequently discarded. Transformed means of RTs were calculated and subjected to a mixed analysis of variance (ANOVA) with phase (follicular, mid-luteal) and time-of-day (optimal, non-optimal) as within-participants factors, and chronotype (Morning-types, Evening-types) as the between-participants factor. The main effect of time-of-day was statistically significant, $F(1, 29) = 11.05$, $p < .002$, $\eta_p^2 = .28$, indicating faster RTs at the optimal time ($M = 283$ ms) than at the non-optimal time ($M = 292$ ms) for all participants. The synchrony effect was modulated by the significant phase $\times$ time-of-day $\times$ chronotype interaction, $F(1, 29) = 4.85$, $p = .036$, $\eta_p^2 = .14$. We further analyzed the interaction separately for each chronotype (see Fig. 1). For the Morning-type participants, the synchrony effect was observed only in the mid-luteal phase, $t(14) = 2.06$, $p = .059$, but not in the follicular phase, $t(14) = .56$, $p = .58$. For the Evening-type participants, the synchrony effect was observed only in the follicular phase, $t(15) = 3.68$, $p = .002$, but not in the mid-luteal phase, $t(15) = 1.19$, $p = .25$. The three-way interaction also revealed an interesting pattern of opposite results when we

compared performance between the two phases at the optimal time-of-day as a function of participants' chronotype. Compared to performance in the follicular phase, the mid-luteal phase tended to produce shorter RTs in the Morning-types, although the difference was not statistically significant, $t(14) = 1.15$, $p = .27$, but longer RTs in the Evening-types, the difference being statistically significant, $t(15) = 2.65$, $p = .018$.

3.3. Sustained Attention to Response Task (SART)

Trials in experimental blocks in which participants did not respond to a go trial or emitted a response on no-go trials when the target digit was presented were excluded from statistical analyses. Transformed means of RTs and accuracy on go trials, and percentage of non-responses on no-go trials were subjected to a mixed analysis of variance (ANOVA) with phase (follicular, mid-luteal) and time-of-day (optimal, non-optimal) as within-participants factors, and chronotype (Morning-types, Evening-types) as the between-participants factor.

For the go trials, in the RTs analysis we found only a marginally significant main effect of chronotype, $F(1, 29) = 3.90$, $p = .058$, $\eta_p^2 = .12$. Morning-types tended to show longer RTs (292 ms) than Evening-types (227 ms). In the analysis of accuracy we found only a main effect of time-of-day, $F(1, 29) = 4.85$, $p = .036$, $\eta_p^2 = .14$. Participants showed higher accuracy at the optimal time (98%) than at the non-optimal time (97%). For no-go trials, the nonresponse percentages are illustrated in Fig. 2. The chronotype $\times$ time-of-day interaction reached statistical significance, $F(1, 29) = 8.34$, $p = .007$, $\eta_p^2 = .22$. No other main effect or interaction was significant. The interaction was further analysed for each chronotype separately. For the Morning-types, the synchrony effect was observed, i.e., higher accuracy at the optimal time (70%) than at the non-optimal time (64%), $F(1, 14) = 4.61$, $p = .05$, $\eta_p^2 = .25$. Although phase did not interact with time-of-day, it is noteworthy that the synchrony effect was significant only in the mid-luteal phase (8.4% of increment; $t(14) = 2.98$, $p = .01$, but not in the follicular phase (3.5% of increment), $t(14) = .81$, $p = .43$. For the Evening-types we observed no significant effects (all $ps > .05$). An inspection at the optimal time-of-day (see Fig. 2) reveals that, as with the PVT, an opposite pattern of results is also observed when comparing the two phases. Compared to the follicular phase, mid-luteal phase accuracy increased in the Morning-types, $t(14) = 1.89$, $p = .08$, but showed a slight decrease in the Evening-types, although not statistically significant, $t(15) = .91$, $p = .38$.

Finally, a correlation between participants' speed on go trials and non-response accuracy on no-go trials showed that Morning-types were slower but more accurate in retaining responses to the target digit, $r = .90$, $p < .001$ whereas Evening-types showed the opposite pattern, $r = .92$, $p < .001$.

4. Discussion

We conducted the present study to determine whether progesterone, a sex hormone that varies according to the phase of the menstrual cycle in women, has an effect on vigilance tasks that require sustained

Table 1

Mean RTs (in ms) in the Psychomotor Vigilance Task; mean RTs (in ms) and accuracy (in percentages) on go trials, and accuracy in retaining responses (in percentages) on no-go trials in the Sustained Attention to Response Task (SART), as a function of menstrual cycle phase (follicular, mid-luteal) and time-of-day (optimal, non-optimal) for both Morning-type and Evening-type chronotypes. Standard deviations are shown in parentheses.

Menstrual cycle phase and Time-of-day	Morning-types				Evening-types			
	PVT		SART		PVT		SART	
	Mean RTs	Mean RTs	Accuracy go trials	Accuracy no-go trials	Mean RTs	Mean RTs	Accuracy go trials	Accuracy no-go trials
Follicular Optimal	294(29)	293(99)	99(1)	67(24)	270(19)	224(91)	97(4)	55(23)
Non-optimal	297(33)	272(103)	96(7)	63(29)	284(22)	230(92)	98(2)	56(22)
Mid-luteal Optimal	289(32)	302(108)	99(1)	73(21)	281(29)	221(86)	95(6)	52(22)
Non-optimal	300(42)	302(109)	99(1)	65(25)	287(24)	232(85)	97(7)	57(21)

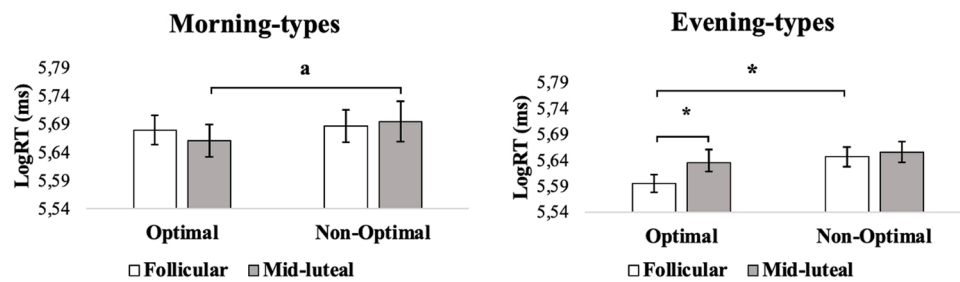


Fig. 1. Results with the PVT. Transformed mean reaction times (RTs) for each chronotype (Morning-types, Evening-types) as a function of time-of-day (optimal, non-optimal) and menstrual cycle phase (follicular, mid-luteal). Error bars represent the standard error from the mean. ^a $p < .06$, ^{*} $p < .05$.

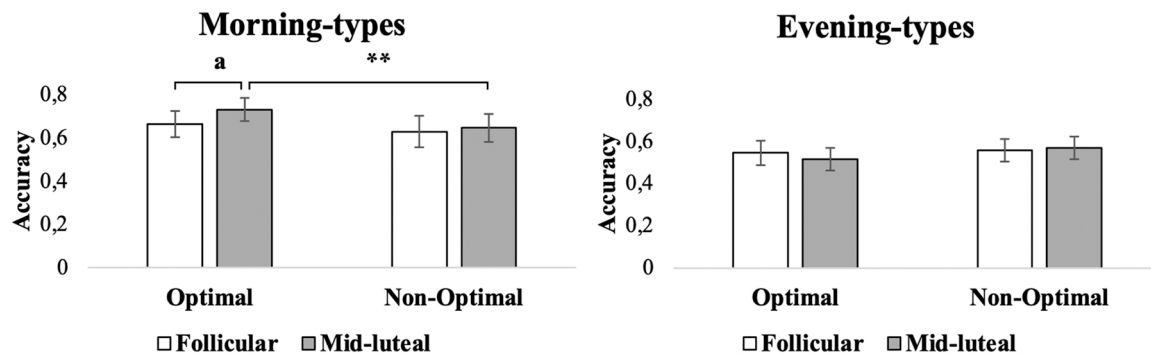


Fig. 2. Results with the SART. Percentage of retained responses to the target digit for each chronotype (Morning-types, Evening-types) as a function of time-of-day (optimal, non-optimal) and menstrual cycle phase (follicular, mid-luteal). Error bars represent the standard error from the mean. ^a $p = .08$, ^{**} $p = .01$.

attention. We used the ovulation test, and thus measurement of the amount of LH, for prediction of the mid-luteal phase, which proved to be an accurate method. This method is in line with previous research in which it has been suggested that the ovulation test is the most suitable test to be applied in menstrual cycle studies (Becker et al., 2005). Interestingly, there is a large interindividual variability in progesterone hormone secretions (Sundström Poromaa and Gingnell, 2014). Therefore, we estimated a margin of error of approximately ± 2 days around the day on which the progesterone peak was expected to be observed, i. e., day 21st. This ensured that testing took place in the range of days of the mid-luteal phase (Pletzer et al., 2017; Scheuringer and Pletzer, 2016).

Here we went further to investigate some relevant factors that might have been neglected in previous research. First, the involvement of different components of vigilance depending on the attentional task being performed. Second, the interaction between participants' preferences in performing their daily activities according to their chronotype and time of testing. It should be noted that this last factor may have important implications for how progesterone modulates certain types of vigilance, as progesterone secretion has been found to be linked to biological rhythms. It is important to note that the time-of-day variable has been treated here in terms of optimality. The optimal time-of-day for each participant depends directly on her chronotype. That is, the optimal time for Morning-types is the morning (08:00 AM), while for Evening-types it is the evening (08:30 PM). This difference in optimality with respect to morning and evening is of crucial importance in explaining the present results. Third, progesterone has been found to affect the secretion of cortisol, a hormone that has been thought to affect cognitive performance (DiMenichi et al., 2018; Dolcos, 2014; Lupien et al., 2009). The results showed that the effects of different phases of the menstrual cycle affected performance as a function of both chronotype and time-of-day interaction (the synchrony effect).

The standard synchrony effect was observed with the PVT, the arousal component of vigilance. Participants of both chronotypes showed differences in performance between the optimal and non-

optimal time-of-day, although the synchrony effect was smaller in the Morning-types, a result that has also been observed previously (Lara et al., 2014; Martínez-Pérez et al., 2020; Molina et al., 2013). In contrast, with the SART, the executive component of vigilance, the synchrony effect was observed in Morning-types, but only when they performed the task in the mid-luteal phase, not in the follicular phase. Evening-types showed no synchrony effect with this task. These results suggest that the cognitive control demands of the SART may have produced an increase in alertness that counteracted the low-level arousal usually observed during the non-optimal time-of-day, affecting participants of both chronotypes (Martínez-Pérez et al., 2020). Importantly, Morning-types were more conservative than Evening-types when performing the SART, leading the former to be more effective in retaining responses to the target digit at the expense of slowing responses to digits on go trials. Taken together, these results suggest that Morning-types, compared with Evening-types, are characterized by greater adjustment, flexibility and efficiency, as well as greater synchrony between endogenous biological rhythms and social demands.

Of particular relevance is the observation that the presence of high levels of progesterone in the mid-luteal phase further enhanced performance in the Morning-types when the task was carried out at their optimal time-of-day, i.e., in the morning. This improvement in performance was clearly expected in the SART, as that task requires a high-level of cognitive control involving brain regions such as the prefrontal cortex, influenced by progesterone (Guerra-Araiza et al., 2000, 2002, 2003; Kato et al., 1994). Importantly, the fact that a similar result is also observed with a task such as the PVT, which does not require a high level of cognitive control, suggests that progesterone has a rather general nonspecific impact on the performance of tasks that simply require maintaining attention over a fairly long period of time. At the physiological level, progesterone exerts modulatory effects in brain regions involved in attentional processes such as the prefrontal cortex. Specifically, there is consensus that progesterone induces the activation of GABAergic receptors through its main metabolites: pregnanolone and allopregnanolone. GABA is the main inhibitory substance in the brain.

For this reason, the mid-luteal phase is considered to have the highest rates of cortisol inhibition (Epperson et al., 2002; Inghilleri et al., 2004; Smith et al., 2002). This pattern would explain the negative results of progesterone on attentional functions observed here in the Evening-type participants.

However, we observed an opposite pattern of results in the two chronotypes just when they performed the vigilance tasks at the optimal time-of-day. Compared to the follicular phase (baseline), the presence of high levels of progesterone in the mid-luteal phase tended to improve performance in the Morning-types (more evident in the SART) and worsen performance in the Evening-types (more evident in the PVT). This differential effect of progesterone on the two chronotypes, when testing was performed at the optimal time-of-day, may be accounted for on the basis of the interaction between the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) hormonal axes. There is evidence that both axes produce bidirectional effects on each other. It is well known that ovulation is regulated by regions that drive circadian rhythms, such as the suprachiasmatic nucleus (Chappell, 2005; De la Iglesia and Schwartz, 2006), as well as the fact that the ovary is a peripheral regulator of circadian rhythm, as there is a rhythmic expression of clock genes controlled by LH in this organ (Fahrenkrug et al., 2006; Karman and Tischkau, 2006). More specifically, it has been observed that progesterone induces a hyperactivation of the HPA axis in healthy women (Roca et al., 2003), although attending to the physiological aspect, it may depend on the basal activation of the HPA axis, which culminates in the secretion of glucocorticoids among which cortisol stands out. Thus, we argue that if there are high concentrations of cortisol, progesterone would act by inhibiting the inhibition of the production of glucocorticoid, it would act as a cortisol agonist. Progesterone can facilitate that cortisol remains longer in circulation and that its secretion does not decrease. Conversely, if endogenous secretion or exogenous administration of progesterone occurs in the absence of cortisol, or if cortisol is present in low concentrations, progesterone may act by inhibiting the release of ACTH and CRH by the pituitary and hypothalamus, respectively (Keller-Wood, 1998; Goldstein et al., 2005; Roca et al., 2003). This hypothesis may also explain the elevated cortisol levels detected in pregnant women whose progesterone levels are normally elevated. Consequently, in Morning-types the cortisol peak occurs in the morning hours (Oginska et al., 2010), roughly coinciding with the participant's test at her optimal time-of-day (8:00 AM). Therefore, it is likely that the performance-enhancing effect observed in the Morning-type participants at their optimal time-of-day, during the mid-luteal phase, is due to the interaction between progesterone and cortisol being present in the body simultaneously. The beneficial effect of progesterone in the mid-luteal phase disappears in the evening, coinciding with the optimal time-of-day for Evening-type participants. It should be noted that cortisol peak is delayed in Evening-types by about 2–4 h compared to Morning-types (Mongrain et al., 2008), so cortisol concentration levels are expected to be lower in the evening, coinciding with the optimal time-of-day for those participants. Consequently, task performance worsened in the mid-luteal phase compared to the follicular phase in the Evening-types participants.

Although in the present study we focused on progesterone levels throughout the menstrual cycle, it should be noted that mid-luteal phase is also associated with elevated estradiol levels, but unlike progesterone, this hormone does not peak in that phase (Jaffé, 1982). Nonetheless, we must also consider some other potential explanations for the effects linking the HPA axis with estradiol. There is evidence that elevated plasma cortisol levels impair the positive effect of estradiol on some cognitive processes. This effect has been observed both in studies under stress conditions (Liston et al., 2009) and in experiments with exogenous cortisol administration (Baker et al., 2012). However, in those studies, plasma cortisol levels were quite elevated, which *a priori* is not the case in our study. Moreover, under continuous exogenous and pulsatile cortisol administration, high or low estradiol levels (as occurs in the mid-luteal phase) inhibit the synthesis of ACTH, a hypothalamic

hormone involved in the final glucocorticoid secretion (Sharma et al., 2014). Given this fact, estradiol would act as a regulator of cortisol synthesis, which at elevated levels would impair cognitive performance. It is possible that this physiological phenomenon occurred in Morning-type participants, who have plasma cortisol in the morning hours, which increases their state of activation and cognitive ability. In contrast, in the Evening-type participants, the absence of cortisol in the morning hours would preclude any influence of estradiol on the performance of these participants.

Several limitations of the present study should be kept in mind. One important limitation concerns the lack of direct measurement of menstrual cycle hormones and consequently, the results should be taken with caution. Future studies should include the measurement of estradiol and progesterone, as well as cortisol concentrations, to corroborate the possible explanations we have put forward in order to establish a causal relationship between these hormones and the cognitive processes involved in tasks that require sustained attention or vigilance. While here we have focused only on progesterone levels throughout the menstrual cycle, the mid-luteal phase is also associated with elevated levels of estradiol, although as we stated above, unlike progesterone this hormone does not peak in that phase. Therefore, further studies that include a periovulatory phase, when estradiol is at its highest concentration, are also needed. It is also important to note that our participants show extreme chronotypes, but it is also very important to evaluate the effects of progesterone in Neither-type participants, who represent by 60% of the population (Adan et al., 2012). Finally, due to the COVID-19 pandemic, the number of participants was dramatically reduced, which meant that some of the tests might lack sufficient statistical power to declare some of the observed differences as statistically significant.

5. Conclusions

The present results highlight the relevance of individual differences in baseline vigilance levels, explored here through differences in women's chronotype, in assessing the effects of sex hormones on sustained attention tasks. Importantly, our results reveal that the beneficial effects of progesterone, which peaks in the mid-luteal phase, may depend on whether or not that sex hormone promotes high concentrations of cortisol, a hormone that has been observed to affect cognitive performance. The interaction of the two hormones appears to be crucial in improving (Morning-types) or worsening (Evening-types) task performance when testing is conducted at the participants' optimal time-of-day.

Ethical standards

The research protocol was approved by the Ethics Committee and the Biosafety in Experimentation Committee of the University of Murcia and was carried out in accordance with the Declaration of Helsinki.

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Authors contribution

LBP: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **VMP:** Conceptualization, Investigation, Writing – original draft. **MT:** Conceptualization, Investigation, Writing – original draft. **GC:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **LJF:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition.

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Declaration of Competing Interest

None of the authors have any conflict of interest to declare.

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