The influence of estradiol and progesterone on neurocognition during three phases of the menstrual cycle: Modulating factors

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1. Introduction

Ovarian hormones are steroids that interact with specific receptors, which induce a wide range of slow genomic and fast non-genomic effects [1,2]. The main ovarian hormones estrogens, as estradiol, and progesterones, as progesterone, are cyclically released in reproductive-aged women. The menstrual cycle typically exhibits the existence of three distinct hormonal phases: the early follicular phase (EFP) with low levels of both estradiol and progesterone; the ovulatory phase (OP) with high levels of estradiol but low levels of progesterone; and the mid-luteal phase (MLP) with high levels of both estradiol and progesterone (Fig. 1; for review see [3]).

Estradiol and progesterone are lipophilic and thus easily pass through the blood-brain barrier; this characteristic allows both hormones to act on many brain structures involved in behavior [2,4,5]. The influence of these sex hormones on cognitive processes is often investigated through studies comparing women during both estradiol and progesterone levels and the mid-luteal phase (MLP) with high estradiol and progesterone levels. However, most studies have failed to include the ovulatory phase, characterized by high estradiol and low progesterone levels. Given the various hormonal changes in the menstrual cycle, we revisited studies suggesting that the menstrual cycle did not affect verbal and spatial abilities [6]. In addition, by comparing women during EFP and MLP, pioneering studies have suggested that these behavioral differences could be attributed to the increase in estradiol and progesterone levels [7] (see Table 1) and estradiol levels when comparing women during EFP and OP [8] (Table 2).

These posited influences of sex hormones on behavior have been linked to brain effects. The brain appears to process spatial and verbal information asymmetrically. Whereas the right hemisphere seems dominant for spatial tasks [9], the left hemisphere seems more dominant for verbal tasks [10,11]. Using the prototypical right- and left-hemispheric spatial and verbal tasks during EFP and MLP concerning the sex hormone levels, Hausmann and Güntürkün [12] observed a
more robust lateralization pattern during menses. Moreover, they reported a reduction in functional asymmetries during the MLP associated with progesterone levels. As a result, they proposed the influential hypothesis of progesterone-mediated interhemispheric decoupling. This hypothesis posits progesterone’s role in reducing cerebral asymmetries by diminishing corticocortical transmission and interhemispheric inhibition via the corpus callosum. Weis et al. [13] found that the inhibitory influence of left dominant hemispheric language areas on the homotopic areas of the right hemisphere is weakest during OP compared to EFP, thus reducing functional lateralization. Moreover, the estradiol levels were negatively correlated with the strength of interhemispheric inhibition, extending the hypothesis of progesterone-mediated interhemispheric decoupling [12] to include a similar effect to that of estradiol [13].

Other studies, however, have failed to observe neither a potential influence of the menstrual cycle on these cognitive processes nor any correlation between behavior and sex hormone levels of participants (for reviews, see [14,15]). However, this absence of effects does not necessarily imply that the menstrual cycle and sex hormones do not influence. Instead, there may be relevant factors that could potentially modulate its emergence. For example, the absence of significant correlations may be due to the variations in sex hormone levels caused by the circadian and ultradian secretory rhythms [16,17]. This variability can be observed even in longitudinal studies, in which each woman is tested simultaneously during several menstrual cycle phases. In this context, Halari et al. [18] carried out an in-depth investigation into possible relationships between sex differences in cognitive abilities and sex hormone levels by examining all participants during the same time of day (between 9.00 h and 10.30 h). However, despite observing expected behavioral sex differences in multiple tasks, they found no hypothesized relationships between sex hormone levels and cognitive performance.

Given this background, the present review aimed to explore the extent to which the absence of behavioral differences among menstrual cycle phases nor significant correlations with the levels of the ovarian hormones, rule out menstrual cycle influences on neurocognitive processes, considering the existence of complex interactions between the effects of estradiol and progesterone on the brain.

2. Estradiol and progesterone effects on the brain

Due to estradiol and progesterone influencing numerous brain structures and neurotransmitter systems, in this section, we focus on the similar and opposite time-course effects of these hormones. Moreover, we examine estradiol effects in the absence of progesterone because the variety of effects exhibited when examining the two hormones together can create difficulty when interpreting results.

The hippocampus is an important brain area for declarative memory encoding and retrieval, along with spatial navigation with allocentric reference frames (spatial strategy), and it is also considered part of the language-memory network [19,20,21,22,23,24,25]. Recent data suggest that sex hormones play an influential role in this brain region [2], such that sex hormones seem to influence spinogenesis, synaptogenesis, and adult neurogenesis of the hippocampal region. For example, in the associated brain regions of ovariectomized rats, the density of dendritic spines decreases gradually during the first 6 days after the procedure. Upon estradiol administration, brain density in CA1 neurons increases after 2 h; it peaks between 2 and 3 days and ultimately decreases gradually over the next 7 days. Moreover, progesterone administration enhances estradiol-induced spine formation within 5 h, but it proceeds to decline spines within 8–12 h more sharply than the following estradiol alone [26] (for review, see [27]). Estradiol also stimulates synaptogenesis on these new dendritic spines in ovariectomized rats, and progesterone appears to interfere with this process [5,28].

Moreover for the adult neurogenesis in the dentate gyrus, short-term ovariectomy reduces cell proliferation of the new neuron progenitors, and acute estradiol replacement restores cell proliferation [29]. Estradiol also influences neurogenesis by increasing the survival of young neurons, but these effects are time-, dose-, age-, and sex-dependent (for review, see [30,31]). Progesterone may antagonize the effects of estradiol on cell proliferation, as a single dose of progesterone given 24 h after estradiol administration exhibits a decrease in the estradiol-induced enhancement of cell proliferation [29].

Sex hormones also modulated the dendritic spines of the prefrontal cortex (PFC), which is vital for a myriad of cognitive functions such as learning, working memory, and executive functions [27,32] (for review, see [33]). In female rat [27] and mice [34] studies, estradiol induces dendritic expansion in the PFC. In addition, animals receiving estradiol plus medroxyprogesterone acetate had significantly more synapses in the PFC than animals receiving estradiol plus progesterone [35] which suggested an effect of estradiol in the absence of progesterone.

In women, the most notable changes in brain volume across the menstrual cycle have been reported for hippocampal volume. For example, increases in hippocampal volume have been observed during OP [36,37,38]. Similarly, global brain gray matter volume peak during ovulation has also been observed [39]. More recent studies, however, have not found any significant effects of the menstrual cycle phase on hippocampal or total brain volume [40] (for systematic reviews, see [41,42]).

Fig. 1. Serum estradiol (pg/ml) and serum progesterone (ng/ml) levels during the early follicular, ovulatory, and mid-luteal phases of the menstrual cycle. The dashed vertical line indicates when ovulation occurs. (adapted from [9]).
| Sex hormone levels | Spatial ability | Verbal ability | Correlations | Possible modulating factor | Reference, design and participants |
|-------------------|----------------|---------------|--------------|----------------------------|-----------------------------------|
| Higher estradiol and progesterone levels during the MLP in comparison with the EFP | Mental rotation or navigation tasks | Other | Fluency tasks | Verbal memory tasks | Brain activation in frontal and parietal areas positively correlated with estradiol levels | Low difficulty for mental rotation task, Small sample size for behavioral data, Schoning et al. [60] (repeated measures; n = 12 women tested twice) |
|                     | 3-D mental rotation test of Peters et al. (1995) | (+) FMRI data: larger activation in the left superior temporal gyrus in EFP in comparison with MLP (0) behavioral data | | | |
|                     | 3-D mental rotation test of Vanderberg & Kuse (1978) | (+) rhyme fluency (0) phonemic fluency (0) semantic fluency | Estradiol levels negatively correlated with mental rotation and positively correlated with phonemic fluency and semantic fluency | Asymmetrical practice effects for mental rotation | Maki et al. [62] (repeated measures; n = 16 women tested twice) |
|                     | 3-D mental rotation test of Vanderberg & Kuse (1978) | (0) hidden figures test | Estradiol levels negatively correlated with the performance on the mental rotation task | Low difficulty for 2-D mirror pictures test | Hausmann et al. [63] (repeated measures; n = 12 women tested twice) |
|                     | Spatial and response navigation task: (+) spatial strategy with landmarks increased during MLP in comparison with the EFP (+) response strategy without landmarks decreased during MLP in comparison with the EFP (-) spatial strategy without landmarks decreased during MLP in comparison with the EFP (-) response strategy with landmarks increased during MLP in comparison with the EFP | (0) phonemic fluency (0) semantic fluency | Progesterone levels negatively related with the accuracy for the spatial strategy and positively related with the accuracy for the response strategy | Low difficulty for verbal fluency tasks | Scheuringer & Pletzer [64] (repeated measures; n = 49 women tested twice) |
|                     | (0) 3-D mental rotation test of Vanderberg & Kuse (1978) | (0) phonemic fluency (0) semantic fluency (0) rhyme fluency (but significant individual differences) | California Verbal Learning Test (CVLT) immediate and delayed recall | No significant correlations, but a trend toward a negative correlation between progesterone and the total words generated across trials on the CVLT | Asymmetrical practice effects for mental rotation and verbal memory tasks, Mordecai et al. [65] (repeated measures; n = 16 women tested twice) |

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| Sex hormone levels | Spatial ability | Verbal ability | Correlations | Possible modulating factor | Reference, design and participants |
|--------------------|----------------|---------------|--------------|---------------------------|-----------------------------------|
| Mental rotation or navigation tasks | Wechsler memory scale subtests: (0) immediate and delayed paired associate learning; (0) immediate and delayed paragraph recall | Paired-associate learning positively correlated with estradiol levels during the MLP | | Phillips & Sherwin [66] (repeated measures; n = 25 women tested twice) |
| | | | | |
| Mental rotation or navigation tasks | (0) immediate and delayed paragraph recall | | | Hatta & Nagaya [67] (repeated measures; n = 27 women tested twice) |
| Mental rotation or navigation tasks | (0) Wechsler Memory Scale-Revised immediate recall | | | |
| Mental rotation or navigation tasks | Not determined | No significant correlations | | Hampson [7] (repeated measures; n = 45 women tested twice) |
| Mental rotation or navigation tasks | (0) 2-D mental rotation test usable for children | | | Epting & Overman [68] (repeated measures; n = 27 women tested twice) |
| | (0) rod and frame test; water level test; spatial array test | | | Silverman & Phillips [81] (study two, repeated measures; n = 23 women tested twice) |
| Mental rotation or navigation tasks | (0) 3-D mental rotation test of Vanderberg & Kuse (1978) | | | Moody [82] (repeated measures; n = 34 women tested twice) |
| Mental rotation or navigation tasks | (0) 3-D space relations test | | | Phillips & Silverman [83] (repeated measures; n = 60 women tested twice) |
| Mental rotation or navigation tasks | (0) 3-D cube comparison test | | | |
| Mental rotation or navigation tasks | (0) 2-D card and flags rotation tests | | | |

(+) Support hypothesis (better performance during EFP for spatial and during MLP for verbal tasks). (0) No differences between EFP and MLP. (-) Contrary to the hypothesis.
| Sex hormone levels | Spatial ability | Verbal ability | Correlations | Possible modulating factor | Reference, design and participants |
|--------------------|----------------|----------------|--------------|----------------------------|----------------------------------|
| Higher estradiol levels during the OP in comparison with the EFP | Mental rotation or navigation tasks | Other | | Estradiol levels were linearly and curvilinearly related with saptial tests | Hampson [8] (repeated measures; n = 50 women tested twice) |
| | (+) 3-D mental rotation task of Kimura (1992): (+) fMRI data: higher increase in perfusion in cortical areas during OP in comparison with EFP (0) behavioral data | Word stem completion: (+) fMRI data: higher increase in perfusion in cortical areas during OP in comparison with EFP (0) behavioral data | | | |
| | (+) 3-D mental rotation tasks modified from Shepard & Metzler (1971) | (0) synonym fluency (0) rhyme fluency | Estradiol levels were negatively correlated with performance on mental rotation and hard clock rotation tests | Low difficulty for mental rotation task Small sample size for behavioral data | Dietrich et al. [69] (repeated measures; n = 6 women tested twice) |
| | Groups divided by COMT Val158Met genotype (met/met women and val/val women) | N-back (0-, 2-, 3-back) fMRI data: (+) higher estradiol levels (and/or met/met genotype) was associated with lower sustained PFC activation in comparison with low estradiol levels (and/or val/val genotype). Mixed Behavioral data: (+) lures trials: performance of val/val women (low baseline DA) improves with high estradiol, and performance of met/met women (high DA) improves with low estradiol (0) no lures trials | No reported | Low difficulty for no-lures trials Genetic polymorphism | Jacobs & D’Esposito [73] (Mixed factorial design; n = 13 val/val women and n = 8 met/met women tested twice) |
| | Not determined | Verb generation: (+) fMRI data (0) behavioral data | No reported | | Rumberg et al. [74] (repeated measures; n = 12 women tested twice) |

(+): Support hypothesis (better performance during EFP/low estradiol for spatial and during OP/high estradiol for verbal tasks). (0): No differences between EFP/low estradiol and OP/high estradiol.
Estradiol and progesterone have similar and opposite time-course effects on various neurotransmitter systems, such as glutamate, gamma-aminobutyric acid (GABA), dopamine, and serotonin; these have been implicated in many cognitive functions [1,43]. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). It is considered a regulator of cognitive processes such as learning and memory through long-term potentiation (LTP) [44,45]. In rodents, estrogen increases the density of N-methyl-D-aspartate (NMDA) receptors in the CA1 region of the hippocampus [28]. These increases facilitate glutamate transmission through the up-regulation of exocytotic machinery [1,46] and enhance the baseline neural excitability and LTP magnitude [47,48].

Conversely, progesterone has been shown to suppress the excitatory glutamate response in a dose-dependent fashion [1] and has also been shown to decrease the baseline neural excitability and magnitude of LTP [49]. As opposed to glutamate, GABA is the most abundant and widely distributed inhibitory neurotransmitter in the CNS and is implicated in the modulation of the activity of local neuronal circuits [50]. Whereas estrogen seems to suppress GABA inhibitory input by decreasing the enzyme synthesis glutamate decarboxylase’s content, progesterone appears to facilitate GABAergic transmission through action over GABA-A receptors [1].

Regarding dopamine (DA), this crucial neurotransmitter is implicated in motivation, reward, and decision-making as well as working memory and navigation with an egocentric reference frame (response strategy) [51,52]. Brain areas that show rich dopaminergic innervation include the striatum, substantia nigra, and hypothalamus [53]. Following the release of DA, the enzyme catechol-O-methyltransferase (COMT) then metabolizes it [54], which regulates the baseline levels of this neurotransmitter in brain structures as the PFC [1]. Estradiol has a modulatory effect on the dorsal striatum by increasing DA synthesis and release, the firing rate of DA neurons, and by reducing DA turnover [2,55,56]. The role of progesterone in the release of DA seems to be more complex; treatment of estradiol-primed animals with progesterone produces a biphasic effect, with initial increases in DA release occurring within 30 min of progesterone treatment, a peak in DA release 4 h after the treatment, and subsequent inhibition of DA release 24 h after progesterone administration [55,57]. The serotonergic system has been mainly involved in neuro-emotional processes but also cognition. Thus, while a high density of serotonergic projections to the hippocampus plays a significant role in different memory processes, spatial navigation, decision making, and social relationships; a high density of serotonergic projections to PFC, however, has been involved in working memory, attention, decision-making and reversal learning (for review see [58]). In this context, while progesterone has been suggested to increase serotonergic neurotransmission, the role of estradiol seems less clear since it produces excitatory and inhibitory effects on this system (for reviews, see [1,55,59]).

3. Implications for the study of neurocognition

The above section suggests that estradiol and progesterone could produce similar and opposite time-dependent effects on the brain. Estradiol could have effects during OP, and the subsequent release of progesterone during the MLP could counteract it. Likewise, in these situations, it may be difficult to observe behavioral differences between EFP and MLP or to obtain significant correlations between sex hormones and participants’ behavior.

Thus, it seems possible that some studies where menstrual cycle effects on the brain or cognition were not observed may not have taken into account these effects. Recently, two reviews have suggested that the menstrual cycle has a limited effect on spatial and verbal abilities [14,15]. All the studies included in the two revisions [7,43,7,43,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80] are summarized in Table 1 (examining EFP and MLP but not the OP, n = 10), Table 2 (examining EFP and OP but not the MLP, n = 6), and Table 3 (examining all, EFP, OP and MLP of the menstrual cycle, n = 7), and these results are also discussed below. Tables do not include the study of Halari [18] (reviewed by [14,15]), which only tested women during one menstrual cycle phase (a group of men was included to examine sex differences).

3.1. Results

3.1.1. Studies examining the EFP and MLP but not the OP (see Table 1 for details)

Table 1 shows the studies (n = 10) of the reviews [14,15], examining EFP and MLP but not OP [7,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]. These studies have a repeated measures design with women tested during EFP and MLP randomized or counterbalanced. These studies were expected to observe better performance during the EFP for spatial tasks and better performance during the MLP for verbal tasks, specifically related to estradiol and progesterone levels.

As expected, eight of the ten studies in Table 1 showed that estradiol and progesterone levels were significantly higher during MLP compared to EFP [60,61,62,63,64,65,66,67]. Two of these studies employed fMRI [60,61] and observed significant correlations between the brain blood-oxygen-level-dependent (BOLD) signal and the sex hormone levels. However, participants did not exhibit any behavioral differences during EFP and MLP. In addition, differences between the activated brain regions during the EFP and MLP were observed with a mental rotation test [60] but not during a synonym generation test [61]. The remaining six studies are behavioral, and four of them examined spatial capacity [62,63,64,65]. Utilizing the Vanderberg and Kuse mental rotation task, Maki et al. [62] and Hausmann et al. [63], but not Mordecai et al. [65], observed significant differences between the EFP and MLP, as well significant negative correlations between performance and estradiol levels. However, with both the 2-D mental rotation mirror pictures and hidden figures tests, no behavioral differences during EFP and MLP or correlations with sex hormone level were observed [63]. Scheuringer and Pletzer [64] observed differences in navigation strategies during EFP and MLP that correlated with progesterone levels during a navigation task.

Three of the behavioral studies examined verbal fluency [62,64,65]. Maki et al. [62] observed mixed results for behavior during EFP and MLP and correlations between performance and sex hormone levels. However, Scheuringer and Pletzer [64] and Mordecai et al. [65] did not observe behavioral differences or correlations with sex hormone levels during these two menstrual cycle phases.

Additionally, three of the behavioral studies examined verbal memory [65,66,67]. Phillips and Sherwin [66] observed no behavioral differences within the menstrual cycle with the Wechsler Memory Scale subtests but found a positive correlation between paired-associate learning subtests and estradiol levels. Hatta and Nagaya [67] and Mordecai et al. [65] observed no behavioral differences or correlations with sex hormone levels between EFP and MLP using Wechsler Memory Scale-Revised and the California Verbal Learning Test, respectively.

The final two studies of this section [7,68] did not determine the participants’ hormone levels. Hampson et al. [7] observed better performance during the EFP for spatial abilities and mixed results for verbal abilities. However, no behavioral differences were observed by Epting and Overman [68] through the examination of spatial abilities.

3.1.2. Studies examining the EFP and OP but not the MLP (see Table 2 for details)

Table 2 shows the studies (n = 6) included in the reviews [14,15], examining EFP or a low estradiol group and OP or a high estradiol group [69,70,71,72,73,74]. Most used a repeated measures design with women tested during EFP and OP in a randomized or counterbalanced order (excluding [71,73]).

As a preliminary step to examining the effects of estradiol on the brain and cognitive processes, five studies observed higher estradiol
Table 3
Studies including early follicular phase (EFP), ovulatory phase (OP) and mid-luteal phase (MLP) of the menstrual cycle.

| Sex hormone levels | Spatial ability | Verbal ability | Correlations | Possible modulating factor | Reference, design and participants |
|--------------------|----------------|---------------|--------------|---------------------------|----------------------------------|
| Higher estradiol levels during OP and MLP in comparison with EFP; and higher progesterone levels during MLP in comparison with EFP and OP | Mental rotation or navigation tasks | Other | Fluency tasks | Verbal memory tasks | Not examined |
| Figure comparison task | (+) behavioral and fMRI data: left visual field advantage (right temporal dominant hemisphere processing) in EFP and OP but not in MLP | (+) connectivity data: stronger connectivity between the right temporal region and heterotopic left brain regions in OP and MLP in comparison with EFP | | | |
| Higher estradiol levels during OP but not during mid/late luteal phase in comparison with EFP; and higher progesterone levels during mid/late luteal phase in comparison with EFP and OP | (0) mental rotation task of Shepard & Metzler (1971) | (0) phonemic fluency | (0) semantic fluency | No significant correlations | No differences in estradiol levels during EFP and MLP |
| Spatial and response navigation task: (+) participants tested in EFP predominantly used a response strategy | (-) participants tested in the mid/late luteal phase predominantly used a spatial strategy | (+) better performance during OP than EFP for acquisition, interference and delayed recall | (+) better performance during mid/late luteal phase than EFP for delayed recall | No significant correlations | No differences in estradiol levels during EFP and MLP |
| (0) behavioral data | | | | | |
| Hussain et al. [77] (Cross sectional; n = 11 for early follicular group, n = 13 for ovulatory group and n = 21 for mid/late luteal group) | | | | | |
| Spatial and response navigation task: (+) fMRI and connectivity data: enhanced hippocampal activity during the OP and enhanced fronto-striatal activity during the MLP phase | Semantic fluency: (+) fMRI and connectivity data: enhanced hippocampal activity during the OP and enhanced fronto-striatal activity during the MLP phase | Hippocampal activation was positively related with estradiol levels and fronto-striatal activation was positively related with progesterone levels | No differences in estradiol levels during EFP and MLP | Pletzer et al. [43] (repeated measures; n = 36 women tested three times) |
| (0) behavioral data | (0) behavioral data | | | | |
| Statistics no reported | | | | | |
| (0) mental rotation task modified from Shepard & Metzler (1971) | (0) phonemic fluency | (0) semantic fluency | | | |
| Weis et al. [75] (repeated measures; n = 40 women tested three times) | | | | | |
| (0) mental rotation task modified from Shepard & Metzler (1971) | (0) phonemic fluency | (0) semantic fluency | | | |
| Griksiene & Ruksenas [76] (repeated measures; n = 20 women tested three times). | | | | | |

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**Table 3 (continued)**

| Sex hormone levels | Spatial ability | Verbal ability | Correlations | Possible modulating factor | Reference, design and participants |
|--------------------|-----------------|----------------|--------------|----------------------------|-----------------------------------|
|                     | Mental rotation or navigation tasks | Other | Fluency tasks | Verbal memory tasks | rotation and verbal fluency tasks | Gordon & Lee [78] (repeated measures; n = 34 women tested three times). |
| No determined | (0) mental rotation task | Verbal working memory task of Gold et al. (1997): (+) better performance during OP in comparison with EFP | (0) no differences between EFP and MLP | - | Rosenberg & Park [79] (repeated measures; n = 8 women tested four times). |
| (-) hidden figures test: better performance in OP than EFP | (0) phonemic fluency: no differences between EFP and OP | Days selected for testing | Solís-Ortiz & Corsi-Cabrera [80] (repeated measures; n = 9 women tested four times: EFP, OP and early and late luteal phases). |
| (-) 3-D mental rotation test of Vanderberg and Kuse (1978): better performance for expected low estradiol groups (EFP, transmasculine individuals receiving testosterone and oral contraceptive users women) in comparison with expected high estradiol groups (OP, MLP) | - | | | Peragine et al. [85] (Cross sectional; n = 27 for early follicular group; n = 56 for ovulatory group; n = 57 for mid-luteal group; n = 24 for transmasculine individuals receiving testosterone; n = 30 for oral contraceptive users). |

(+) Support hypothesis (better performance during EFP for spatial and during OP and/or MLP for verbal tasks). (0) No differences among menstrual cycle phases. (-) Contrary to the hypothesis.
levels during OP compared to EFP [69,70,71,72,73]. Three of these studies used fMRI [69,70,73], and results indicated differences in the brain BOLD signal depending on the menstrual cycle phase [69,73] or correlations between BOLD signal and estradiol levels [70]. However, the behavioral results of these studies are more complex, such that Jacobs and D’Esposito [73] observed mixed results depending on the menstrual cycle phase, trial type, and genetic polymorphisms related to baseline DA levels with a verbal working memory task. However, researchers observed no behavioral differences with mental rotation [69, 70] and verbal fluency [69] tasks during EFP and OP. In the remaining two behavioral studies [71,72], Hampson et al. [71] observed differences between low- and high-estradiol groups in some mental rotation tests but not in others (see Table 2), and no differences in verbal fluency tasks; Kozaki and Yasukouchi [72] observed no menstrual cycle effects on mental rotation task.

The last study of this section [74] observed no differences in brain BOLD signal nor behavioral differences during EFP and OP on a verb generation task, but this study did not determine the participants’ hormone levels.

3.1.3. Studies including EFP, OP, and MLP (see Table 3 for details)

Table 3 shows studies (n = 7) examining all EFP, OP, and MLP groups [43,75,76,77,78,79,80]. Most used a repeated measures design with the women tested during the three phases in a randomized or counterbalanced order (excluding [77]).

Weis et al. [75] and Griskiene and Ruksenas [76] observed higher estradiol levels during both OP and MLP compared with EFP and higher progesterone levels during MLP compared to both EFP and OP. Although Weis et al. [75] did not examine correlations with sex hormones, they observed differences among the three menstrual cycle phases in brain activation, connectivity, and behavior by using fMRI during the performance of a figure comparison task. However, in Griskiene and Ruksenas’ [76] behavioral study, no differences or correlations between the sex hormone levels and the performance on spatial and verbal tasks were observed among the three phases of the menstrual cycle.

In addition, although Hussain et al. [77] and Pletzer et al. [43] conducted hormone assays during their studies, they observed some unexpected hormone levels (i.e., no differences between estradiol levels during EFP and MLP). Despite this, they observed positive effects during the performance of verbal memory tasks [77] and mixed results during navigation [43,77] and fluency tasks [43].

Furthermore, Gordon and Lee [78] did not report the statistical differences among participants, and Rosenberg and Park [79] and Solis-Ortiz and Corsi-Cabrera [80] did not determine the sex hormone levels. Mixed results were observed with verbal memory tasks [79], and no differences among menstrual cycle phases were observed with mental rotation [78,79] and verbal fluency tasks [78]. Finally, Solis-Ortiz and Corsi-Cabrera [80] observed better performance in OP than EFP with the hidden figures test and no differences between EFP and OP with the phonemic fluency task.

3.2. Modulating factors

The first requisite for understanding the possible influence of the sex hormones and menstrual cycle on neurocognition is to verify the expected concentrations of sex hormones in participants [3]. Therefore, the results of studies with no sex hormone measures should be taken with caution [7,68,74,76,79,80]. By comparing significant and non-significant neurobehavioral effects of the different studies revisited, it is possible to identify some modulating factors that could explain some of the discrepancies described in the previous section.

First, one of the most relevant factors seems to be the cognitive load caused by tasks with greater or lesser difficulty. This factor was first found by Hampson [71] with mental rotation tasks. It could explain the discrepancies not only in most of the studies with mental rotation tasks [60,62,63,68,69,70,71,72,76,78,79] but also in some studies that test verbal fluency with phonemic and rhyme fluency tasks [7,62,64,71,76,78], as well as in the study of Jacobs and D’Esposito [73] that examines verbal working memory; excluding the study of Mordecai et al. [65].

Regarding mental rotation tasks, the expected results were observed with the 3D-test of Vandenberg and Kuse [62,63,71], in which participants are required to identify which two of four choices represent the rotated version of a 3D- target figure. However, no behavioral differences were observed among the menstrual cycle phases with easier mental rotation tasks—such as was seen in the task of Peters [60], Kimura [69], Shepard and Metzler [72,76,78], and in the study of Zhu et al. [70] —in which participants were required to compare a pair of target–stimulus figures. This pattern is also the case with the task used by Eppling and Overman [68] with a target and two choices, the 2-D mirror pictures test [63], and potentially the task used by Rosenberg and Park [79] in which participants must decide which of the four choices was not the rotation of the target. Moreover, by manipulating the difficulty of mental rotation tasks, better performance for a low estradiol group compared to a high estradiol group was observed for the hard but not for the easy version of the clock rotation test [71].

Regarding the verbal fluency, the expected results were observed with rhyme fluency, in which participants have to generate as many words as possible that rhyme with a cue word; this was not the case with the easier phonemic fluency task (i.e., generate as many words as possible that began with a particular letter) [62]. These results are compatible with the absence of differences among menstrual cycle phases observed with the phonemic fluency task [7,64,76,78]. However, Hampson [71] observed no differences between high- and low-estradiol groups with a rhyme fluency task; by comparing the results of the studies of Maki et al. [62] and Hampson [71], the high levels of both estradiol and progesterone during MLP [62] may have caused effects different from the ones produced by the increase in estradiol, but not progesterone levels [71].

Concerning verbal memory, in lure trials (with high cognitive load), but not in no-lures trials (with low cognitive load), behavioral differences between EFP and OP were observed by Jacobs and D’Esposito [73]. However, the COMT genotype and estradiol also modulated these results. Thus, while the performance of val/val women (low baseline DA) improves with high estradiol levels, the performance of met/met women (high baseline DA) improves with low estradiol levels [73]. Thus, these results showed that genetic polymorphisms constitute another modulating factor that may affect the results.

Against the possible influence of the task difficulty on the performance, the study of Mordecai et al. [65] (see Table 1) observed no behavioral differences between EFP and MLP with a Vandenberg and Kuse test, with a rhyme fluency task, and with a verbal memory delayed recall. However, they observed asymmetrical practice effects (i.e., better performance on mental rotation for women tested first during EFP and delayed recall for women tested first during MLP). The presence of asymmetrical hormonal effects was first found by Hampson [7] with spatial tests and posteriorly by Maki et al. [62] with mental rotation and verbal tasks. This effect means that participants who initially perform a test in a physiological state conducive to good performance may develop better skills for doing the test a second time, even if the second test takes place under less favorable endocrine conditions. Thus, this relevant factor should be considered when the same women are tested in different menstrual cycle phases. This modulating factor is quite interesting as it suggests that it is possible to enhance women’s cognitive abilities through training that considers the menstrual cycle stages.

Another factor that could limit statistical power is the sample size because it makes it challenging to observe significant behavioral differences among menstrual cycle phases [61,70,74], even in circumstances where there are differences in the brain BOLD signal [60,69]. In fact, by using larger samples (n = 40), Weis et al. [75] observed differences among menstrual cycles in brain activation, connectivity, and behavior.

Another important modulating factor seems to be the age of...
participants, as complete adult levels of ovarian hormone secretion are not attained until women are in their early 20 s on average [3]. This factor may have influenced the study of Epting and Overman [68]. Thus, with the Rod and Frame test, Hampson [7], but not Epting and Overman [68], observed a better performance during the EFP in comparison with the MLP. However, the mean age of participants was 23.7 years for [7] and 19.1 years for [68].

The last modulating factor that emerges from these studies is selecting an accurate timing for the behavioral testing. It is preferable to calculate the OP and MLP counting backward from the date of the next estimated menses as the duration of the luteal phase is considered more stable and relatively fixed at 13–15 days [3]. It is also preferable to only consider a narrow range of days for testing as valid to avoid significant variations in the levels of sex hormones. This factor may have influenced Hussain et al. ’s [77] study in which they used the start date of the previous cycle as a reference and tested a group of mid/late-luteal between day 20 and the end of the cycle. As shown in Fig. 1, the variation in estradiol and progesterone levels during this range of dates is high because estradiol and progesterone levels are high during MLP, and they decrease during the last days of the cycle. In fact, the estradiol levels in their mid/late luteal group did not differ from the estradiol levels of the group tested during the EFP [77]. Similarly, no differences between estradiol levels during EFP and MLP were observed by [43,76], making the interpreting the results more challenging. This factor may have also influenced the study of Rumberg et al. [74], in which the count was forward, and the interval was relatively large (11–18 days) for the OP; and the study of Solís-Ortiz and Corsi-Cabrera [80] in which the count was forward. Unfortunately, they do not determine hormone levels [74, 80], so this possibility cannot be confirmed.

4. Conclusions

Recent reviews suggest limited neurocognitive differences among menstrual cycles [14,15], showing that the influence of hormones over cognition has yet to be definitively understood.

Despite this claim, most studies reviewed exhibited mixed results or no differences among menstrual cycle phases. Four important conclusions can be drawn when comparing the significant and non-significant effects in this series of studies.

First, there seem to be factors that could modulate the influence of the menstrual cycle and sex hormones on neurocognition. These factors are related to the age [68] and the number of participants [60,61,69,70], the selection of an accurate timing for the behavioral testing [43,47], the influence of genetic polymorphisms [73], the asymmetric practice effects of sex hormones [7,62,65], and especially the difficulty of the task [7,60,62,63,64,68,69,70,71,72,73,76,78,79]. As a result, researchers should consider these factors when interpreting future studies.

Second, the most robust finding supported the best performance in the difficult 3-D test of Vandenberg and Kuse in the EFP compared to the MLP [62,63]. In this context, Silverman and Phillips [81] were the first to use the 3-D mental rotations task in a menstrual cycle study observing better performance during EFP in comparison with MLP (see Table 1). This result was subsequently replicated with greater methodological control [82]; additionally, the expected menstrual cycle differences were observed for 3-D mental rotation tests but not with 2-D mental rotation tests [83] (see Table 1). In 2014, Hampson et al. [71] showed that difficulty, but not dimensionality, is a critical factor for menstrual cycle effects on mental rotation tasks where better performance in a low-estradiol group in comparison with the high-estradiol group was observed [71]. In addition, a negative correlation between estradiol and the test performance has been observed by examining EFP and MLP [62,63] and low- and high-estradiol groups [71]. Collectively, these data suggest that estradiol could interfere with the performance on mental rotation tasks and that its effect is not affected by the increase in progesterone levels during the MLP (see [84] for review). Recently in this context, by using a higher number of groups, Peragine et al. [85] (see Table 3) seemed to confirm this possibility. Their findings noting that various groups with reduced estradiol levels (EFP, oral contraceptive users, and women receiving gender-affirming testosterone therapy) had better performance than groups with higher estradiol levels (women tested during OP and women tested during MLP) on the Vandenberg and Kuse mental rotation task.

In contrast, the results of studies examining navigation or verbal abilities seem to be less consistent (see Tables). Thus, it is also possible that the effects of menstrual cycle/sex hormones on mental rotation tasks could be stronger than effects on navigation or verbal tasks [71]. As indicated earlier, it seems interesting to explore the possible influence of task difficulty also with verbal fluency [62], and verbal memory [73], but also with navigation tasks [86]. Thus, differences across menstrual cycle phases during the use of the response strategy in a difficult navigation task (i.e., without landmarks) but not in an easier navigation task (i.e., with landmarks) have been observed [86].

The third conclusion is derived from the reviewed studies that use fMRI. It seems possible to observe differences among menstrual cycle phases in the brain BOLD signal, even with easy mental rotation [60,69] and verbal fluency tasks [43] that do not show behavioral differences [43,60,62,64,65,69,72,76,79]. Brain processing may differ regardless of the final behavioral outcome, and the influence of sex hormones across menstrual cycles may reflect differences in the cognitive strategy used to solve the tasks. This possibility has also been investigated using navigation tasks. Thus, Pletzer et al. [43] observed differences among menstrual cycle phases in the brain BOLD signal and connectivity, but not in the use of spatial and response strategies.

Finally, less consistent results seem to be observed during the MLP. Almost half of the articles reviewed with no significant effects compare the participants’ performance during the EFP and MLP. As the levels of both estradiol and progesterone are higher during MLP, the behavior during this menstrual cycle phase can be influenced by increased levels of estradiol, progesterone, both hormones, or neither. Thus, the absence of differences between EFP and MLP is somewhat challenging to interpret as it could indicate that estradiol and progesterone do not influence the examined cognitive process, that their effects are task-specific, or that are consequences of the complex interactions between the cerebral effects of estradiol and progesterone (see Section 2) as has been suggested [43,61,62,66,71,87,88]. Moreover, if progesterone countervails the effects of increased estradiol levels, the behavioral effects observed during MLP may be similar to those observed during EFP [61,64,65,66,67,86] but different in regards to those observed during OP [86,89,90]. As a result, the OP group is particularly relevant, not only because its high levels of estradiol and low levels of progesterone allow us to know the effect of estradiol when comparing OP with EFP, but also because it allows discerning between some effects of both hormones (when comparing all EFP, OP and MLP). Thus, to understand the influence of sex hormones across the menstrual cycle, it would be advisable to include at least three different phases: the low estradiol- and progesterone-EPF, the high estradiol- and low progesterone-OP, and the high estradiol- and progesterone-MLP.

In conclusion, considering the ease with which these hormones access the brain and their influence in numerous structures and neurotransmission systems that modulate cognitive processes, it is necessary to detect the possible presence of modulatory factors before affirming that neurobehav榜单ial differences within the menstrual cycle do not occur. The neurocognitive effects of sex hormones may also represent an important source of variability in cognitive neuroscience and experimental psychology research. Researchers have frequently conducted experiments that include men and women in the same experimental group without sex or menstrual cycle control in these disciplines. Thus, the effects analyzed in this review could also help understand some of the difficulties in reproducibility described [91].
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Declaration of Competing Interest

The authors declare no conflicts of interest.

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