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MENSTRUAL CYCLE AND COGNITIVE FUNCTIONS

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Abstract

Menstrual cycle is characterized by fluctuations of the main ovarian sex hormones, estradiol and progesterone. Estradiol reaches its peak around day 12 of the average 28-day cycle, during the late follicular or preovulatory phase, while progesterone peaks in the mid luteal phase. In animals, estradiol has been shown to induce neurogenesis and increase spinal density in the hippocampus, as well as potentiate dopaminergic signaling in the prefrontal cortex. In women, studies have shown that sex hormones, while not effecting overall learning ability, do modulate certain cognitive functions. Most prominent of these is the preference for response strategy in 4/8 virtual maze task during early and late follicular phase, as opposed to spatial strategy, which women are statistically more likely to use during mid to late luteal phase. In addition, when tested on a verbal memory test, women in the ovulatory phase, when estradiol levels are high, recalled significantly more words during the first five trials, after interference trial and after time delay when compared to women in luteal phase of the cycle. This suggests that high estradiol levels are associated with beneficial effects on working memory, which could, in part, be explained by its agonist-like effects on dopamine signaling in prefrontal cortex.

KEYWORDS: cognition, estradiol, progesterone, spatial memory, working memory

INTRODUCTION

While there are no differences in overall intelligence between women and men, studies have shown certain differences in their cognitive abilities.[1] Most prominent of these being male's advantage on some visuospatial tasks, such as spatial rotation and target accuracy tasks, and female's advantage on verbal fluency, visual memory and fine motor control tasks.[2] Many of these have been analyzed and confirmed, not only in humans, but also in rodents and non-human primates. A much less noticeable, but nonetheless striking, phenomenon is the difference in female performance on certain tasks throughout the menstrual cycle. In normally cycling women, the influence of the menstrual cycle phase on cognition is associated with estradiol (E2) and progesterone (P4) concentrations in specific brain regions.[3] Furthermore, studies show that female monkeys' brains express a greater number of dopaminergic D2 receptors during the luteal phase in comparison to the follicular phase of the menstrual cycle.[4] Based on the suggestion that E2 also increases the number of dopaminergic (DA) projections from the ventral tegmental area (VTA) to the prefrontal cortex (PFC), as shown by tests done on rats, some scientists postulate that E2 influences cognitive tasks reliant on DA signaling in the PFC.[5] Much less is known about the influences of P4 on cognitive performance. However, an active P4 metabolite, allopregnanolone, has shown anti-depressant effects in rats.[6] The aim of this review is to highlight the role of E2 and P4 in modulation of cognitive performance through different phases of the menstrual cycle.

MENSTRUAL CYCLE

1. Hypothalamic-pituitary-gonadal axis

The reproductive period of a woman, from menarche to menopause, is filled with repetitive monthly cycles – menstrual cycles, lasting, on average, 28 days. These cycles encompass cyclic changes in two organs, the ovaries and endometrium, which are known as an ovarian and endometrial cycles, respectively. These monthly cycles are driven by the hypothalamic-pituitary-gonadal axis. Hypothalamic gonadotropin-releasing hormone (GnRH) neurons are located in the nucleus arcuatus (ARC) and preoptic area (POA), with those in the ARC generating an "hourly" rhythm, with pulses spaced 60 to 90 minutes apart, and those in POA generating a monthly rhythm of GnRH secretion, with a massive increase at mid-cycle responsible for a luteinizing hormone (LH) peak.[7] Released GnRH is transported by the portal vessels to the anterior pituitary, where it stimulates the synthesis of gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the gonadotrophs. FSH stimulates folliculogenesis in the first phase of the ovarian cycle, which is hence termed the follicular phase. LH, on the other hand, reaching its peak around day 14 of the cycle, triggers ovulation and luteinization of granulosa and theca interna cells, which then form the corpus luteum. At the moment of ovulation, the ovarian cycle has entered its final, luteal phase (Figure 1).[7]

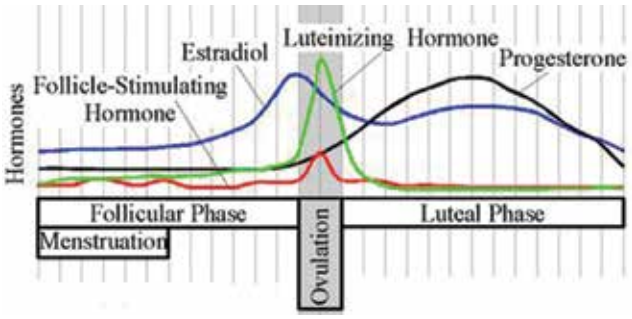

Figure 1. Course of the hormonal concentrations within the ovarian cycle.
Source: Image "Estradiol.Cycle" by Ekem – from Wikimedia Commons. Available under the GNU Free Documentation License (GFDL), Version 1.2 or any later version and under the CC BY-SA 3.0 Unported license (https://creativecommons.org/licenses/by-sa/3.0/deed.en). Published June 6, 2006. Accessed April 30, 2017.

2. Ovarian steroids

The precursor for ovarian steroids, cholesterol, is taken up from the blood or synthetized *de novo* inside the ovary, depending on the vascularization of the cell's immediate environment. Theca cells convert cholesterol into androgens, dehydroepiandrosterone (DHEA) and androstenedione, which are then taken up by the granulosa cells, containing FSH-induced P-450 aromatase (P-450arom) enzyme, and converted by it into estrone (E1), which is then converted by 17β-hydroxysteroid dehydrogenase (17β-HSD) to a more potent estrogen, E2, the primary circulating estrogen in nonpregnant females. Alternatively, 17β-HSD can convert androstendione to testosterone, which the aromatase can then convert to E2. The serum E2 concentration steadily rises during the follicular phase and reaches its peak in the preovulatory phase, around day 12 of the cycle. During the luteal phase of the cycle, the biochemistry of granulosa and theca cells is changed. Due to the invasion of blood vessels toward the granulosa-lutein cells, as well as LH stimulation of both granulosa-luteal and theca-luteal cells, the action of taking up and processing of cholesterol is facilitated. As a result, serum concentrations of progesterone (P4) rise and peak in the mid luteal phase, around day 21 of the cycle (Figure 1).[7]

OVARIAN STEROIDS AND THE HIPPOCAMPUS

E2 has been shown to influence adult neurogenesis in the subgranular zone of the rat's dentate gyrus by increasing cell proliferation rate, as well as dendritic spine number and synaptic density in the *Cornu Ammonis* 1 (CA1) region of the hippocampus (Figure 2).[8,9] This, in turn, is associated with modulation of hippocampus-dependent cognitive functions. However, the relationship between E2 levels and performance on tasks that measure these functions is not linear, but rather of an inverted "U" shape. Therefore, both lowest and highest levels of E2 correlate with impaired performance on hippocampus-dependent tasks.[2]
Even though no task is dependent purely on a single neural system, there are tasks which predominantly activate hippocampal or some other brain regions.[2] Spatial memory is one of the hippocampus-dependent cognitive functions,[10] and it can be divided into spatial working memory, which involves trial-specific information and hence also recruits prefrontal cortex (PFC), and spatial reference memory.[2] The classic test for studying spatial learning and memory is

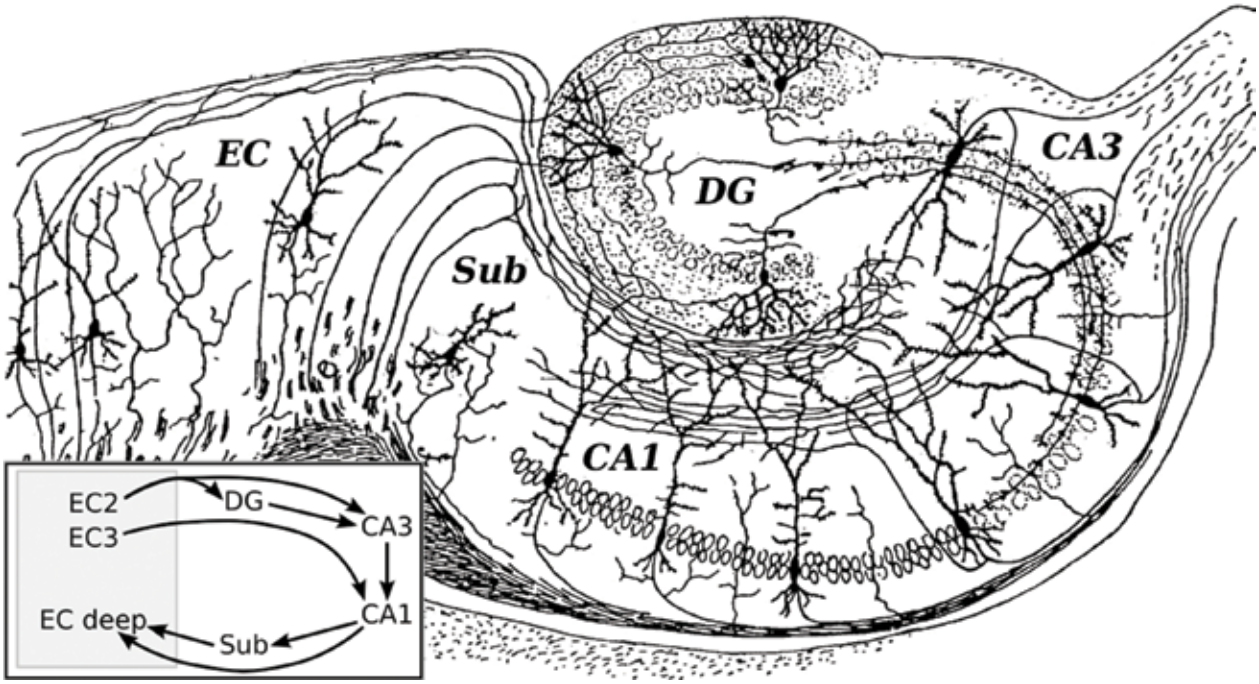

Figure 2. Structure of the hippocampus. Neurogenesis takes place in subgranular zone of dentate gyrus (DG). Estradiol (E2) increases spinal and synaptic density of Cornu Ammonis 1 (CA1) pyramidal cells.
Source: Image "CajalHippocampus (modified)" by Santiago Ramón y Cajal (original) and Looie496 (derivative) – from Wikimedia Commons, public domain. Published 1911 (original) and April 19, 2008 (derivative). Accessed April 30, 2017.

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the Morris water maze task, in which the subject is placed inside a water-filled pool surrounded by high walls labeled with visual cues that serve as reference points. Using these visual cues, the subject must find a hidden platform that it can climb onto.[11] Studies on rodents show that males outperform females in proestrous (high estradiol), but not in diestrous (low estradiol) on the standard Morris water maze task.[12] Behavioral task studies reviewing the selection between a striatal-mediated response strategy and a hippocampal-dependent spatial strategy show differences in strategy preference through different menstrual cycle phases. To test this selection, a 4 on 8 virtual maze (4/8 VM) was created using a computer game and made to resemble the structure of a radial arm maze (Figure 3). At the end of each arm were stairs leading to a pit, with four of them containing an object, while the landscape surrounding the maze contained cues to be used as reference points. Every trial consisted of two parts. In Part 1, four arms were barred and the objects were placed in the pits at the end of the unbarred arms, whereas in Part 2, all eight arms were unbarred and the objects were placed at the end of arms that had been blocked in the Part 1. In each trial, the pattern of unbarred and barred arms was different. After finishing the task, the participants were asked to explain how they solved it. If the used approach was based on counting or recognizing a specific pattern (i.e. open, open, blocked arm), they were categorized as response learners, whereas if it was based on using surrounding landmarks, without any counting or pattern identification, they were categorized as spatial learners.[13] Women tested during the early follicular and preovulatory phase predominantly used a response strategy, while women tested during mid or late luteal phase mostly used spatial strategy. Furthermore, women in preovulatory phase were even more likely to use a response strategy when compared to women in early follicular phase. This indicates that women in the luteal phase, when P4 concentrations are high and E2 levels moderately high, are more likely to use a more cognitively demanding spatial strategy, whereas women in follicular phase are more likely to use a response strategy.[14]

The fact that highest E2 levels, achieved in the preovulatory phase, are not associated with preferential hippocampus-dependent spatial strategy selection, even though E2 has been shown to increase hippocampal synaptic density, could be explained by progesterone's attenuating effect on E2-induced neurotrophic actions. In essence, some studies indicate that an acute P4 injection after E2 treatment, antagonizes the E2-induced increase in hippocampal spine density.[15]

OVARIAN STEROIDS AND THE PREFRONTAL CORTEX (PFC)

The PFC is implicated in higher cognitive and emotional processes, such as short-term/working memory, including hippocampus-dependent spatial working memory. A standard verbal memory test is the Rey Auditory Verbal Learning Test (RAVLT). The participants are read a list of 15 words (List A) for five trials and then asked to recall as many words as they can, after which they are read a list of 15 different words (List B) and again asked to recall as many words as they can. After this interference trial, participants are asked to recall the words from the List A and again after a 30 min delay.

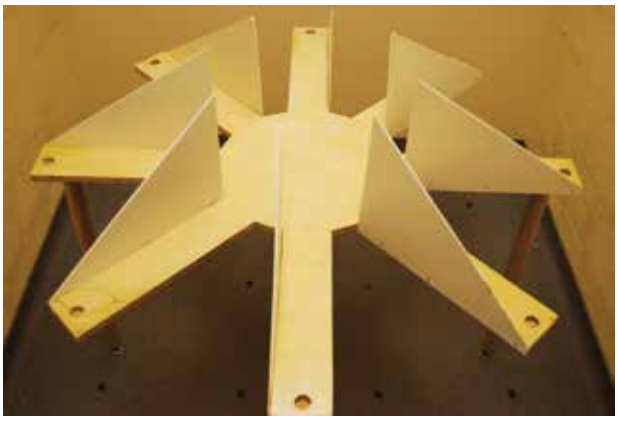

Figure 3. Radial arm maze. The structure was taken as a basis for 4/8 virtual maze (4/8 VM), created using a computer game.
Source: Image "Simple_Radial_Maze" by Mcole13~commonswiki – from Wikimedia Commons. Available under the CC BY-SA 3.0 Unported license (https://creativecommons.org/licenses/by-sa/3.0/deed.en). Published July 13, 2008. Accessed April 30, 2017.

Performance is measured by the number of words recalled after an interference trial and 30 min delay. Results revealed that women tested during the preovulatory phase, when E2 levels are high, recalled considerably more words after each of the five acquisition trials, after the interference trial, and after a 30 min delay than women tested in mid luteal and early follicular phase. In addition, women tested during the early follicular phase recalled significantly fewer words after a 30 min delay, compared to women in mid luteal phase.[15] In sum, these results suggest a positive correlation between E2 levels and verbal working memory.

ESTRADIOL (E2) AND DOPAMINE (DA)

As reviewed before, in animals, E2 increases the number of dopaminergic projections to the PFC and could thus influence working memory, a PFC-dependent function that is highly reliant on DA signaling.[5,16,17] However, it is important to note that the relationship between PFC function and DA also follows an inverted "U" shape, meaning that the maximal PFC function is achieved with optimal DA levels.[16,17] Furthermore, it has been suggested that taking the baseline DA into account is essential for understanding E2 effects on working memory. In essence, whether the E2 effects on PFC-dependent cognitive functions will be favorable or harmful depends on catechol-O-methyltransferase (COMT) genotype, such that E2 potentiated DA signaling in individuals with Val158Met genotype, and COMT enzymatic activity.[17]

CONCLUSION

Menstrual cycle hormones, namely estradiol and progesterone, impact cognitive function by modulating the preference between spatial and response strategy, depending on whether the woman is in the luteal or follicular phase, respectively. A lesser difference in response strategy selection between early and late follicular phase suggests that progesterone levels, rather than estradiol levels, determine the preference toward spatial strategy. Estradiol levels, on the other hand, correlate positively with performance in working memory test, possibly through their effects on dopamine signaling.

REFERENCES:

1. Halpern DF, LaMay ML. The Smarter Sex: A Critical Review of Sex Differences in Intelligence. *Educ Psychol Rev*. 2000;12(2):229-246. doi:10.1023/A:1009027516424.
2. Hamson DK, Roes MM, Galea LAM. Sex Hormones and Cognition: Neuroendocrine Influences on Memory and Learning. *Compr Physiol*. 2016;6(3):1295-1337. doi:10.1002/cphy.c150031.
3. Toffoletto S, Lanzenberger R, Gingnell M, Sundström-Poromaa I, Comasco E. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: A systematic review. *Psychoneuroendocrinology*. 2014;50:28-52. doi:10.1016/j.psyneuen.2014.07.025.
4. Czoty PW, Riddick NV, Gage HD, et al. Effect of Menstrual Cycle Phase on Dopamine D2 Receptor Availability in Female Cynomolgus Monkeys. *Neuropsychopharmacology*. 2009;34(3):548-554. doi:10.1038/npp.2008.3.
5. Shansky RM, Lipps J. Stress-induced cognitive dysfunction: hormone-neurotransmitter interactions in the prefrontal cortex. *Front Hum Neurosci*. 2013;7:123. doi:10.3389/fnhum.2013.00123.
6. Nin MS, Ferri MK, Couto-Pereira NS, et al. The effect of intra-nucleus accumbens administration of allopregnanolone on δ and γ2 GABAA receptor subunit mRNA expression in the hippocampus and on depressive-like and grooming behaviors in rats. *Pharmacol Biochem Behav.* 2012;103(2):359-366. doi:10.1016/j.pbb.2012.09.002.
7. Boron WF, Boulpaep EL. The Female Reproductive System. In: *Medical Physiology: A Cellular and Molecular Approach*. Philadelphia, PA: Elsevier; 2017:1109-1129.
8. Duarte-Guterman P, Yagi S, Chow C, Galea LAM. Hippocampal learning, memory, and neurogenesis: Effects of sex and estrogens across the lifespan in adults. *Horm Behav.* 2015;74:37-52. doi:10.1016/j.yhbeh.2015.05.024.
9. Woolley CS. Estrogen-Mediated Structural and Functional Synaptic Plasticity in the Female Rat Hippocampus. *Horm Behav*. 1998;34(2):140-148. doi:10.1006/hbeh.1998.1466.
10. O'Keefe J, Nadel L. The Hippocampus as a Cognitive Map. Oxford, UK: Clarendon Press (Oxford University Press); 1978.
11. Vorhees CV, Williams MT. Morris water maze: procedures for assessing spatial and related forms of learning and memory. *Nat Protoc.* 2006;1(2):848-858. doi:10.1038/nprot.2006.116.Morris.
12. Frye CA. Estrus-associated decrements in a water maze task are limited to acquisition. *Physiol Behav.* 1995;57(1):5-14. doi:10.1016/0031-9384(94)00197-D.
13. Bohbot VD, Gupta M, Banner H, Dahmani L. Caudate nucleus-dependent response strategies in a virtual navigation task are associated with lower basal cortisol and impaired episodic memory. *Neurobiol Learn Mem*. 2011;96(2):173-180. doi:10.1016/j.nlm.2011.04.007.
14. Hussain D, Hanafi S, Konishi K, Brake WG, Bohbot VD. Modulation of spatial and response strategies by phase of the menstrual cycle in women tested in a virtual navigation task. *Psychoneuroendocrinology*. 2016;70:108-117. doi:10.1016/j.psyneuen.2016.05.008.
15. Tanapat P, Hastings NB, Gould E. Ovarian steroids influence cell proliferation in the dentate gyrus of the adult female rat in a dose- and time-dependent manner. *J Comp Neurol*. 2005;481(3):252-265. doi:10.1002/cne.20385.
16. Cai JX, Arnsten AFT. Dose-Dependent Effects of the Dopamine D1 Receptor Agonists A77636 or SKF81297 On Spatial Working Memory in Aged Monkeys. *J Pharmacol Exp Ther*. 1997;283(1):183-189.
17. Jacobs E, D'Esposito M. Estrogen shapes dopamine-dependent cognitive processes: Implications for women's health. *J Neurosci*. 2011;31(14):5286-5293. doi:10.1523/JNEUROSCI.6394-10.2011.

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MENSTRUALNI CIKLUS I KOGNITIVNE FUNKCIJE

Sažetak

Menstrualni ciklus karakteriziraju promjene u serumskim koncentracijama glavnih spolnih hormona jajnika, estradiola i progesterona. Ako se kao prosječno trajanje ciklusa uzme period od 28 dana, koncentracija estradiola vrhunac doseže oko 12. dana cikusa, u kasnoj folikularnoj, odnosno preovulatornoj fazi. Progesteron, s druge strane, postiže maksimalnu koncentraciju tijekom luteinske faze ciklusa. Studije na životinjama pokazale su da estradiol inducira neurogenezu i povećava gustoću dendritičkih trnova u hipokampusu te potencira učinak dopamina unutar prefrontalnog korteksa. Iako ženski spolni hormoni ne utječu na sveobuhvatnu sposobnost učenja, studije na ženama pokazale su kako ipak moduliraju određene kognitivne funkcije. Najizraženije jest preferiranje određenog tipa strategije u rješavanju virtualnog navigacijskog zadatka (4/8 virtualni labirint). Pokazalo se da žene u ranoj i kasnoj folikularnoj fazi češće biraju strategiju odgovora, dok se one u luteinskoj fazi koriste prostornom strategijom. Rezultati testiranja verbalne memorije pokazali su da su žene u kasnoj folikularnoj fazi ciklusa sposobne zapamtiti veći broj riječi tijekom prvih pet pokušaja, nakon interferencije i nakon vremenske odgode. Rezultati pokazuju da su visoke razine estradiola povezane s boljim ishodom na testovima koji ispituju radnu memoriju, što bi se dijelom moglo objasniti potencirajućim učincima estradiola na dopaminergičke signalne puteve unutar prefrontalnog korteksa.

KLJUČNE RIJEČI: estradiol, kognicija, progesteron, prostorna memorija, radna memorija

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