Proceedings of the Annual Meeting of the Cognitive Science Society

Title

Category learning across the menstrual cycle: Learning exceptions to the rule varies by hormonal milieu

Journal

Proceedings of the Annual Meeting of the Cognitive Science Society, 44(44)

Authors

Perovic, Mateja
Heffernan, Emily M.
Einstein, Gillian
et al.

Publication Date

2022

Category learning across the menstrual cycle: Learning exceptions to the rule varies by hormonal milieu

Mateja Perović (m.perovic@mail.utoronto.ca)
Emily M. Heffernan (emily.heffernan@mail.utoronto.ca)
Gillian Einstein (gillian.einstein@utoronto.ca)
Michael L. Mack (michael.mack@utoronto.ca)
Department of Psychology, University of Toronto
100 St George St, Toronto, ON M5S 3G3 Canada

Abstract

Ways in which ovarian hormones affect cognition have been long overlooked in psychology and neuroscience research despite strong evidence of their effects on the brain. In order to address this gap, we study performance on a rule-plus-exception category learning task, a complex task that requires careful coordination of core cognitive mechanisms, across the menstrual cycle. Results show that the menstrual cycle distinctly affects learning of exceptions in a manner that matches the typical estradiol cycle. Furthermore, participants in their high estradiol phase outperform participants in their low estradiol phase, and show steeper learning slopes than men in exception-learning. These results provide novel evidence of the role of estradiol in category learning, underscore the importance of recruiting diverse samples in cognitive neuroscience research, and highlight the ways in which cognition varies throughout the fundamental biological cycles of the human experience.

Keywords: category learning; menstrual cycle; sex differences; hormones and behavior

Introduction

Despite efforts to reduce the longstanding sex bias in neuroscience research, the effects of ovarian hormones on human cognition remain poorly understood. In light of rising evidence that 17β-estradiol (E2) – the most bioactive estrogen – affects brain structure and function in both sexes (Frick, Kim & Koss, 2018), it is critical to our understanding of cognition to expand efforts to study cohorts representative of diversity in human endocrine milieus. One approach to accomplishing this is examining differences in cognition across the menstrual cycle.

The average menstrual cycle is 29.5 days long, with typical variation ranging from 21-35 days (Buffet, Djakoure, Maitre & Bouchard, 1998; Treloar, 1967), and broadly divided into two phases – follicular and luteal – defined by changes in levels of ovarian hormones (Fig. 1). The follicular phase begins with the onset of menses. Its early stage is characterized by low levels of E2 and progesterone. The late follicular or pre-ovulatory phase is characterized by a rise in E2, which reaches its peak shortly before ovulation. The luteal phase follows, with levels of E2 decreasing significantly and settling to moderate levels as progesterone increases during the mid-luteal phase, and decreasing in the late luteal phase as menses approaches (Marc, Fritz & Leon, 2011). There is, however, considerable variation in hormone levels across the cycle especially in the pre-ovulatory phase (Beltz & Moser, 2020).

A key brain area affected by hormonal changes across the menstrual cycle is the hippocampus. Evidence from rodent models suggests that E2 is a key modulator of hippocampal function and associated learning (Frick, Kim, Tuscher & Fortress, 2015) and memory (Frick, Kim & Koss, 2018). Estrogen receptors α (ERα) and β (ERβ) as well as the G protein-coupled estrogen receptor 1 (GPER1) densely populate the region (Mitra et al., 2003; Hazell et al., 2009). Through action on these receptors, E2 has extensive effects on hippocampal dendritic spine density (Frankfurt & Luine, 2015), neurogenesis (Mahmoud, Wainwright & Galea, 2016), cell signaling (Frick et al., 2018), and synaptic plasticity (Babayan & Kramar, 2013).

Human studies provide further evidence of E2's role in hippocampal structure and activity. E2 levels across the menstrual cycle are positively associated with hippocampal grey matter volume (Barth, Steele & Mueller, 2016; Lisofsky et al., 2015; Pletzer, Harris & Hidalgo-Lopez, 2018; Protopopescu et al., 2008), activity during affective, visuospatial and verbal processing (Albert, Pruessner & Newhouse, 2015; Dreher et al., 2007; Pletzer, Harris, Scheuringer & Hidalgo-Lopez, 2018), and functional connectivity with other brain regions (Lisofsky et al., 2015). Furthermore, administration of E2 to naturally cycling women in the early follicular phase increases hippocampal activity when the increase is within physiological ranges typical of the pre-ovulatory phase (Bayer et al., 2018).

One of the cognitive processes that are likely sensitive to such E2-dependent alterations in hippocampal connectivity is learning of exceptions to category rules. Although it engages multiple brain regions (Zeithamova et al., 2019), category

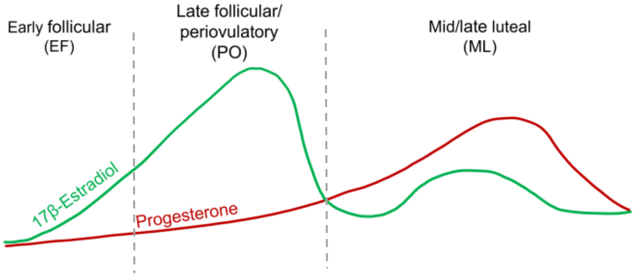

Figure 1: Typical changes in ovarian hormones across the menstrual cycle

In J. Culbertson, A. Perfors, H. Rabagliati & V. Ramenzoni (Eds.), *Proceedings of the 44th Annual Conference of the Cognitive Science Society.*

learning is heavily reliant on the hippocampus (Bowman & Zeithamova, 2018; Davis et al., 2012a, 2012b; Heffernan, Schlichting & Mack, 2021; Mack et al., 2016; Schapiro et al., 2018; Schlichting, Gumus, Zhu & Mack, 2021). The process of learning general patterns in category structure as well as noticing and remembering exceptional category members (e.g., birds fly; penguins are birds despite being flightless) necessitates relational binding and rapid formation of multifeatured memory representations, which are key aspects of hippocampal function (Olsen, Moses, Riggs & Ryan, 2012). Previous work suggests that other types of relational memory are sensitive to changes in E2 (Rentz et al., 2017).

In order to explore the effect of the menstrual cycle on category learning, we administered a rule-plus-exception (RPE) task to participants in three stages of the menstrual cycle – early follicular (EF), late follicular/pre-ovulatory (LF/PO), mid/late luteal (ML) – as well as a male group for a low-E2 comparison. Given the impact of E2 on hippocampal volume and responsivity, we predicted that learning of exceptions would vary in a way corresponding to the cycle of E2, with participants in the high-E2, LF/PO phase showing evidence of more efficient learning and outperforming participants in the low-E2, EF phase and men. We further predicted that there would be no difference between groups in learning category prototypes or rule followers.

Methods

Participants

Participants were recruited through the Prolific online recruiting platform, prescreening for age (18-35), normal or corrected-to-normal vision, and English fluency. A total of 260 participants completed the study.

Participants were excluded if they reported: irregular menstrual cycles (n = 15), use of hormonal birth control (n = 62), use of hormone replacement therapy (n = 1), a history of neurological conditions that may affect cognitive performance (e.g., stroke, traumatic brain injury; n = 2), or if they had an accuracy of under 0.75 for any stimulus type in at least one trial block of the RPE task or if over 20% of their reaction times fell outside of the 0.15 – 2s range (n = 9).

After exclusions, 171 participants remained for analysis (Age: 29.59 ± 5.05 years; Education: 15.89 ± 3.41 years). There were 39 participants in the EF phase, 40 in the LF/PO phase, 39 in the ML phase, and 53 men. Average menstrual cycle length was 27.87 ± 5.03. Average days of cycle per group were as follows: 4 ± 3.58 for PO, 13.1 ± 3.25 for LF/PO, and 21.5 ± 3.42 for ML.

Procedure

Participants completed a category learning task and a questionnaire assessing demographic and health-related information. Participants received monetary compensation for participation in the study.

Category Learning Task Participants completed a RPE categorization task (Heffernan et al., 2021) consisting of three learning blocks and a no-feedback test block. Throughout the experiment, participants viewed 10 images of flowers with tree binary-valued diagnostic dimensions (Figure 2A). Flower stimuli were classified as prototypes (maximally dissimilar across categories), rule-followers (more similar to their category prototype than to the other category prototype), and exceptions (more similar to the prototype of the opposite category). There were four prototypes (two in each category for each value of the nondiagnostic feature), four rule-followers, and two exceptions (for which the nondiagnostic feature varied randomly), for a total of 10 stimuli. Participants completed three learning blocks of 48 trials each. They were shown a flower in each trial and asked if it preferred sun or shade. They were then given feedback on accuracy of response (Figure 2B). Participants then completed a no-feedback test block, also with 48 trials.

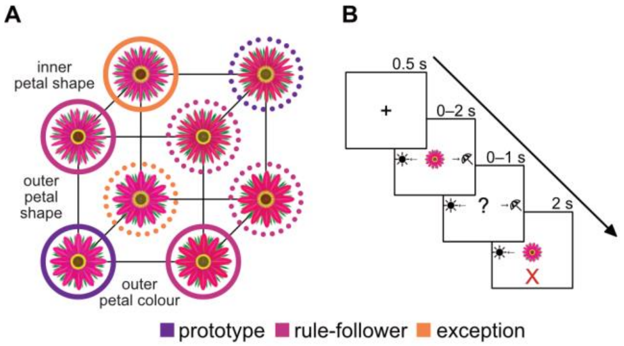

Figure 2: Category structure and experimental trial schematic. A) Stimuli consisted of three binary-valued dimensions with categories defined by a rule-plus-exception structure (solid and dotted circles note stimuli in the two categories). Stimuli were classified as prototypes (purple), rule-followers (magenta), or exceptions (orange) based on their feature values and category label. B) Learning trials consisted of fixation (0.5s), presentation of the flower stimulus (2s), then a response window (1s), and ended with corrective feedback (2s).

Menstrual Cycle Phase Determination To account for variability in length of menstrual cycles (21-35 days; Treloar et al., 1967), menstrual cycle phases were determined according to each participant's self-reported cycle length and current day of cycle. The phases, with predicted hormone levels, were: EF – approximately 1-7 days after menses onset; low E2 and progesterone, LF/PO – approximately 8-17 days after menses onset; high E2 and low progesterone, ML – approximately 1-11 days prior to menses onset; moderate E2 and high progesterone.

Statistical Analyses

All statistical analyses were completed in R 4.0.3. In order to analyze patterns in overall retention of exceptions, we fit a generalized linear model predicting average categorization accuracy by group (EF, LF/PO, ML, male) in the test trial of the task. Then, we fit a b-spline polynomial regression model with a scaled variable denoting participants' current point in the menstrual cycle (cycle point = current day of cycle / cycle length) as a predictor of categorization accuracy in the test block. This allowed us to examine if the pattern of categorization accuracy across the standardized cycle corresponded to assumed changes in ovarian hormone levels across the menstrual cycle (Fig. 1). We specified two knots in the spline estimation, corresponding to days that would mark the changes between the menstrual cycle phases. Participants were included as random effects in the analyses. The spline model was compared to a linear model of categorization accuracy by point in cycle to ensure significantly improved model estimation.

The process of learning was analyzed across learning blocks using generalized linear mixed-effects models predicting categorization accuracy by participant group and type of stimuli (Exception, Rule follower, Prototype), and with participants included as random effects in all analyses. The model was estimated using the lme4 and lmerTest packages. This analysis was followed up by a generalized linear model examination of learning slopes (i.e., difference scores between blocks) by group for exceptions.

Results

Overall Retention

We analyzed the no-feedback test block to assess the overall learning of the category structure across the different groups. Linear models showed that the LF/PO group had higher categorization accuracy for exceptions than the EF group ($\beta = -0.11$, $SE = 0.05$, $t(167) = -2.31$, $p = 0.02$), but that it did not significantly differ from the ML ($\beta = -0.06$, $SE = 0.05$, $t(167) = -1.33$, $p = 0.18$) or male ($\beta = -0.07$, $SE = 0.04$, $t(167) = -1.47$, $p = 0.14$) groups. The EF and ML groups also did not differ in accuracy for exceptions ($\beta = 0.05$, $SE = 0.05$, $t(167) = 0.98$, $p = 0.33$), and neither did the EF and male groups ($\beta = 0.05$, $SE = 0.05$, $t(167) = 1.01$, $p = 0.31$) nor the ML and male groups ($\beta = -0.00$, $SE = 0.05$, $t(167) = -0.37$, $p = 0.97$). There were no differences between groups in terms of categorization accuracy for rule followers or prototypes in the test block (all $p > .05$).

To better characterize the difference in exception learning across the menstrual cycle, we calculated a scaled cycle point variable for each participant and modeled its effect on categorization accuracy in the test block with b-spline regression. Model comparison of the linear and spline regression models of categorization accuracy by cycle point indicated that the spline regression model provided a significantly better fit ($\text{AIC}_{\text{linear}} = -267.13$, $\text{AIC}_{\text{spline}} = -272.43$, $\chi^2(12) = 29.3$, $p < 0.01$).

In particular, the pattern of categorization accuracy across cycle points (Fig. 4) demonstrates a selective impact on exception learning that corresponds with typical changes in E2 levels across the menstrual cycle (Fig. 1). Specifically, we observe an increase in categorization accuracy for exceptions across the EF phase, peaking in LF/PO, and decreasing again in the ML phase.

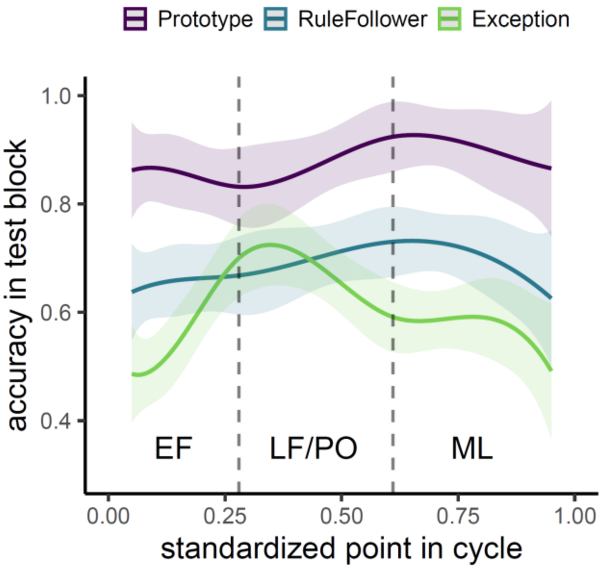

Figure 4: Categorization accuracy in the test block for different stimulus types (prototype – purple, rule follower – blue, exception – green) across standardized points in the menstrual cycle. Dotted lines represent theoretical boundaries between the three cycle phases.

Learning Process

We analyzed performance across learning blocks to assess the process of learning exceptions by group. Results of linear mixed-effects models show that the EF group had lower accuracy for exceptions across learning blocks relative to the LF/PO ($\beta = 0.07$, $p = 0.01$, 95% CI [0.02, 0.12]) and ML groups ($\beta = 0.06$, $p = 0.03$, 95% CI [0.01, 0.11]), but not relative to the male group ($\beta = 0.03$, $p = 0.15$, 95% CI [-0.01, 0.08]). The LF/PO and ML groups did not differ in accuracy for exceptions across learning blocks ($\beta = -0.02$, $p = 0.53$, 95% CI [-0.07, 0.03]), and neither did the LF/PO and male groups ($\beta = -0.04$, $p = 0.12$, 95% CI [-0.09, 0.01]) nor the ML and male groups ($\beta = -0.02$, $p = 0.36$, 95% CI [-0.07, 0.03]). There were no differences between groups in terms of accuracy for rule followers or prototypes across learning blocks (all $p > .05$).

A follow-up generalized linear model analysis of learning slopes (i.e., difference scores between blocks 3 and 2) indicated that categorization accuracy of the LF/PO group for exceptions improved more quickly than that of men ($\beta = -0.09$, $SE = 0.04$, $t(164) = -2.19$, $p = 0.03$), but at a similar rate as the EF ($\beta = -0.04$, $SE = 0.04$, $t(164) = -0.92$, $p = 0.36$) and ML ($\beta = -0.03$, $SE = 0.04$, $t(164) = -0.74$, $p = 0.46$) groups. Improvements in accuracy between the last learning block and the test trial were similar across groups (all $p > .05$).

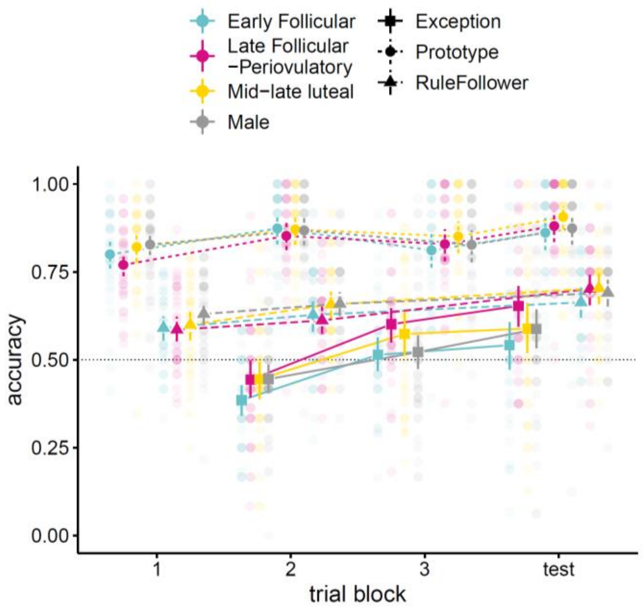

Figure 3: Categorization accuracy across all trial blocks. Average accuracy for stimulus type (prototype – circle, rule follower – triangle, exception – square) in each learning and test block is depicted separately for the different cycle phase groups (EF – cyan, LF/PO – magenta, ML – yellow) and males (grey). Error bars represent bootstrapped 95% confidence intervals and transparent points depict individual participant accuracies. The dotted grey line represents chance level (0.5).

Discussion

This is the first study to examine category learning across the menstrual cycle and consequently tap into possible effects of ovarian hormones on learning exceptions to category structures. We find that the menstrual cycle affects learning of exceptions in a distinct way that matches the typical estradiol cycle, with participants in the high-E2, preovulatory, phase of the menstrual cycle outperforming those in the low-E2, early follicular, phase. Over the course of the exception learning process, participants in the preovulatory and mid-late luteal (moderate E2) phases both outperform early follicular participants, and those in the preovulatory phase improve at recognizing exceptions more quickly than men do.

That participants in the preovulatory phase would show improved performance relative to those in the early follicular phase and the male group, with participants in the mid-late luteal phase also showing better performance than early follicular participants during learning, suggests a role of E2 in facilitating learning of exceptions. This is in line with literature showing that E2 supports a range of learning tasks in rodent models (Frick et al., 2015) and human studies showing that differences in hippocampal-dependent tasks vary by ovarian milieu (Hamson, Roes & Galea, 2016; Hausmann et al., 2000; Peragine et al., 2020). Furthermore, performance on associative memory tasks which, like category learning, require rapid relational binding, is also positively associated with E2 levels (Rentz et al., 2017).

While findings on the effects of menstrual cycle phase on hippocampal-dependent tasks are mixed (Bernal & Paolieri, 2022), a key feature in studies that find significant differences is task load. Effects of ovarian hormones on behavior are often subtle, so complex tasks are needed to detect them (Bernal & Paolieri, 2022; Hampson, Levy-Cooperman & Korman, 2014). This makes the current RPE task particularly well-suited to studying the effects of the menstrual cycle on cognition.

The RPE task is likely affected by E2 through its action on the hippocampal subfields implicated in pattern separation and completion. These processes are needed for the task as it requires generalization with and separation from previously learned categories. Presumably, the CA1-dependent formation of rule-based category representations (Schapiro et al., 2018) takes place during the initial stages of the task. Once exceptions are introduced, the mismatch of these stimuli to previously stored stimuli is signaled, engendering pattern-separation processes in the dentate gyrus and CA3, thus resulting in exception learning (Davis et al., 2012; Mack, Love & Preston, 2018; Schlichting et al., 2021). Notably, E2 increases synaptic density in the CA1 (Frick et al., 2018), long-term potentiation at CA3-CA1 synapses (Taxier, Gross & Frick, 2020) and potentiates synaptic transmission in the CA1, CA3 and the dentate gyrus, with the greatest magnitude of potentiation observed in the CA3 (Kim et al., 2006). Collectively, these findings suggest a key role of E2 in supporting category learning.

A major strength of the current study is the use of three phases of the menstrual cycle. Most studies on cognition across the menstrual cycle only include two phases (Bernal & Paolieri, 2022), and may thus be less sensitive to effects of hormonal changes. Comparison of the EF and LF/PO phases is especially relevant as it allows examination of low and high estradiol periods while levels of progesterone are low. For comparison – most studies on cognition across the menstrual cycle compare the EF phase to the ML phase – when E2 is moderate and progesterone is high, thus introducing a possible confounding factor. The ML phase, however, may provide an opportunity to examine effects of progesterone as it reaches its peak. In fact, we do see preliminary evidence for a potential increase in accuracy for both prototypes and rule followers during the ML phase (see Fig. 4), which may suggest domain-specific effects of estradiol and progesterone.

A further strength of the current approach is the use of non-linear methods to examine changes across the menstrual cycle. In contrast to analysis of the menstrual cycle phases as discrete categories, which may obscure variance within the phases, the polynomial approach allows us to note continuous changes in category learning across the cycle. This is especially informative as there are significant individual differences in hormonal changes across the menstrual cycle, with the late follicular/ovulatory phase being the most variable (Beltz & Moser, 2020). Non-linear approaches may open a door to more nuanced understanding of the effects of this variance in phase timing on cognition.

The main limitation of the current study is that there are no direct hormone measures. As such, we cannot be certain that the determined cycle phases correspond to assumed levels of estradiol and progesterone. However, prior literature suggests that self-report data of menstrual cycle phase aligns with serum hormone levels (Hussain et al., 2016) and the average days of cycle per group in the current study are akin to those reported in literature on cognition across the three menstrual phases with confirmed hormone levels (Pletzer et al., 2019). Future work would benefit from inclusion of blood or saliva hormone assays.

Furthermore, administering the current RPE task in the scanner would elucidate the neural mechanisms of ovarian hormones' effects on category learning. This is especially pertinent given that E2 and progesterone can affect functional connectivity with no changes in task performance – administration of E2 to women in the early follicular phase increases hippocampal activity (Bayer et al., 2018) and E2 increases hippocampal activation during the pre-ovulatory phase while progesterone increases fronto-striatal activation during the luteal phase (Pletzer et al., 2019), all in the absence of behavioral changes.

Any follow-up fMRI studies should aim to also examine brain regions beyond the hippocampus as ovarian hormones have whole-brain functional effects (Pritschet et al., 2020; DeFilippi et al., 2021) and hippocampal connectivity to the frontal and parietal cortices – two regions heavily implicated in category learning (Seger & Miller, 2010; Zeithamova et al., 2019) – varies across the menstrual cycle (Arelin et al., 2015, Lisofsky et al., 2015).

Overall, this work provides novel evidence of the role of estradiol in learning exceptions to category rules, adding a new factor to the multifaceted literature on category learning and further elucidating the long-overlooked effects of ovarian hormones on human cognition. Our models of exception learning across the menstrual cycle, and in comparison to men, provide a starting point to investigating effects of estradiol in learning exceptions. Furthermore, this work underscores the importance of taking diversity across humans and especially in the human hormonal milieu into account during both recruitment and modelling stages of cognitive neuroscience research.

Acknowledgments

This research is supported by Ontario Graduate Scholarship to MP, Natural Sciences and Engineering Research Council (NSERC) Canada Graduate Scholarship to EH, NSERC Discovery Grants to MLM (RGPIN-2017-06753), Canada Foundation for Innovation and Ontario Research Fund (36601) to MLM, and the Brain Canada Future Leaders in Canadian Brain Research Grant to MLM, Jacqueline Ford Gender and Health Fund to GE, Wilfred and Joyce Posluns Chair in Womens Brain Health and Aging from the Posluns Family Foundation, Women's Brain Health Initiative, Canadian Institutes of Health Research, Alzheimer's Society of Canada, and Ontario Brain Institute (WJP-150643) to GE, Canadian Consortium on Neurodegeneration in Aging (CCNA) Phase II (grant CCNA 049-04) to GE.

References

Albert, K., Pruessner, J., & Newhouse, P. (2015). Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle. *Psychoneuroendocrinology*, *59*, 14-24.

Arélin, K., Mueller, K., Barth, C., Rekkas, P. V., Kratzsch, J., Burmann, I., ... & Sacher, J. (2015). Progesterone mediates brain functional connectivity changes during the menstrual cycle—a pilot resting state MRI study. *Frontiers in neuroscience*, *9*, 44.

Babayan, A. H., & Kramár, E. A. (2013). Rapid effects of oestrogen on synaptic plasticity: interactions with actin and its signalling proteins. *Journal of neuroendocrinology*, *25*(11), 1163-1172.

Barth, C., Steele, C. J., Mueller, K., Rekkas, V. P., Arélin, K., Pampel, A., ... & Sacher, J. (2016). In-vivo dynamics of the human hippocampus across the menstrual cycle. *Scientific reports*, 6(1), 1-9.

Bayer, J., Gläscher, J., Finsterbusch, J., Schulte, L. H., & Sommer, T. (2018). Linear and inverted U-shaped dose-response functions describe estrogen effects on hippocampal activity in young women. *Nature communications*, *9*(1), 1-12.

Beltz, A.M. and Moser, J.S. (2020), Ovarian hormones: a long overlooked but critical contributor to cognitive brain structures and function. *Annals of the New York Academy of Sciences*, 1464: 156-180.

Bernal, A., & Paolieri, D. (2022). The influence of estradiol and progesterone on neurocognition during three phases of the menstrual cycle: modulating factors. *Behavioural Brain Research*, *417*, 113593.

Bowman, C. R., & Zeithamova, D. (2018). Abstract memory representations in the ventromedial prefrontal cortex and hippocampus support concept generalization. *Journal of Neuroscience*, 38.

Buffet, N. C., Djakoure, C., Maitre, S. C., & Bouchard, P. (1998). Regulation of the human menstrual cycle. *Frontiers in neuroendocrinology*, *19*(3), 151-186.

Davis, T., Love, B. C., & Preston, A. R. (2012a). Learning the exception to the rule: Model-based fMRI reveals specialized representations for surprising category members. *Cerebral Cortex*, 22, 260–273.

Davis, T., Love, B. C., & Preston, A. R. (2012b). Striatal and hippocampal entropy and recognition signals in category learning: Simultaneous processes revealed by model-based fMRI. *Journal of Experimental Psychology: Learning Memory and Cognition*, 38, 821–839.

De Filippi, E., Uribe, C., Avila-Varela, D. S., Martínez-Molina, N., Gashaj, V., Pritschet, L., Santander, T., Jacobs, E. G., Kringelbach, M. L., Sanz Perl, Y., Deco, G., & Escrichs, A. (2021). The Menstrual Cycle Modulates

Whole-Brain Turbulent Dynamics. *Frontiers in neuroscience*, 15, 753820.

Dreher, J. C., Schmidt, P. J., Kohn, P., Furman, D., Rubinow, D., & Berman, K. F. (2007). Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences*, 104(7), 2465-2470.

Frankfurt, M., & Luine, V. (2015). The evolving role of dendritic spines and memory: interaction (s) with estradiol. *Hormones and behavior*, *74*, 28-36.

Frick, K. M., Kim, J., & Koss, W. A. (2018). Estradiol and hippocampal memory in female and male rodents. *Current opinion in behavioral sciences*, *23*, 65-74.

Frick, K. M., Kim, J., Tuscher, J. J., & Fortress, A. M. (2015). Sex steroid hormones matter for learning and memory: estrogenic regulation of hippocampal function in male and female rodents. *Learning & Memory*, *22*(9), 472-493.

Hampson, E., Levy-Cooperman, N. A., & Korman, J. M. (2014). Estradiol and mental rotation: relation to dimensionality, difficulty, or angular disparity?. *Hormones and behavior*, *65*(3), 238-248.

Hamson, D. K., Roes, M. M., & Galea, L. A. (2016). Sex Hormones and Cognition: Neuroendocrine Influences on Memory and Learning. *Comprehensive Physiology*, *6*(3), 1295–1337.

Hausmann, M., Slabbekoorn, D., Van Goozen, S. H., Cohen-Kettenis, P. T., & Güntürkün, O. (2000). Sex hormones affect spatial abilities during the menstrual cycle. *Behavioral neuroscience*, *114*(6), 1245.

Hazell, G. G., Yao, S. T., Roper, J. A., Prossnitz, E. R., O'Carroll, A. M., & Lolait, S. J. (2009). Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. *The Journal of endocrinology*, *202*(2), 223.

Heffernan, E.M., Schlichting, M.L. & Mack, M.L. (2021). Learning exceptions to the rule in human and model via hippocampal encoding. *Scientific Reports*, 11, 21429.

Hussain, D., Hanafi, S., Konishi, K., Brake, W. G., & Bohbot, V. D. (2016). Modulation of spatial and response strategies by phase of the menstrual cycle in women tested in a virtual navigation task. *Psychoneuroendocrinology*, *70*, 108-117.

Kim, M. T., Soussou, W., Gholmieh, G., Ahuja, A., Tanguay, A., Berger, T. W., & Brinton, R. D. (2006). 17β-Estradiol potentiates field excitatory postsynaptic potentials within each subfield of the hippocampus with greatest potentiation of the associational/commissural afferents of CA3. *Neuroscience*, *141*(1), 391-406.

Lisofsky, N., Mårtensson, J., Eckert, A., Lindenberger, U., Gallinat, J., & Kühn, S. (2015). Hippocampal volume and functional connectivity changes during the female menstrual cycle. *Neuroimage*, 118, 154-162.

Mack, M. L., Love, B. C., & Preston, A. R. (2016). Dynamic updating of hippocampal object representations reflects new conceptual knowledge. *Proceedings of the National Academy of Sciences of the United States of America*, 113, 13203–13208.

Mack, M. L., Love, B. C., & Preston, A. R. (2018). Building concepts one episode at a time: The hippocampus and concept formation. *Neuroscience letters*, *680*, 31-38.

Mahmoud, R., Wainwright, S. R., & Galea, L. A. (2016). Sex hormones and adult hippocampal neurogenesis: Regulation, implications, and potential mechanisms. *Frontiers in Neuroendocrinology*, *41*, 129-152.

Marc, A., Fritz, M. D., & Leon, S. (2011). Clinical gynecologic endocrinology and infertility. *Eight Edition*, *1*(12), 498-531.

Mitra, S. W., Hoskin, E., Yudkovitz, J., Pear, L., Wilkinson, H. A., Hayashi, S., Pfaff, D. W., Ogawa, S., Rohrer, S. P., Schaeffer, J. M., McEwen, B. S., & Alves, S. E. (2003). Immunolocalization of estrogen receptor β in the mouse brain: comparison with estrogen receptor α. *Endocrinology*, *144*(5), 2055-2067.

Olsen, R. K., Moses, S. N., Riggs, L., & Ryan, J. D. (2012). The hippocampus supports multiple cognitive processes through relational binding and comparison. *Frontiers in human neuroscience*, *6*, 146.

Peragine, D., Simeon-Spezzaferro, C., Brown, A., Gervais, N. J., Hampson, E., & Einstein, G. (2020). Sex difference or hormonal difference in mental rotation? The influence of ovarian milieu. *Psychoneuroendocrinology*, *115*, 104488.

Pletzer, B., Harris, T. A., Scheuringer, A., & Hidalgo-Lopez, E. (2019). The cycling brain: menstrual cycle related fluctuations in hippocampal and fronto-striatal activation and connectivity during cognitive tasks. *Neuropsychopharmacology*, 44(11), 1867-1875.

Pletzer, B., Harris, T., & Hidalgo-Lopez, E. (2018). Subcortical structural changes along the menstrual cycle: beyond the hippocampus. *Scientific reports*, *8*(1), 1-6.

Pritschet, L., Santander, T., Taylor, C. M., Layher, E., Yu, S., Miller, M. B., ... & Jacobs, E. G. (2020). Functional reorganization of brain networks across the human menstrual cycle. *NeuroImage*, *220*, 117091.

Protopopescu, X., Butler, T., Pan, H., Root, J., Altemus, M., Polanecsky, M., ... & Stern, E. (2008). Hippocampal structural changes across the menstrual cycle. *Hippocampus*, *18*(10), 985-988.

Rentz, D. M., Weiss, B. K., Jacobs, E. G., Cherkerzian, S., Klibanski, A., Remington, A., ... & Goldstein, J. M. (2017). Sex differences in episodic memory in early midlife: impact of reproductive aging. *Menopause (New York, NY)*, *24*(4), 400.

Schapiro, A. C., McDevitt, E. A., Rogers, T. T., Mednick, S. C., & Norman, K. A. (2018). Human hippocampal replay during rest prioritizes weakly learned information and predicts memory performance. *Nature Communications*, 9, 1–11.

Schlichting, M. L., Gumus, M., Zhu, T., & Mack, M. L. (2021). The structure of hippocampal circuitry relates to rapid category learning in humans. *bioRxiv*.

Seger, C. A., & Miller, E. K. (2010). Category learning in the brain. *Annual review of neuroscience*, *33*, 203-219.

Taxier, L. R., Gross, K. S., & Frick, K. M. (2020). Oestradiol as a neuromodulator of learning and memory. *Nature Reviews Neuroscience*, *21*(10), 535-550.

Treloar, A. E. (1967). Variation of the human menstrual cycle through reproductive life. *International Journal of Fertility*, *12*, 77-126.

Zeithamova, D., Mack, M. L., Braunlich, K., Davis, T., Seger, C. A., van Kesteren, M. T. R., & Wutz, A. (2019). Brain Mechanisms of Concept Learning. *The Journal of Neuroscience*, 39, 8259–8266.