Hippocampus-related exception categorization varies across the menstrual cycle

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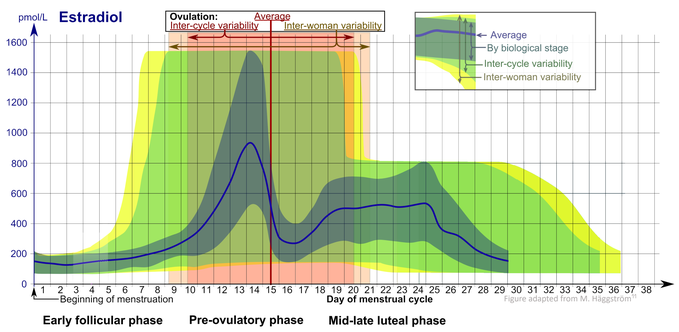
Introduction

17β-estradiol (E2) – the most bioactive estrogen – is strongly associated with hippocampal structure and function[1,2,3,4].

Category learning is a hippocampal-dependent core cognitive process [5,6,7] potentially affected by these E2-driven effects.

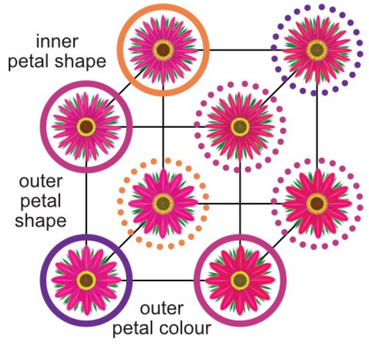
We **hypothesized that E2-mediated changes to hippocampal function across the menstrual cycle would be reflected in cycle-dependent differences in category learning performance.**



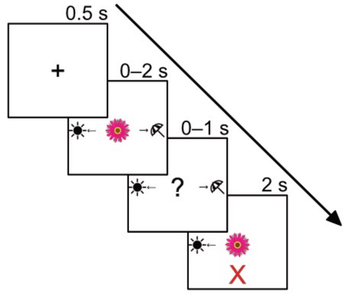
Methods

Participants. N = 171 (Age: 29.59 ± 5.05 years; Education: 15.89 ± 3.41 years). There were 39 participants in the early follicular phase (EF; low E2), 40 in the late follicular/pre-ovulatory phase (PO; high E2), 39 in the mid-late luteal phase (ML; moderate E2), and 53 male participants. Average menstrual cycle length was 27.87 ± 5.03. Average days of cycle per group were: 4 ± 3.58 for PO, 13.1 ± 3.25 for LF/PO, and 21.5 ± 3.42 for ML.

Task category structure



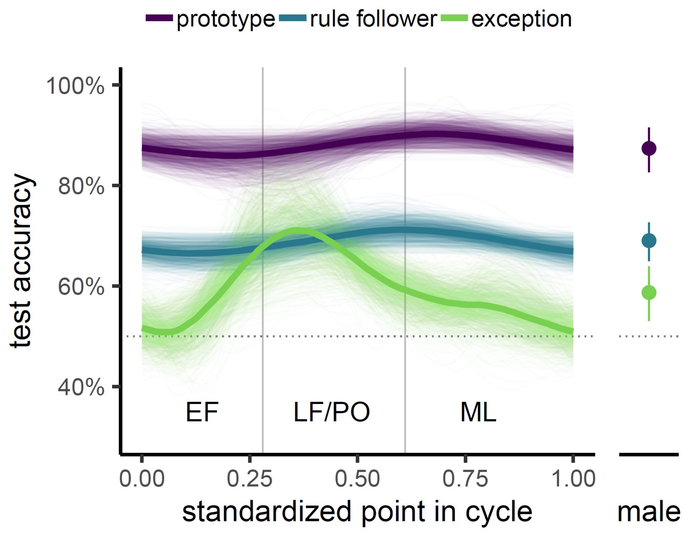
Trial structure



prototype rule-follower exception

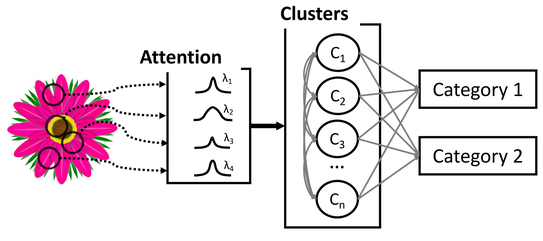
Results

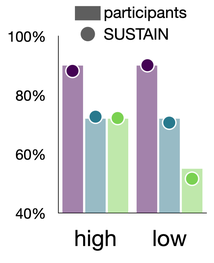
Test performance. Significant effect of cycle point (*EDF*=1.31, *F*(8)=13.13, *p*=.048) with a distinctly non-linear effect on categorization of exceptions (*EDF*=2.93, *F*(8)=85.17, *p*<.001).



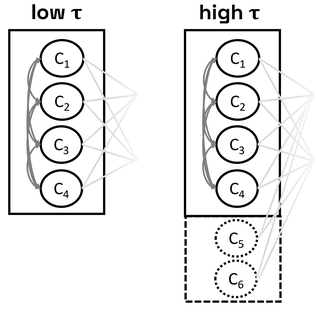
(cycle point = current day of cycle / cycle length)

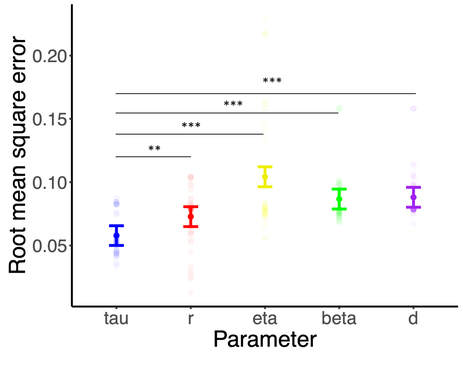
Computational model of learning (SUSTAIN).[6,12] Results were best replicated by model when τ was allowed to vary by group (high vs. low E2). RMSE was lowest for the τ model, relative to models that varied r (*t*(246)=2.65, *p*<0.01), η (*t*(246)=8.23, *p*<0.001), β (*t*(246)=5.11, *p*<0.001), and d (*t*(246)=5.36, *p*<0.001).





τ = responsiveness of model to unexpected events





Discussion

The menstrual cycle affects learning of exceptions in a distinct way that parallels the typical E2 cycle, and high-E2 participants learn exceptions faster than those in the male group.

This aligns with research showing that E2 supports learning in rodent models[8] as well as hippocampal-dependent tasks in humans [9,10].

Computational modeling reveals that participants with high-E2 may be more likely to create new memory representations in response to exceptions[12].

The observed effect is likely driven by E2's action on the hippocampal subfields implicated in pattern separation and completion.

Conclusions

The menstrual cycle affects learning of exceptions to category rules in a way that mirrors the typical estradiol cycle. Participants in the high estradiol phase may be more responsive to unexpected events during category learning. Estradiol likely affects category learning through action on hippocampal pattern separation and completion pathways.

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