

Perimenopause Status and Progesterone Levels Affect Episodic Memory at Midlife

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INTRODUCTION

- Episodic memory (EM) decline is an early and consistent symptom of late-onset sporadic Alzheimer's disease (AD), with female adults accounting for ~2/3 cases¹. However, the reason for this sex difference in AD prevalence remains unclear.
- Recent evidence suggests that AD-related neuropathology precedes symptom onset, making early midlife (~40-55 years) a critical age for early detection of female adults at risk of developing AD².
- Midlife is the period when most female adults experience the menopause transition (perimenopause), involving fluctuations in ovarian hormones, such as 17 β -estradiol (E2) and progesterone, and increased subjective cognitive complaints^{3,4}.
- Few studies have directly examined whether **perimenopausal adults exhibit objective EM deficits compared to premenopausal adults**, as well as the **contribution of individual differences in ovarian hormone levels to EM performance**.

METHODS

Participants:

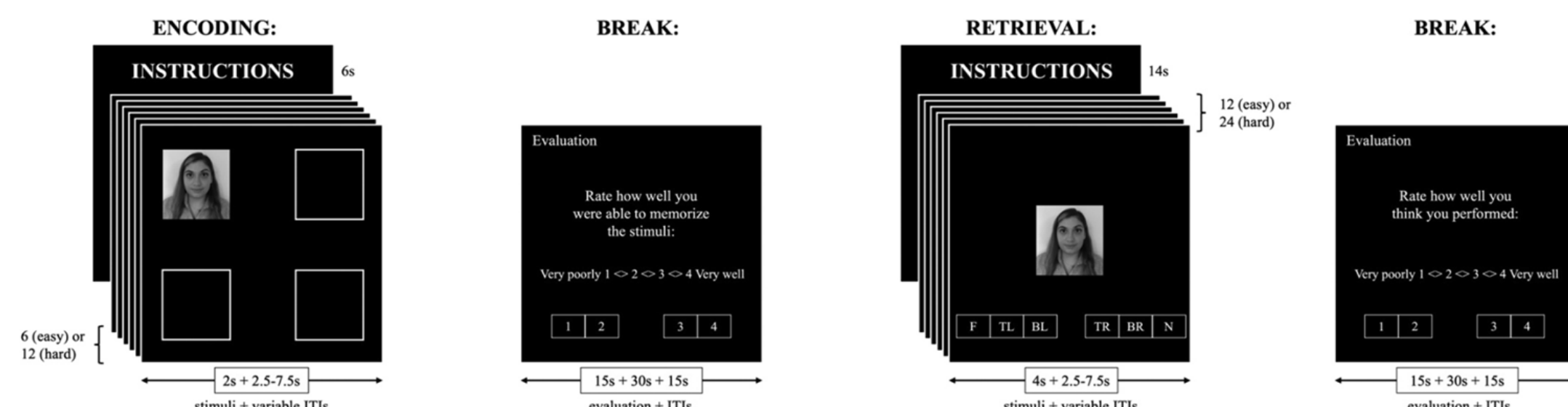
- 66 healthy, middle-aged female adults ($n_{\text{Premenopausal}} = 35$, $n_{\text{Perimenopausal}} = 31$; age range: 39.55–56.68) were drawn from the Montreal site of the Brain Health at Midlife and Menopause (BHMM) study⁵.
- Menopause status was determined using the Stages of Reproductive Aging Workshop (STRAW) +10 criteria³.
- Hormone levels were measured using chemiluminescent immunoassay of blood samples.

EM task:

- Participants performed four easy (low encoding load) and four hard (high encoding load) runs of a face-location EM task.

Outcome measures:

- Accuracy and reaction time for retrieving face-location associations (correct source; CS) and correctly identifying novel face stimuli as “new” (correct rejection; CR).
- Intra-individual variability in these measures across task runs.



Analyses:

- Linear mixed-effects regression was used to analyze the effects of menopause status, task difficulty, and gonadal hormones on EM task performance.

$$\text{CS/CR measure} \sim \beta_0 + \alpha_i + \beta_{\text{Menopause Status}} + \beta_{\text{Task Difficulty}} + \beta_{\text{E2}} + \beta_{\text{Progesterone}} + \beta_{\text{Education}} + \epsilon$$

- To avoid collinearity between menopause status and chronological age, separate linear mixed-effects models in premenopausal and perimenopausal participants were used to examine within-group effects of task difficulty, age, and gonadal hormones on EM task performance.

$$\text{CS/CR measure} \sim \beta_0 + \alpha_i + \beta_{\text{Task Difficulty}} + \beta_{\text{Age}} + \beta_{\text{E2}} + \beta_{\text{Progesterone}} + \beta_{\text{Education}} + \epsilon$$

RESULTS

	Overall <i>n</i> = 66	Premenopausal <i>n</i> = 35	Perimenopausal <i>n</i> = 31
Age (years) *	47.72 (4.58)	44.87 (3.21)	50.93 (3.70)
Education (years) *	15.99 (2.05)	16.50 (2.04)	15.42 (1.95)
Race/Ethnicity			
Black	2 (3.03)	1 (2.85)	1 (3.22)
Chinese	1 (1.52)	1 (2.85)	0 (0.00)
Indigenous	1 (1.52)	0 (0.00)	1 (3.22)
Latin American	3 (4.55)	2 (5.71)	1 (3.22)
South Asian	2 (3.03)	2 (5.71)	0 (0.00)
White	56 (84.85)	28 (80.00)	28 (90.32)
White & Latin American	1 (1.52)	1 (2.85)	0 (0.00)
E2 (pmol/L)	369.97 (276.96)	343.75 (232.86)	399.57 (320.99)
Progesterone (nmol/L) *	11.13 (15.86)	15.42 (17.53)	6.29 (12.29)

Table 1. Participant demographics stratified by menopause status.

Values are expressed as $M(SD)$ or $n(\%)$. * indicates a significant difference between menopause groups, as determined by a t -test or the Mann-Whitney U test. Missing hormone data were imputed.

Participants were excluded if they failed to provide at least one CS judgement or if they performed below chance on face recognition memory (hit rate < 0.42; CR rate < 0.08).

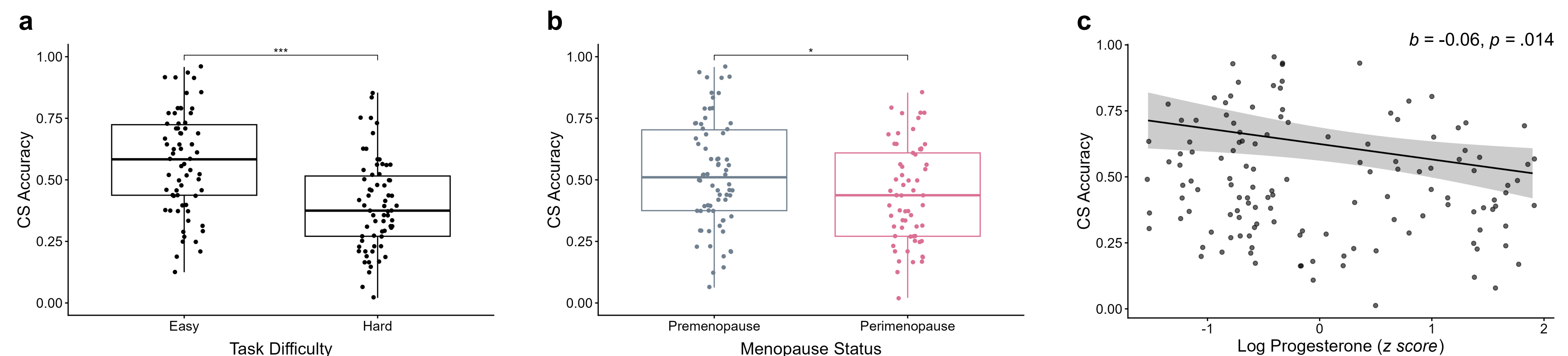


Figure 1. Analysis 1 effect plots. (a) All participants demonstrated reduced CS accuracy on hard task runs compared to easy runs ($b = 0.09$, $p < .001$), and (b) perimenopausal adults showed lower CS accuracy compared to premenopausal adults, when controlling for task difficulty, gonadal hormones, and education ($b = 0.09$, $p = .021$). (c) Greater progesterone predicted reduced CS accuracy across all participants. * $p < .05$, *** $p < .001$.

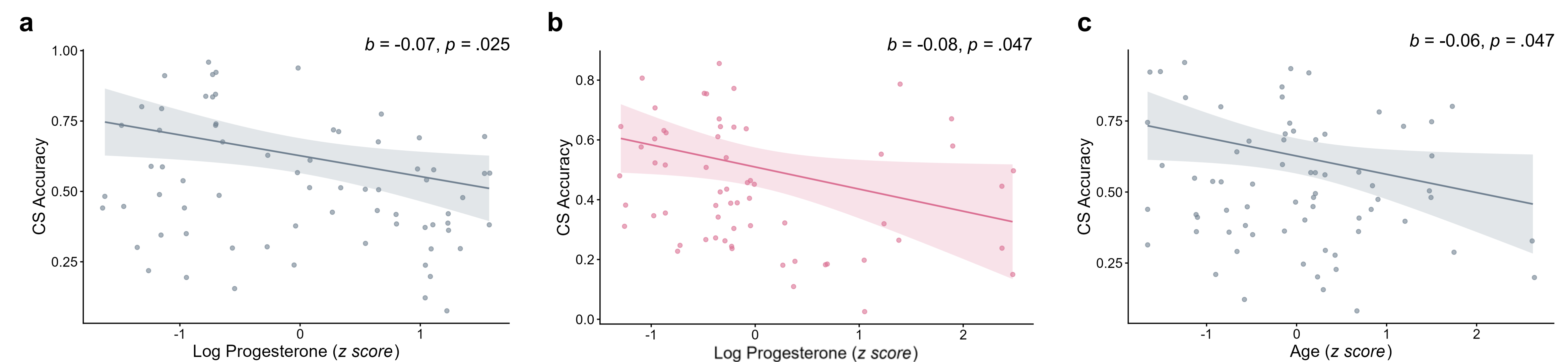


Figure 2. Analysis 2 effect plots. Greater progesterone was associated with lower CS accuracy in both (a) premenopausal and (b) perimenopausal adults, while (c) increasing age predicted reduced CS accuracy in premenopausal adults, exclusively.

CONCLUSION

- Perimenopausal adults performed significantly worse than premenopausal adults on the face-location spatial context memory task, highlighting that this task was sensitive to detecting differences in objective EM performance at perimenopause.
- Progesterone levels predicted individual differences in spatial context memory, but this effect was not specific to a particular menopause group.
- Age did not predict memory performance in perimenopausal participants, indicating that the reduction in spatial context memory performance observed in perimenopausal compared to premenopausal adults was not driven by a greater effect of age in this group.
- Longitudinal research is needed to determine if the memory deficits observed at perimenopause are chronic and potentially indicative of increased AD risk; or if they are transient and reflective of menopause-related neuroplasticity.**

References: ¹Podcasy & Epperson (2016), *Dialogues Clin. Neurosci.*; ²O'Brien et al. (2020), *J. Neurol.*; ³Harlow et al. (2012), *Menopause*; ⁴Greendale et al. (2020), *JAMA*; ⁵Crestol et al. (2023), *J. Neurosci.*