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Implicit memory varies across the menstrual cycle: estrogen effects in young women

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Abstract

Evidence that ovarian steroid hormones such as estrogen and progesterone affect cognition comes from studies of memory in older women receiving estrogen replacement therapy and studies of sexually dimorphic skills in young women across the menstrual cycle. Sixteen women (ages 18–28) completed tests of memory (implicit category exemplar generation, category-cued recall, implicit fragmented object identification) and sexually dimorphic skills (fine motor coordination, verbal fluency, mental rotations) at the early follicular (low estrogen and progesterone) and midluteal (high estrogen and progesterone) phases of the menstrual cycle. Performance on category exemplar generation, a test of conceptual implicit memory, was better at the midluteal than the follicular phase. In contrast, performance on a test of explicit memory, category-cued recall, did not vary across the menstrual cycle. At Session 1, women in the follicular phase performed better on the fragmented object identification task than did those in the midluteal phase. This unexpected finding suggests that high levels of ovarian hormones might inhibit perceptual object priming. Results confirmed previous reports of decreased mental rotations and improved motor skills and fluency in the midluteal phase. Estradiol levels correlated positively with verbal fluency and negatively with mental rotations and perceptual priming, which suggest that estrogen, and not progesterone, was responsible for the observed changes in cognition. Mood did not vary across the cycle phases. Overall, the findings suggest that estrogen may facilitate the automatic activation of verbal representations in memory.

Keywords: Estrogen; Menstrual cycle; Cognition; Memory; Mood

1. Introduction

There is increasing interest in the role of sex steroid hormones on neuropsychological functioning, particularly with regard to the possibility that estrogen may enhance memory. Much of this interest stems from recent reports that estrogen replacement therapy (ERT) may lower the risk of Alzheimer's disease and may lessen normal, age-related memory decline. (For reviews, see [21,45]). Although studies of the cognitive effects of estrogen in postmenopausal women have focused mostly on memory and other abilities that decline with age, studies in younger women have focused primarily on sexually dimorphic abilities. Males generally show an advantage in visuospatial abilities and certain mathematical abilities compared with females, whereas females generally show a comparative advantage in verbal abilities, perceptual speed and accuracy, and fine motor skills. (For reviews, see [16,27].) In young women, naturally occurring increases in estrogen are associated with improvements on tasks that favor females and with declines on tasks that favor males [20]. The present study bridges these two domains of research by examining sexually dimorphic abilities and different types of memory (i.e. explicit and implicit) in young women across the menstrual cycle. Our goals were to broaden the investigation of hormonally mediated cognitive abilities and to increase our understanding of the neurobiological substrates of different types of memory.

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Natural fluctuations in ovarian hormones across the menstrual cycle allow for noninvasive studies of the effects of estrogen on cognition in young women. For women with 28- to 29-day cycle lengths, the menstrual cycle may be divided into two general phases, the follicular and luteal phases [55]. The follicular or proliferative phase extends from Day 1 (the first day of menstruation) to Day 14. Low serum concentrations of both 17-β-estradiol, the most abundant form of estrogen, and progesterone characterize the early follicular phase. Estradiol peaks in the preovulatory surge just prior to ovulation, though progesterone levels remain low. The follicular phase ends at the time of ovulation. The luteal or secretory phase generally extends from Days 14 to 28 and is characterized by high concentrations of both estrogen and progesterone. Cycle phase can be estimated by counting backward to the first day of menstruation. Although this counting method has been used legitimately in some previous research, the approach has been associated with an error rate of 15 [34] to 50% [13]. Confirmation of expected hormone concentrations by radioimmunoassay (RIA) is critical for validating menstrual phase, because accuracy in determining menstrual phase is likely a major factor contributing to incongruent results across previous studies.

Studies indicate that fluctuations in estradiol underlie a reliable pattern of cognitive change across the menstrual cycle. In one study, 45 women completed a battery of cognitive tests during the early follicular and midluteal phases of the menstrual cycle [18]. The battery included 'female' tests of verbal fluency, articulation, manual coordination, and perceptual speed, as well as 'male' tests of deductive reasoning and spatial ability. As predicted, during the midluteal (high estrogen and progesterone) phase, deductive reasoning and spatial ability decreased and verbal articulation improved. Hormonal effects were also evident in an asymmetrical carryover effect, wherein women who first performed spatial tests when hormone levels were low (and therefore conducive to performance) maintained a high level of performance on a second test session when hormone levels were high (and normally detrimental to spatial performance). In a second study, Hampson [17] tested women during both the preovulatory estradiol surge and the follicular phase to control for the potential effects of progesterone on performance. Results paralleled those in the previous study, and hormonal assays revealed a curvilinear relationship between estradiol and spatial ability, with optimal performance associated with intermediate levels. Together, the results suggested that estradiol rather than progesterone was responsible for the observed cognitive effects.

Studies indicating a reliable advantage for women on verbal recall tasks [27] led to speculation that estrogen may enhance verbal memory. Phillips and Sherwin [34] conducted the only published study on memory performance across RIA-validated phases of the menstrual cycle. They reported poorer delayed figural memory during the follicular compared with the luteal phase, but no difference in immediate or delayed paragraph recall. This pattern of results was surprising given their previous findings of enhanced verbal but not figural memory with ERT in surgically menopausal women [46]. A number of subsequent studies corroborated findings of better verbal memory among ERT users compared to nonusers [22,25,31,44] (but see also [1]), and one indicated improvements in figural memory as well [39]. Together, these data suggest that estrogen may improve memory in younger and older women, though the particular domains of memory affected require additional investigation.

The precise mechanism by which estrogen influences memory is not known definitively, but there is reason to believe that the hippocampus and the inferior parietal lobule may mediate the effect. First, animal studies show enhanced survival and growth of neurons in the hippocampus with estradiol. (For a review, see [33]). Moreover, cross-sectional [38] and longitudinal [29] neuroimaging studies in postmenopausal women show hormone-associated differences in patterns of blood flow in the hippocampal formation during performance of figural and verbal delayed memory tasks. Based on findings from a randomized crossover trial of ERT in postmenopausal women, Shaywitz and colleagues speculated that estrogen might improve verbal memory by enhancing short-term storage of phonological stimuli [43]. Compared to placebo, the ERT-treated group in that study showed increased activation of the inferior parietal lobule during storage of nonsense words. That same brain region shows activation associated with the storage and retrieval of phonological material during a working memory task [24] and structural sex differences in regional brain volume [11]. Together, these studies suggest several mechanisms by which estrogen may enhance verbal memory.

To date, studies of hormonal effects on memory have focused on recall and recognition tests. These are termed explicit memory tests because they make explicit reference to a previous event and require deliberate recollection [14]. In contrast, instructions for implicit tests do not call for deliberate recollection, but prior exposure to certain items nevertheless influences (i.e. primes) later processing of those items. For example, in the category exemplar generation (CEG) test, participants study uncommon category exemplars (e.g. plum) and subsequently receive instructions to generate members of a particular category, such as fruit [12]. Priming is evident when participants generate studied exemplars at above-chance levels. The CEG test is considered a test of conceptual implicit memory because it draws on the meaning or semantic associates of studied items.

Perceptual implicit tests, in contrast, draw on the physical characteristics of studied items. In the fragmented object identification (FOI) test, for example, participants first identify line drawings of common objects and then identify fragmented versions of both previously seen and new objects that are shown in increasing levels of completeness [49]. Perceptual priming is evident by earlier identification (i.e. at a more degraded level) of the repeated objects compared with the new objects. Conceptual and perceptual implicit tests have been dissociated in different patient groups and in normal individuals by various experimental manipulations [40]. Moreover, PET studies of conceptual priming indicate bilateral involvement of the inferior parietal lobule during task performance, along with activation of left frontal and temporal cortex [4]. These neuroimaging findings suggest the biological plausibility of estrogen effects on verbal implicit memory through activation of the temporal and inferior parietal lobules.

No studies have directly examined the influence of menstrual phase or ERT use on implicit memory. Indirect evidence that estrogen might affect implicit memory comes from findings of a sex difference on the CEG test. Data from our previous study of implicit memory across the lifespan [30] indicate a slight female advantage on CEG priming ($P = 0.06$) and a significant advantage on conceptual explicit memory (see Appendix A). Conversely, studies of memory during pregnancy lead to the speculation that unusually high levels of sex steroid hormones may detrimentally affect performance on both explicit and implicit memory tests [5,7,23,42]. Pregnancy is characterized by dramatic hormonal fluctuations, including unusually high levels of estrogen, progesterone, oxytocin, and other hormones [15]. Pregnant women report [5,10,35,42] and demonstrate [6,26,42,47] impaired explicit memory for words (but see [5]). Studies of implicit memory in pregnancy provide less consistent results, even among studies using the same test of lexical implicit memory (i.e. word-stem completion). Two studies reported impairments among pregnant women [5,42], and two other studies found no difference between pregnant and nonpregnant women on the test [7,23]. Isolating and understanding the influence of estrogen on memory in pregnancy is difficult because the hormonal milieu is complex and fluctuates throughout pregnancy and the relation between estrogen levels and memory performance may be nonlinear.

In the present study, we investigated performance on tests of CEG priming, FOI priming, explicit memory, and sexually dimorphic skills, such as mental rotations, fine motor coordination, and verbal fluency, across the early follicular (low estrogen) and midluteal (high estrogen) phases of the menstrual cycle. We hypothesized that CEG priming, conceptual explicit memory, verbal fluency, and fine motor skill would increase at the midluteal phase of the menstrual cycle, that mental rotations would increase during the early follicular phase, and that FOI priming would not differ across the two phases. We also examined cognitive performance in relation to estradiol and progesterone to gain insight into the possible modulatory role of those hormones.

2. Method

2.1. Participants

Sixteen female undergraduates aged 18–28 ($M = 20.13$, $SD = 3.18$) at York University in Toronto, Ontario participated in the study. Four other students completed at least one test session but were excluded from the study because RIA results failed to show the expected difference in serum estradiol level across the two menstrual cycle phases. Inclusionary criteria were: (a) a history of regular (i.e. 28- to 29-day) menstrual cycles, with no history of skipping cycles; (b) no prior oral contraceptive use; (c) no current use of medications known to influence the central nervous system; and (d) no evidence of alcohol abuse, defined as a score of less than 7 on the Michigan Alcohol Screening Test) [41]. Thirteen participants were right-handed. All participants spoke fluent English and received $15.00 plus credit toward their Introductory Psychology course for their participation.

2.2. Materials

Because participants were tested twice, we created two parallel forms of the testing materials for the implicit and explicit category exemplar tests and for the FOI tests. We selected forms based on data from 167 nondemented adults showing that they produced equivalent levels of performance (Maki et al., unpublished data). Test items for the category exemplar tests were low- to medium-frequency category exemplars selected from 12 semantic categories [2]. Each of the parallel test forms consisted of three exemplar lists, each containing 12 items from a different semantic category. The three lists were used as targets and baseline items in the CEG test and targets in the explicit cued recall test. In addition, there were two parallel lists of 12 filler items (two exemplars from each of six new semantic categories) for use in the study tests. The CEG target and baseline lists were counterbalanced so that each list served in the baseline and target conditions equally often. All three types of lists were counterbalanced across menstrual cycle phases.

The items in the FOI tests [49] were line drawings of common objects (e.g. 'sock') selected from the set of stimuli developed by Snodgrass and Vanderwart [50].

Each session included 21 items, seven targets appearing in both the study and test phases, seven fillers shown only in the study phase, and seven new objects shown only in the test phase. Participants viewed complete forms of the items during the study phase and fragmented forms during the test phase. There were eight levels of fragmentation for each test item, and each level appeared individually on standard size sheets of paper arranged in a three-ring binder.

2.3. Procedure

Participants were told that the purpose of the study was to examine the relationship between hormones and cognition and that a small vial of blood would be drawn at the end of each session to determine serum estrogen and progesterone levels at the time of testing. Each participant completed parallel batteries of cognitive tests at two individual 90-min sessions, once during the early follicular phase and once during the midluteal phase. Half of the participants were first tested during the follicular phase, and the other half were first tested during the midluteal phase. Initial estimates of cycle phase were made by counting forward from the first day of the last menstrual period (Day 1) to the follicular phase on Day 2 or 3 and the midluteal phase between Days 19 and 24. These initial estimates were later confirmed with RIAs of serum estradiol and progesterone levels; participants failing to show a difference in hormone levels were excluded from the study as previously described. Tests were administered in the order below.

2.3.1. Study phase (attention/vigilance task)

Participants heard a list of 54 category exemplars (i.e. 18 items presented once and 18 other items presented twice each). Their task was to indicate when a particular word had been read previously in that list by saying repeat or raising their hand. This putative vigilance task served as the study phase for the implicit and explicit memory tests.

2.3.2. FOI study task

Participants viewed and named a series of 14 unfragmented objects (i.e. seven targets and seven fillers) presented at a rate of 3–5 s.

2.4. Fluency tasks

The rhyme fluency test directed participants to generate as many words as possible that rhymed with a cue word. There were two 30-s trials with word cues having few possible rhymes (e.g. 'curls') and one 60-s trial with a word cue having many possible rhymes (e.g. 'name'). The phonemic fluency test consisted of two 60-s trials directing participants to generate as many words as possible that began with a particular letter (e.g. 'C,' 'L'), excluding proper names, numbers, or variations of the same word. The dependent measure for both fluency tests was the number of correct responses. The two parallel sets of rhyme and letter cues were counterbalanced across cycle phases. The category fluency test consisted of one 60-s trial directing participants to generate as many words as possible that were exemplars of an unprimed semantic category (e.g. vegetables). This task provided a measure of semantic fluency (i.e. total number of correct responses) and served as a baseline estimate of the probability that participants would generate target exemplars without having first encountered them in the study task. The rhyme and letter fluency tasks provided measures of verbal fluency and helped to disguise the implicit CEG test as another fluency test.

2.5. CEG test

The CEG test phase paralleled the category fluency test except that the semantic cue represented the primed category from the study task. The outcome measure was the number of primed exemplars generated (maximum = 12). For the explicit category recall test, the experimenter supplied the name of another category used during the CEG study phase (either vegetables or body parts) and explicitly instructed participants to recall as many category exemplars from the study phase as possible in 60 s. The outcome measure was the number of targets correctly recalled (maximum = 12).

We computed the CEG prime score as the difference between the number of primed and unprimed hits. We estimated unprimed hits by averaging the number of unstudied target exemplars that other participants generated to the same category cue when it served as a cue in the category fluency test. This controlled for the probability of generating a particular target exemplar by chance and was important because the difference between the number of target and baseline exemplars generated varied significantly across the different categories, $F(1,\ 14) = 2.54,\ P < 0.05$. We calculated separate baseline estimates for the luteal and follicular phases, because phase-related differences in fluency (i.e. better fluency with higher estrogen levels) can affect the number of chance hits. To control for individual differences that might influence exemplar production (e.g. fluency, general cognitive ability), we also calculated a within-subject baseline by averaging the number of unstudied targets that the participant generated to a different category cue that was matched for frequency.

2.6. FOI test

Participants viewed 14 objects, half of which had been studied previously. Beginning with the most de-

graded level, participants viewed increasingly complete pictures of each object until they were able to name it. Each level of fragmentation was displayed for 10 s. The dependent measure was a priming measure derived from the identification threshold (IDT), operationalized as the number of seconds needed to identify the object (maximum = 80). Identification time was recorded with a stopwatch. To estimate priming, we calculated a facilitation score reflecting the ratio of actual improvement in IDT to possible improvement using the equation: (NIDT-RIDT)/(NIDT), where NIDT and RIDT represent, respectively, the IDTs for new (baseline) objects and repeated (i.e. target) objects, and 1 s represents the lowest possible IDT [48]. We used a within-subjects baseline to analyze FOI performance, because IDTs for baseline and target conditions did not vary across picture sets ($P > 0.70$).

2.7. Mental rotations test

On each trial, participants viewed a target three-dimensional drawing of a set of connected cubes along with four alternative drawings, two of which were rotated versions of the target [51]. Participants were instructed to identify the rotated versions of the targets and were told that a point would be subtracted for every incorrect answer. After three practice trials, participants had 10 min to complete the 24 test items. The dependent measure was the number of correct minus incorrect responses (potential range = −24–24 points).

2.8. Grooved pegboard

The Grooved Pegboard Test measures manual speed and dexterity [37]. Participants insert grooved pegs into consecutive holes on a board containing angled slots as quickly as possible. Two trials of each hand were administered, alternating between the dominant and nondominant hand. The experimenter noted the number of drops and recorded completion time on each trial with a handheld stopwatch. The dependent measure was the mean completion time of the two trials, calculated separately for each hand.

2.9. Mood

Participants then completed the PANAS, a 20-item list of adjectives describing positive (e.g. active, determined) and negative (e.g. irritable, distressed) affect. Participants rated each adjective on a 5-point Likert scale ranging from 'very slightly' to 'extremely' based on how they felt that day [53]. The outcome measures were the average responses for negative and positive items. The CES-D measured depressive symptoms [36]. Participants responded to each of 20 items assessing the extent to which they felt a particular way in the past week (e.g. 'I felt sad.') on a 4-point scale ranging from 'rarely' to 'most of the time.'

2.10. Plasma hormone assays

Samples of blood were drawn at the end of each testing session, stored in plain tubes (i.e. with no preservatives), placed in thermolined bags, and transported within 8 h to an independent laboratory. Samples were placed into refrigerators set at 4 °C, and the MDS Laboratory in Toronto conducted RIAs within 24 h from point of draw using the Coat-A-Count method [8,9]. Reliability measures for both RIA procedures (estradiol and progesterone) were calculated internally at the MDS Laboratory over a 3–5-year period. The maximum tolerance for variability at the laboratory is set at 10% (i.e. a minimum of 90% time-based reliability), which is a high standard in the industry.

3. Results

Statistical analyses were conducted using SPSS statistical software (version 8.0 for Windows; SPSS, Chicago, IL), with alpha set at 0.05. Statistical analyses were conducted with phase order as a between subjects factor. Where analyses indicated a significant effect of phase order on performance, we ran an ANOVA on Session 1 data with cycle phase as a grouping variable to control for those effects.

3.1. Hormone levels

As shown in Table 1, serum concentrations of estradiol and progesterone were significantly higher during the midluteal compared with the follicular phase, $ts(15) = 7.88$ and 3.28, respectively, $P < 0.01$.

3.2. CEG test

Performance on the study task did not differ across menstrual phases; participants detected repeated words with 99 and 97% accuracy during the follicular and midluteal phases, respectively. We first conducted one-sample t-tests to determine whether there was significant priming above baseline in both phases (i.e. whether prime scores differed from 0). Table 2 shows the mean number of items produced as a function of cycle phase (i.e. follicular versus midluteal) and condition (i.e. primed hits versus chance hits using the between-subjects baseline) and the results from the corresponding t-tests. There was a striking difference in the pattern of priming across the two phases. During the follicular phase, women showed no significant priming above baseline, $t(15) = 1.47$, $P = 0.16$. In contrast, during the midluteal phase, they showed significant priming above baseline, $t(15) = 5.30$, $P < 0.001$.

Table 1
Serum hormone levels and cognitive test scores (M and SD) as a function of menstrual phase

Variables	Cycle phase		
	Follicular	Midluteal	*P*-value
Hormone levels			
17-β-Estradiol (pmol/l)[b]	109.50 (35.04)	496.88 (212.69)	<0.01
Progesterone (nmol/l)[b]	2.38 (0.81)	23.13 (25.00)	<0.01
Verbal fluency			
Rhyme fluency[a]	14.00 (4.13)	15.69 (3.81)	0.02
Letter fluency	24.56 (5.23)	27.31 (8.70)	0.17
Category fluency	12.25 (2.86)	13.81 (3.19)	0.13
Composite *z*-score[a]	-0.26 (0.73)	0.26 (1.09)	0.02
Fine motor skills			
Grooved pegboard			
Dominant hand[b]	59.31 (4.42)	54.25 (5.56)	<0.01
Nondominant hand[b]	66.25 (8.33)	61.94 (7.18)	<0.01
Visuospatial			
Mental rotations test[b]	27.81 (9.32)	18.94 (9.57)	<0.01
Mood			
Positive and negative affect scale			
Positive affect	3.04 (0.82)	3.33 (0.76)	0.12
Negative affect	1.38 (0.33)	1.56 (0.51)	0.08
CES-depression scale	17.12 (10.09)	14.88 (6.42)	0.29

CES, Center for Epidemiological Studies. See text for scoring calculations.
[a] $P<0.05$, two-tailed.
[b] $P<0.01$, two-tailed.

Next, to determine if the magnitude of priming varied significantly with cycle phase, we conducted an ANOVA on prime scores with cycle phase (follicular versus midluteal) as a within-subject variable and phase order (follicular–midluteal versus midluteal–follicular) as a between-subjects variable. The magnitude of priming varied significantly across the menstrual phases, with more priming during the midluteal than during the follicular phase, $F(1, 14) = 6.52$, $P < 0.05$. No other effect approached significance. A reanalysis of the CEG data using the within-subjects estimate of baseline replicated the pattern of results obtained with the between-subjects baseline, though the magnitude of the effects was smaller.

3.3. Explicit category-cued recall

As shown in Table 2, conceptual explicit memory did not vary with menstrual cycle phase, $P > 0.31$. Our failure to find an effect of estrogen on explicit memory was not due to a ceiling effect, as the average scores ranged from 2 to 8 out of a maximum score of 12.

3.4. FOI priming

Performance on the FOI study task did not differ across menstrual phases; all participants were 100% accurate in naming target (complete) objects at both phases. Table 2 shows the IDTs for baseline (new) and target (studied) conditions used in the calculation of facilitation (prime) scores for both cycle phases. We first conducted one-sample *t*-tests on facilitation scores to determine whether the tasks produced priming. As

Table 2
Baseline, target, and prime scores on the implicit category exemplar generation and fragmented object identification tests and explicit category recall test as a function of menstrual phase

		Cycle phase					
		Follicular			Midluteal		
	Measure	Target	Baseline	Prime Score	Target	Baseline	Prime score
Implicit							
CEG-total[a]	Mean	3.06	2.38	0.69	4.44	2.56	1.88[b]
	S.D.	1.57	0.87	1.87	1.26	0.50	1.41
FOI	Mean	27.94	38.56	26.76[b]	29.38	37.00	18.65[b]
	S.D.	3.30	4.08	11.52	6.10	4.95	23.07
				Total			Total
Explicit							
Recall	Mean			5.69			4.94
	S.D.			1.54			1.77

CEG = Category exemplar generation. FOI = Fragmented object identification. The FOI baseline and target values are the Identification Thresholds for new and repeated items, respectively. The CEG baseline and target values are the number of unstudied and studied exemplars generated, respectively. See Text for calculations of prime scores; *t*-tests indicate whether prime scores differed from 0 in each condition.
[a] $P<0.05$, two-tailed for phase difference.
[b] $P<0.01$, two-tailed for priming above baseline.

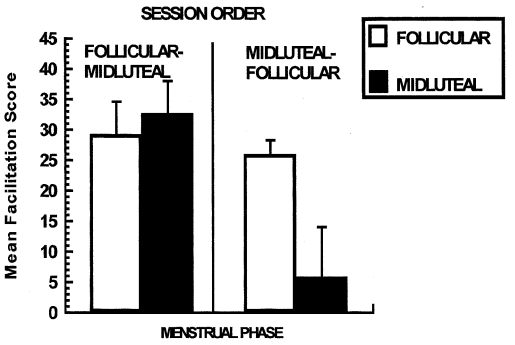

Fig. 1. Mean prime scores on the FOI test as a function of session order and menstrual cycle phase. Error bars are standard errors.

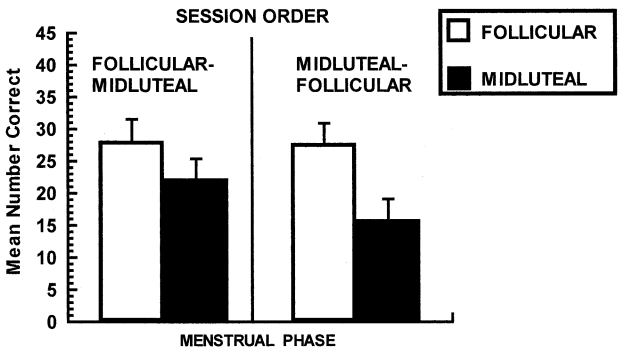

Fig. 2. Mean number correct on the Mental Rotations test as a function of session order and cycle phase during the first session. Error bars are standard errors.

shown in Table 2, women showed significant priming in both the follicular and the midluteal phases, $t(15) = 7.68$ and 3.43, respectively, $P < 0.01$. Next, to determine if the magnitude of priming varied significantly with cycle phase, we conducted an ANOVA on facilitation scores with cycle phase (follicular versus midluteal) as a within-subject variable and phase order (follicular–midluteal versus midluteal–follicular) as a between-subjects variable. The overall magnitude of FOI priming did not differ across menstrual phases, $F(1, 14) = 2.22$, $P = 0.16$. However, as shown in Fig. 1, the follicular–midluteal group showed more priming than the midluteal–follicular group, $F(1, 14) = 6.26$, $P < 0.05$. Notably, the cycle-related change in priming was greater in the midluteal–follicular group than in the follicular–midluteal group, $F(1, 14) = 4.40$, $P = 0.05$.

To examine the effects of menstrual phase while controlling for the significant order effect, we conducted an ANOVA on facilitation scores during Session 1 as a function of group (i.e. follicular–midluteal versus midluteal–follicular). This between-subjects analysis revealed a significant effect of menstrual phase. Women tested during the follicular phase showed significantly more priming than those tested in the midluteal phase, $F(1, 14) = 5.51$, $P < 0.05$. All together, these data suggest that high levels of ovarian steroid hormones might inhibit FOI priming and that women who first perform the task while circulating levels of those hormones are low maintain a high level of performance when tested again during less conducive hormonal conditions (i.e. midluteal phase).

3.5. Additional neuropsychological tests

Table 1 shows the mean scores on the other tests as a function of cycle phase.

3.5.1. Fluency

Following Hampson [18,19], we created a composite fluency score by first computing z-scores for each of the three fluency measures (based on the average across the two sessions) and then averaging the three z-scores to create one composite score. As predicted, overall fluency, reflected in the composite z-score, was better during the midluteal than the follicular phase, $F(1, 16) = 6.46$, $P < 0.05$. Participants generated more rhymes during the midluteal compared with the follicular phase, $F(1, 14) = 6.02$, $P < 0.05$, but performance on the letter and category fluency tests did not change significantly across the two phases. There was no effect of phase order nor was there an interaction between phase order and cycle phase on any of the fluency measures.

3.5.2. Grooved pegboard

As predicted, fine motor performance was faster during the midluteal compared with the follicular phase, $F(1, 14) = 26.91$, $P < 0.001$. Performance with the dominant hand was faster than with the nondominant hand, $F(1, 14) = 28.03$, $P < 0.001$.

3.5.3. Mental rotations

As predicted, performance on the mental rotations task was better during the follicular compared with the luteal phase, $F(1, 14) = 57.33$, $P < 0.001$. As shown in Fig. 2, there was also a significant interaction between cycle phase and phase order, with those first tested during the follicular phase showing a smaller phase-related change in performance than those first tested during the midluteal phase, $F(1, 14) = 6.55$, $P < 0.05$. A between-subjects analysis of Session 1 data revealed a similar effect of cycle phase, $F(1, 14) = 6.35$, $P < 0.05$. These results indicate that mental rotations skill is better when ovarian steroid levels are relatively low and that low hormone levels during the initial encounter with the task facilitate subsequent performance under conditions when hormone levels are higher.

3.5.4. Mood

There was no significant effect of cycle phase on the positive or negative affectivity subscales of the PANAS or on the CES-D scale, $t(15) = 1.65$, 1.85, and 1.09, ns, respectively.

3.6. Correlational analyses

We conducted three sets of Pearson product-moment correlations. The first, shown in Table 3, examined the relationship between hormone levels and neuropsychological test performance during Session 1. Estradiol levels correlated significantly and positively with phonological fluency, category fluency, and composite fluency score and correlated significantly and negatively with mental rotations. There was also a trend toward a positive correlation between estradiol and CEG priming ($P = 0.12$, two-tail) and a negative correlation between estradiol and FOI priming ($P = 0.08$, two-tail). A second set of analyses revealed no significant correlation between any of the mood measures and any of the test scores. A third set revealed no significant correlation or any suggestion of a trend between explicit memory and the number of hits on the CEG test or between explicit memory and FOI priming for either session. These data suggest that participants did not use explicit memory strategies on either implicit test, did not become aware of the implicit testing procedure at Session 1, and did not use that knowledge to influence their strategies on subsequent testing.

4. Discussion

4.1. Summary

The primary goal of this study was to determine whether implicit, explicit, or both types of memory fluctuate with circulating ovarian hormone levels across the menstrual cycle. As predicted, CEG priming was superior during the midluteal compared with the early follicular phase, but, counter to predictions, category-cued explicit recall did not differ across the two phases. These data suggest that high levels of ovarian hormones facilitate conceptual implicit memory in young women, but have no significant effect on explicit memory in young women. Also counter to expectations, we found evidence of hormonal effects on FOI priming. At Session 1, there was greater FOI priming among women in the follicular phase than those in the midluteal phase, suggesting that high levels of ovarian hormones inhibit perceptual object priming. Performance on sexually dimorphic tests showed the expected pattern of change, with high hormone levels associated with decreased mental rotations and improved verbal fluency and fine motor skills. The mental rotations and FOI tests showed an asymmetrical carryover effect, with greater enhancement in performance during the luteal phase when the tasks were first encountered during the follicular phase. Correlational analyses revealed a significant positive association of estradiol level with verbal fluency and a negative association of estradiol with mental rotations. There was also a trend toward a significant positive association of estradiol level with CEG priming and a negative association of estradiol with FOI priming. These findings suggest that estrogen, and not progesterone, was responsible for the observed changes in cognition. There was no significant change in positive or negative affect or in self-reported depressive symptoms across the cycle phases nor any significant correlation between mood and memory measures. These findings argue against the possibility that the observed cognitive changes were due to hormonal effects on mood. Taken together, the results support past studies indicating that estrogen positively influences performance on tasks that favor females and negatively influences performance on tasks that favor males. These results are the first to suggest that estrogen influences implicit memory.

4.2. CEG results

There are a number of possible explanations for the finding of enhanced conceptual priming in the midluteal phase compared with the follicular phase. Estrogen-related increases in CEG priming cannot be accounted

Table 3
Correlations between serum hormone levels and cognitive test scores during session 1

	Neuropsychological measures											
	Implicit		Fluency				Fine Motor		Spatial	Mood		
	FOI	CEG	Rhyme	Letter	Category	All	Dom	Nondom	Rotation	Positive	Negative	CES-D
Assay												
Estradiol	−0.45	0.40	0.40	0.68[c]	0.64[c]	0.69[c]	0.29	0.36	−0.51[b]	−0.07	0.26	−0.28
Progesterone[a]	−0.15	0.27	−0.27	0.34	0.41	0.08	0.18	−0.13	−0.19	−0.30	0.05	−0.48

FOI, Fragmented object identification; CEG, Category exemplar generation; Dom, dominant hand; Nondom, nondominant hand; CES-D, center for epidemiological studies–depression scale.

[a] $n = 15$ because one outlier had progesterone levels that were >2.5 S.D. above the mean.

[b] $P < 0.05$, two-tailed.

[c] $P < 0.01$, two-tailed.

for by generally enhanced verbal fluency, because priming by definition controls for such effects by comparing to baseline. Nevertheless, the pattern of positive correlations among estradiol levels, category fluency and CEG priming suggests that the two verbal tasks tap into a common process [30] that is facilitated by estrogen. Category fluency and priming both rely on phonological processing. Neuroimaging studies show activations in parietal regions during storage and retrieval of phonological material [24]. Estrogen therapy has been shown to increase activation in the inferior parietal lobule during verbal working memory tasks [43]. Thus, estrogen may influence conceptual priming by influencing phonological processing. Estrogen-related enhancements in semantic organization might also modulate both verbal fluency and CEG priming. ERT users show greater spontaneous semantic clustering of words at study compared with nonusers [31], and semantic clustering facilitates CEG priming [3,32].

There was no evidence that estrogen influenced CEG priming indirectly by enhancing explicit memory. In contrast to CEG performance, explicit category recall did not vary with cycle phase or with estrogen levels. Also, category recall did not correlate significantly with estrogen level even though the tests were procedurally identical except for instructions to deliberately retrieve targets in the cued recall condition. Explicit memory can influence or contaminate CEG priming. Patients with hippocampal dysfunction show impaired CEG priming [28], particularly when study conditions involve deep encoding of exemplars (e.g. generating them from a sentence frame). Although we used a shallow encoding process (i.e. attending to target frequency), prior research using the same procedure found that 13% of the variance on the test is attributable to explicit memory [30]. In contrast to that study, however, we did not include instructions to try to remember study items for later recall, which may have decreased the use of explicit strategies in our participants. The lack of a relationship between performance on the implicit and explicit memory tests suggest that estrogen may enhance CEG priming through a mechanism that is not dependent upon hippocampal function. If the mechanism were dependent on hippocampal function, then one would also expect a beneficial effect of estrogen on explicit memory performance in this sample. Instead, estrogen seems to enhance CEG priming by enhancing the automatic activation of verbal representations in memory.

4.3. Explicit memory

Our finding of no estrogen-related change in explicit verbal recall in premenopausal women replicates a previous report [34] but seems to contrast with findings of a beneficial effect of hormone replacement on explicit verbal memory in postmenopausal women [22,25,31,44]. One possibility is that studies, including the present one, may have failed to detect a true effect of estrogen on explicit memory because of insufficient power or the use of insensitive instruments. The former explanation seems more likely than the latter one, because past research has shown the category-cued recall test to be sensitive to the effects of age [30] and sex (Maki, unpublished data). Alternatively, our findings may be valid, and estrogen may have no effect on explicit verbal memory in younger women despite its apparent beneficial effects in older women. Phillips and Sherwin [34] offered two explanations for the apparent discrepancy. First, a critical lowering of estrogen levels may be required before effects are observed. Second, increases in progesterone during the luteal phase may counter the effect of estrogen on memory. These explanations, however, fail to account for their finding of enhanced delayed figural memory at the midluteal phase and for their finding of a positive association between progesterone and memory during the luteal phase. An alternative possibility is that a critical lowering of explicit memory performance may be required before beneficial effects are observed. In postmenopausal women, ERT helps to preserve memory function, but does not raise memory performance to unusually high levels [39,44]. Ongoing studies underway in our lab should provide more direct insight into possible age-related differences in the effects of estrogen on cognitive functioning, including figural, verbal, and implicit memory.

4.4. Perceptual implicit memory

In contrast to the CEG finding, there was no change in FOI priming across the menstrual cycle. There was a significant interaction between cycle phase and phase at first testing, indicating an effect of repeated testing on performance. Post-hoc tests revealed an unexpected finding that priming during the follicular phase was significant and of the same magnitude regardless of phase order, but only those who first encountered the FOI task during the follicular phase also showed priming during the luteal phase. When we controlled for the effect of prior experience in post-hoc tests by examining performance only during Session 1, we observed a significant phase effect, with better FOI priming during the follicular than the midluteal phase. Estradiol correlated significantly and negatively with FOI priming in Session 1, suggesting that high levels of estrogen inhibit visual perceptual priming with objects. Future studies with larger samples are needed to confirm this preliminary suggestion that ovarian hormones may have a negative impact

on FOI priming, particularly because we had limited power to detect an overall significant effect of ovarian hormones on FOI priming.

Explanations for this unexpected finding are lacking, because little is known about skills that contribute to FOI priming and vary negatively with estrogen level (Snodgrass, personal communication, April 24, 1999). We found no significant correlation between mental rotations and FOI priming, suggesting that although both tests vary negatively with estradiol, they tap different abilities. FOI performance may be mediated in part by spatial visualization, a skill that also shows significant sex differences as measured by tests of figural disembedding in which participants identify a simple geometric figure embedded within a more complex pattern [52]. Studies are underway to examine the relationship between spatial visualization and FOI priming.

4.5. Sexually dimorphic abilities

Our results extend past findings of variations in sexually dimorphic abilities across the menstrual cycle. Women in the present study showed enhanced verbal fluency and fine motor skill and decreased mental rotations performance during the luteal phase. Of studies examining verbal fluency across the menstrual cycle [17,18], only this one revealed a significant enhancement during the high estrogen phase. Although Hampson's studies also employed a measure of letter fluency, we employed a measure of rhyme fluency that was particularly sensitive to the effects of estrogen. Our findings on the Grooved Pegboard Test replicate and extend past findings with the Purdue Pegboard test (assembly condition only), the Manual Sequence Box, and the Finger Tapping Test [18,19]. Similarly, our findings on the Mental Rotations Test extend previous findings with the Rod and Frame Test [19] and a measure of spatial ability composed of the Rod and Frame Test, Hidden Figures, and the Space Relations Test [17]. Our comparatively large effect size of about a standard deviation is not surprising given that the Mental Rotations Test produces one of the larger and more reliable sex differences [52]. Our finding of a significant negative relationship between estrogen and mental rotations contrasts with Hampson's report of an inverted-U function between estrogen and Space Relations scores. Although she reports a larger range of estradiol levels due to the selection of women during the ovulatory surge, the patterns differ within comparable ranges. This discrepancy may reflect our lower statistical power, as her sample was nearly three times as large as ours.

4.6. Carryover effects

We observed a greater carryover effect on both the mental rotations and FOI tests from the low to high estrogen phase than from the reverse. Hampson [18] was the first to observe an interaction between phase order and cycle phase on a composite measure of spatial ability, largely due to one component test, Hidden Figures. As with our FOI findings, she found a significant effect of cycle phase only in an analysis of Session 1 data. Two explanations were posited. First, 'subjects who initially perform a test in a physiological state conducive to good performance may develop better skills for doing the task a second time, even if retesting takes place under less favorable endocrine circumstances' (p. 35). Second, 'as subjects achieve greater facility with the task, nonspatial sources of variance (e.g. perceptual speed), which respond to gonadal hormones in a different manner, may assume greater importance' (p. 38). Evidence in favor of the second explanation was found in a higher correlation between perceptual speed and Hidden Figures performance on the second test session relative to the first. Weekes and Zaidel [54] found a similar asymmetrical carryover effect in a study involving a bilateral lexical decision task. The asymmetrical carryover effect would appear to be adaptive, in that experience differentially enhances those skills that may decline with lower hormone levels.

5. Conclusion

The goal of the present study was to examine hormonal effects on tests of implicit and explicit memory as well as on tests of sexually dimorphic skills. New findings revealed activational effects of ovarian sex steroid hormones, in particular estradiol, on perceptual and conceptual implicit memory, suggesting that estrogen modulates neurobiological substrates of memory outside the hippocampus. Other results corroborated previous reports of enhanced verbal fluency and fine motor skill and decreased mental rotations at the mid-luteal compared with the early follicular phase. Although our findings increase the understanding of neuroendocrine substrates of certain cognitive skills, their practical implications are limited, because everyday activities seldom require the isolated skills involved in the various sexually dimorphic tasks employed. Moreover, the neuroendocrine system may compensate for hormone-related declines in certain skills, as suggested by our finding of a positive carryover of visuospatial skills from low to high estrogen conditions. Ongoing studies may lend further insights into the effects of estrogen on automatic memory processes and the generalizability of findings from pre- to postmenopausal women.

Appendix A. Unpublished data on sex differences: means (standard errors) and significance

Variable	Sex		
	Women	Men	*P*-value
Demographic variables			
N	20	19	
Age, years		32.00 (1.83)	0.34
Education, years	16.25 (0.36)	16.15 (0.39)	0.86
Blessed Memory Test, errors	0.90 (0.19)	0.32 (0.17)	0.02[a]
Outcome measures			
CEG Priming[a,b]	1.90 (0.28)	1.22 (0.22)	0.06
Category Recall,% correct[a]	60.83 (3.09)	48.25 (3.74)	0.01a
Category Fluency, # correct[a]	21.50 (1.80)	17.95 (1.81)	0.15
FOI Priming, facilitation score[c]	0.59 (0.03)	0.58 (0.04)	0.47
FOI Skill Learning, facilitation score[c]	0.08 (0.03)	0.12 (0.04)	0.35

Note. Unpublished data on potential sex differences in participants ranging from 22 to 40 years old in a study of implicit memory across the lifespan [30].

[a]Same procedures, tests, and outcome measures used in this study; see text.

[b]Values are shown for twice-presented items, the measure shown to be the most sensitive to the effects of age in the previous study [30]. Priming for once-presented items did not vary with age and would not be expected to be sensitive to sex differences.

[c]Procedure differed from the present study by showing fragmented objects at study.*, significant difference in unpaired *t*-tests, $P < 0.05$.

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