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Effects of menstrual cycle phase and oral contraceptive use on verbal memory

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ABSTRACT

Surgical or pharmacological suppression of ovarian hormones leads to declines in verbal memory, and estrogen treatment reverses these deficits. In the current study, we investigated the effects of menstrual cycle phase and oral contraceptives on verbal memory, as measured by the California Verbal Learning Test, in two groups of premenopausal women — 16 naturally cycling women and 20 current users of estrogen-based oral contraceptives (OCs). Naturally cycling women were assessed twice — once during the early follicular phase (Days 2–4) and once during the midluteal phase (Days 20–22) of the menstrual cycle. OC users were tested on the same cycle days, corresponding to inactive and active pill phases, respectively. We predicted that naturally cycling women would show improved verbal memory during the midluteal phase, when estradiol levels are high, compared with the follicular phase, when estradiol levels are low. We also predicted that OC users, who show no change in endogenous estradiol across the cycle, would show no change in verbal memory. Contrary to predictions, naturally cycling women showed no changes in verbal memory across the cycle, whereas OC users showed enhanced memory during the active pill phase ($p<.05$). None of the secondary cognitive outcome measures varied with cycle phase or OC use including measures of visuospatial memory, verbal fluency, visuospatial abilities, and attention. Overall, these results suggest that verbal memory performance in premenopausal women varies across the cycle with OC use, but does not vary systematically with changes in endogenous estradiol.

Introduction

Surgical or pharmacological suppression of endogenous ovarian hormones leads to declines in verbal memory, a cognitive ability that shows an advantage for females compared to males (Kramer et al., 1988), and add-back estrogen reverses these deficits (Sherwin, 1988; Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996). These findings suggest that endogenous estrogen helps to maintain superior verbal memory skills in women. Menstrual cycle studies offer a non-invasive approach for studying cognitive changes in relation to fluctuations in endogenous estrogen. In these studies, women complete cognitive tests at two or more phases of the menstrual cycle, and test sessions are timed to coincide with minimal and maximal gonadal hormone secretion. For example, women might complete cognitive tests once when estradiol and progesterone levels are at nadir levels (early follicular phase, Days 2–5) and once when estradiol and progesterone levels are high (midluteal phase, Days 19–24). The earliest (Day 1) and later (Days 25–28) cycle days are avoided (unless specifically targeted) to minimize the effects of cycle-related variations in mood. Optimally, plasma hormone levels are assayed to quantify peripheral hormone levels and validate self-reported cycle phase. These levels can then be evaluated in relation to cognitive test performance to identify specific predictors of performance.

A variety of cognitive skills have been studied as a function of menstrual phase. There is evidence to suggest that sexually dimorphic cognitive abilities in particular change across the menstrual cycle (Hampson, 1990a, 1990b). Hampson found that verbal articulation and speeded manual skills – skills that favor females – improved during cycle phases characterized by high estrogen and/or progesterone secretion, whereas visuospatial ability – a skill that favors men – was higher during the follicular cycle phase. Later, Maki et al. (2002) reported enhanced verbal fluency, verbal implicit memory, and fine motor skills – skills that favor females – during the midluteal (high estrogen and progesterone) phase and enhanced visuospatial skills during the follicular phase. Several studies using radioimmunoassays to validate cycle phase failed to find any changes in verbal memory across the cycle (Phillips and Sherwin, 1992; Maki et al., 2002; O'Reilly et al., 2004). There is evidence that non-verbal memory performance is heightened during the midluteal phase of the cycle when estradiol levels are high. Phillips and Sherwin (1992) found that delayed visual memory for geometric figures, a test that shows no sex difference, was better in the midluteal phase compared to the early follicular phase. In contrast, non-human primates show a follicular phase advantage on a spatial memory task, the delayed recognition span test, a test that is dependent upon medial temporal lobe structures (Lacreuse et al.,

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2001). Rats show a similar advantage on the spatial novel object recognition test during estrus when estradiol and progesterone levels are low (Sutcliffe et al., 2007). Evidence from studies such as these provides insights into the effects of ovarian hormones on cognitive test performance in premenopausal women, but do not clearly support the view that memory improves in relation to endogenous estradiol across the cycle.

Insights into the effects of exogenous sex steroid hormones on cognition in premenopausal women can be gained from studies of oral contraceptives (OCs). Such studies are also clinically important because of the large number of women using OCs. A survey by the Centers for Disease Control estimated that 11.2 million women in the U.S., approximately 19% of all U.S. women, used OCs in 2002 (Mosher et al., 2004). Combined OCs containing both ethinyl estradiol and a progestin prevent ovulation by inhibiting the pituitary production and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This inhibition of ovulation reduces estradiol secretion and halts progesterone production (Rivera et al., 1999). Thus, although OC use leads to increased exposure to exogenous estrogen and progestin, the resulting suppression of ovulation is evidenced by low endogenous estradiol and progesterone levels. With OC use, endogenous production of estradiol and progesterone decreases to levels that are typical of the follicular phase of nonusers but are higher than those found in postmenopausal women (Mishell et al., 1972), though there is appreciable interindividual variability in the amount of endogenous estrogens produced in OC users (Fitzgerald et al., 1999). Combined OCs typically include a 7-day hormone-free interval of inactive placebo pills during which the pituitary ovarian axis slowly regains activity (van Heusden and Fauser, 2002) This process begins with an increase in FSH levels, which leads to estradiol production. Estradiol levels have been found to remain suppressed until Day 6 of the inactive placebo phase (i.e., Day 27 of cycle) when they become significantly greater than during the active pill phase (Willis et al., 2006). Importantly, OCs also reduce production of testosterone (Fern et al., 1978).

Surprisingly little is known about the effects of OCs on cognitive functioning, despite their frequent use. Previous studies have not compared memory performance during active versus inactive pill phases (i.e., corresponding to luteal versus follicular). A four-week open cross-over study involved two test sessions during unspecified luteal phase cycle days, once on and off OCs, and found no significant changes in the Benton Visual Retention Test, or tests of associative learning and pattern recognition memory (Silber et al., 1987). Similarly, in a double-blind, placebo-controlled, randomized study, Grinspoon et al. (2003) found no effects of 3 months of treatment with a triphasic OC (Ortho Tri-Cyclen®; norgestimate/ethinyl estradiol) on performance on the Wechsler Memory Scale-Revised or Complex Figure Recall Test in amenorrheic women tested during unspecified cycle days. Further, OCs have been shown to blunt the negative effects of cortisol on memory retrieval (Kuhlmann and Wolf, 2005), suggesting a potential mechanism by which OCs can influence memory.

Our primary aim was to contrast the effects of endogenous estrogen (i.e., fluctuations across the menstrual cycle) and exogenous estrogen (i.e., estrogen administration via OC use) on verbal memory in younger women across the menstrual cycle. Based on expectations that verbal memory would increase in relation to endogenous estradiol, we hypothesized that (1) nonusers would have enhanced verbal memory during the midluteal versus early follicular phase, and (2) verbal memory performance of OC users would not change across the cycle from inactive to active pill phases due to stable endogenous estradiol levels across phases. Our secondary aim was to contrast the effects of endogenous and exogenous estrogen on other cognitive domains across the cycle. We predicted that sexually dimorphic abilities would fluctuate across the cycle in nonusers such that verbal fluency would be enhanced during the luteal phase and mental rotations would be enhanced during the follicular phase. Given the lack of fluctuation in endogenous estradiol across the cycle in OC users, we expected no fluctuations in sexually dimorphic tasks among OC users. We predicted no changes in non-verbal memory or attention across the cycle or with OC use. We included a measure of attention to ensure that any significant differences in cognition detected could not be attributed to attentional fluctuations.

Methods

Subjects

Subjects were recruited through bulletin board notices, internet websites, and fliers in the local community. Seventy-three premenopausal women aged 18–40 (M=24.93, SD=5.28) were enrolled in the study which took place at the University of Illinois at Chicago. Inclusionary criteria were: (a) age 18–40, (b) regular menstrual cycles (28± 5 days), with no history of skipping cycles, and maintenance of cycle regularity during the course of the study, and (c) use of the same ethinyl estradiol-based OCs (i.e., for users) for at least 6 months or no use of any OC for at least 6 months (i.e., for nonusers). See Results section for the specific OC regimens used. Exclusionary criteria were: (d) current use of medications known to influence the central nervous system (e.g., antidepressants) and initiation of such medications during the course of the study, (e) use of progestin-only contraceptives in the last 6 months, (f) history of psychiatric disorders such as Major Depression or an anxiety disorder or a new diagnosis of such a disorder during the course of the study, (g) history of traumatic brain injury, and (h) evidence of alcohol abuse or dependence (>7 on the Michigan Alcohol Screening Test) (Selzer, 1971). Additional inclusionary criteria for nonusers were established based on the normal range for the estrogen assay: i) early follicular estradiol levels below 90 pg/ml (DPC, Diagnostics Products Corporation, Los Angeles, CA); and j) midluteal estradiol levels between 27 and 246 pg/ml (DPC, Diagnostics Products Corporation, Los Angeles, CA). Lastly, to evaluate changes in memory in relation to changes in estradiol, estradiol levels for nonusers were required to increase by at least 20 pg/ml from the early follicular to midluteal phase. All participants spoke fluent English and received a total of $50.00 for time and travel ($20 after the first session and $30 after the second session).

Thirty-seven of the 73 women were excluded from data analyses for the following reasons. Twenty-five women (34% of total enrollees; 67% of excluded cases) did not complete the second test session, 1 (1.5% of the total enrollees; 3% of excluded cases) was over 40 years of age, 1 (1.5% of the total enrollees; 3% of excluded cases) was scheduled incorrectly, 2 (3% of the total enrollees; 5% of excluded cases) had estradiol values that failed to validate self-reported cycle phase, 5 (7% of the total enrollees; 14% of excluded cases) nonusers did not show an increase of at least 20 pg/ml of estradiol between self-reported early follicular and midluteal phases, and 3 (4% of the total enrollees; 8% of excluded cases) nonusers had progesterone levels during the follicular phase that were more than three standard deviations from the mean. The 37 excluded women did not differ from the 36 enrolled women on age, cumulative years of education, race, average reported levels of depression as measured by the Center for Epidemiological Depression Scale (CES-D), reported menstrual symptoms as measured by the Menstrual Distress Questionnaire (MDQ), or on positive or negative affect as measured by the Positive and Negative Affect Schedule (PANAS), t (71)=−0.11, *ns*, t (71)=0.29, *ns*, χ^2 (3, n=72)=3.29, *ns*, and t (71)=−0.21, *ns*, t (71)=0.03, *ns*, t (71)= 1.44, *ns*, and t (71)=1.34, *ns*, respectively.

Measures

Verbal memory

California Verbal Learning Test (CVLT). This test yields measures of immediate recall, delayed recall, and delayed recognition. A target list of 16 words from four semantic categories (e.g., articles of clothing) is read aloud 5 times. The participant is asked to recall as many words as possible after each presentation. A distractor list of words is then presented, and the participant is asked to recall as many words as possible from that distractor list. Next, the participant is asked to recall as many words as possible from the original target list. Following a 20-minute delay, the participant is asked to recall the original target list. Outcome measures include the total number of words recalled across the 5 learning trials, after the short delay, and after the long delay (Delis et al., 1987).

Verbal fluency

Phonemic. This test was designed to measure the speeded production of verbal responses under particular constraints. Participants were directed to generate as many words as possible in 60-s that began with a particular letter ('P', 'L'), excluding proper names (e.g. names of people or places) or words with a similar ending. Alternate letters ('C', 'W') were chosen for the second session to minimize practice effects. The outcome measure is the total correct words generated across the two trials.

Rhyme. This test assesses the ability to generate words with particular phonological constraints. Participants were asked to generate as many words as possible that rhyme with a particular cue word. There were 3 timed trials involving the presentation of a rhyme cue with either a common (*easy*) or uncommon (*difficult*) phonemic ending. The