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Estradiol concentrations and working memory performance in women of reproductive age

Elizabeth Hampson [a,b,*], Erin E. Morley [a]

[a] Department of Psychology, University of Western Ontario, London, ON, Canada
[b] Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada

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Summary
Objective: Estrogen has been proposed to exert a regulatory influence on the working memory system via actions in the female prefrontal cortex. Tests of this hypothesis have been limited almost exclusively to postmenopausal women and pharmacological interventions. We explored whether estradiol discernibly influences working memory within the natural range of variation in concentrations characteristic of the menstrual cycle.
Method: The performance of healthy women (n = 39) not using hormonal contraceptives, and a control group of age- and education-matched men (n = 31), was compared on a spatial working memory task. Cognitive testing was done blind to ovarian status. Women were retrospectively classified into low- or high-estradiol groups based on the results of radioimmunoassays of saliva collected immediately before and after the cognitive testing.
Results: Women with higher levels of circulating estradiol made significantly fewer errors on the working memory task than women tested under low estradiol. Pearson's correlations showed that the level of salivary estradiol but not progesterone was correlated inversely with the number of working memory errors produced. Women tested at high levels of circulating estradiol tended to be more accurate than men. Superior performance by the high estradiol group was seen on the working memory task but not on two control tasks, indicating selectivity of the effects.
Conclusions: Consistent with previous studies of postmenopausal women, higher levels of circulating estradiol were associated with better working memory performance. These results add further support to the hypothesis that the working memory system is modulated by estradiol in women, and show that the effects can be observed under non-pharmacological conditions.

* Corresponding author at: Department of Psychology, University of Western Ontario, London, ON, N6A 5C2, Canada. Tel.: +1 519 661 2111x84675; fax: +1 519 661 3961.
E-mail address: ehampson@uwo.ca (E. Hampson).

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The prefrontal cortex (PFC) may be an important site of estrogen activity in the adult female brain. Estradiol concentrations in PFC are several-fold higher than in the hippocampus (Bixo et al., 1995) and the presence of estrogen receptor alpha (ERα) has been suggested by observations of ERα mRNA transcript or, recently, electron microscopy of the primate PFC (Wang et al., 2010). Importantly, ERα has been observed in dorsolateral PFC (DLPFC), a region implicated in working memory (WM). Specifically, the DLPFC is involved in the on-line maintenance or manipulation of material held in short-term store, but appears not to be critical for tasks that require only simple passive recall (Goldman-Rakic, 1996; Postle et al., 1999).

In postmenopausal women and nonhuman primates, exogenous estrogen administration has been shown to improve performance on memory tasks that depend on the integrity of the PFC, including the *n*-back and delayed response tasks (Duff and Hampson, 2000; Keenan et al., 2001; Rapp et al., 2003; Krug et al., 2006). In a randomized controlled trial, estradiol treatment increased activation in the DLPFC during a visual WM task, relative to placebo (Smith et al., 2006). Adverse effects of estrogen withdrawal on working memory have been demonstrated in young women treated with leuprolide acetate, a gonadotropin-releasing hormone (GnRH) analog used clinically to suppress ovarian function (Grigorova et al., 2006).

Whether circulating estrogens influence prefrontal function under non-pharmacological conditions is not known. The purpose of the present study was to investigate the association, if any, between the level of circulating estradiol and WM in women tested under natural everyday conditions. Differences in estradiol levels were due, not to pharmacological intervention, but to variation linked to the ovarian cycle. Because it is estradiol per se that is hypothesized to be the basis for variation in WM performance, our primary focus was estradiol concentrations, and the ovarian cycle was allowed to vary randomly, serving as an implicit means to ensure a sufficient range in estradiol levels. For comparison, a control group of age- and education-matched males was tested. It was predicted, based on previous studies in postmenopausal women, that higher levels of circulating estradiol would be associated with better WM performance.

1. Method

1.1. Participants

Participants were healthy male ($n = 31$) and female ($n = 39$) undergraduates, ages 17—37 years ($M = 21.63$, $SD = 3.60$) who volunteered for a study titled ''Keeping Track of Colours'' and constituted young control groups for a larger study of aging, menopause, and cognition. As part of the study protocol, each participant provided 2 saliva samples and, immediately following the cognitive testing, completed a health and demographics questionnaire. Most of the women were nulliparous. Women who reported on the health questionnaire that they currently used hormonal contraception ($n = 35$) are not included in the present report. Oral contraceptives suppress ovarian hormone production and steroids contained in these medications are not readily detected by routine assays. One male who reported the use of a psychoactive medication, and one woman of perimenopausal age, also were excluded. Participants had normal color vision as ascertained by self-report and by their ability to discriminate a set of color swatches presented by the examiner prior to the WM task. All participants gave written informed consent.

1.2. Procedure

A brief set of cognitive tests and questionnaires was completed during a single 1-h session. All participants were tested individually by the same trained examiner, who was blind to each participants' endocrine status. Phase of the ovarian cycle was allowed to vary randomly. Women were retrospectively classified into one of two groups for statistical analysis (described below), based on the objective results of immunoassays of two saliva specimens collected during the test session.

1.2.1. Working memory

The spatial working memory task (SPWM) (e.g., Duff and Hampson, 2000; Fournier et al., 2007) was used. We previously found significantly better performance on the SPWM in postmenopausal women receiving hormone replacement therapy (HRT), relative to matched women not receiving HRT (Duff and Hampson, 2000). The task was administered as described in Duff and Hampson (2000). Briefly, participants sat in front of a 4 × 5 array of hinged doors. Behind each door was a colored dot that became visible only when the door was opened. There were 10 different colors in the array, randomly arranged. Participants were asked to find all 10 matching pairs of colors in as few choices as possible, by opening two doors at a time. A trial was considered complete when all 10 matching pairs were found. Therefore, throughout the task participants had to create, hold on-line, and continuously update a mental representation of which locations had already been matched and which locations remained to be matched. A working memory error (WME) was defined as revisiting a pair of locations that had already been searched. Participants completed 3 consecutive trials plus a delayed recall 30—40 min later. The number of WMEs and cumulative time to completion for each trial were recorded.

The SPWM is modeled after a search task used to study WM in nonhuman primates (Passingham, 1985), which has been shown to be severely impaired by lesions of the DLPFC.

1.2.2. Other tasks

The Mental Rotations Test (MRT; Vandenberg and Kuse, 1978) was used as a comparison task that was expected to show a different relation to circulating estradiol levels. Previous work suggests that women's performance on the MRT is better at low not high estradiol levels, such as those found at menses in naturally cycling women (e.g., Maki et al., 2002). The task consisted of 24 items. Each item depicted a complex target object constructed from cubes, with 4 'arms' that projected in various directions. Placed to the right of each target object were 4 possible response alternatives laid out in multiple choice format. Two of the alternatives showed the target object seen from a different point of view. The other two alternatives depicted objects that looked similar but were incorrect, in that the target object

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