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Influence of estradiol on functional brain organization for working memory

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Abstract

Working memory is a cognitive function that is affected by aging and disease. To better understand the neural substrates for working memory, the present study examined the influence of estradiol on working memory using functional magnetic resonance imaging. Pre-menopausal women were tested on a verbal n-back task during the early (EF) and late follicular (LF) phases of the menstrual cycle. Although brain activation patterns were similar across the two phases, the most striking pattern that emerged was that estradiol had different associations with the two hemispheres. Increased activation in left frontal circuitry in the LF phase was associated with increased estradiol levels and decrements in working memory performance. In contrast, increased activation in right hemisphere regions in the LF phase was associated with improved task performance. The present study showed that better performance in the LF than the EF phase was associated with a pattern of reduced recruitment of the left-hemisphere and increased recruitment of the right-hemisphere in the LF compared to EF phase. We speculate that estradiol interferes with left-hemisphere working-memory processing in the LF phase, but that recruitment of the right hemisphere can compensate for left-hemisphere interference. This may be related to the proposal that estradiol can reduce cerebral asymmetries by modulating transcallosal communication (Hausmann, 2005).

Keywords

functional magnetic resonance imaging; n-back; menstrual cycle; performance; hemispheric lateralization

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1.1 Introduction

Influence of estradiol on functional brain organization for working memory Memory function is essential for daily activities. Working memory is defined as the online maintenance of information over relatively short time periods while that information is updated or manipulated (Daneman and Carpenter, 1980). Retaining information over short delays, which is a component of working memory, is referred to as short-term memory. Working memory includes the additional component of manipulating the content of memory during the delay interval. Working memory is an essential underlying operation for many higher-order cognitive tasks, like mathematical computation (Morris et al., 1998; Wilson and Swanson, 2001). Moreover, aging, and neurological and psychiatric disorders are associated with impairments of working memory (Budson, 2009). Better understanding of factors that modulate brain structure and function related to working memory is needed in order to develop interventions for age- and illness-related working memory impairment.

One of the influences that may modulate working memory is estradiol. Postmenopausal women report problems with memory, suggesting that loss of estradiol may contribute to memory difficulties. Postmenopausal memory complaints are associated with impairments of working memory and memory encoding but not retentive memory (i.e., storing information for later retrieval; Weber and Mapstone, 2009). Indeed, studies indicate that both working memory and short-term memory improve following estrogen-based hormone-replacement therapy in post-menopausal women (Duff and Hampson, 2000; Krug et al., 2006; Shaywitz et al., 2003). In addition, long-term suppression of ovarian function with leuprolide acetate depot treatment in pre-menopausal women leads to declines in working memory performance (Grigороva et al., 2006). However, other studies show no improvement (Berent-Spillson et al., 2010; Grigороva and Sherwin, 2006; Janowsky and Chavez, 2000) on working or short-term memory following estrogen-based treatment in post-menopausal women. Thus the effect of estradiol on working memory remains unclear based on the results of studies involving direct manipulations of estradiol level.

The influence of estradiol on working memory can also be examined by assessing performance across the menstrual cycle when estradiol levels naturally fluctuate. Rosenberg and Park (2002) showed that in normally cycling pre-menopausal women, working memory performance was better during high-estrogen phases of the menstrual cycle (e.g., cycle days 14 and 21 compared to days 0 and 7). Although the authors concluded that estradiol mediated this improvement, they did not measure hormones directly; therefore, it is not known whether estradiol or progesterone was the mediating factor. Vranic and Hromatko (2008) showed that working memory performance with visual stimuli (i.e., faces) was better during high-estradiol phases relative to the low-estradiol phase. However, in that study the “high-estradiol” phases included either the late follicular or mid-luteal phase, the latter of which is associated with higher levels of both progesterone and estradiol. Therefore, a direct effect of estradiol on working memory has not been established unequivocally in these menstrual cycle studies.

In contrast, other menstrual cycle studies have shown that estradiol interferes with working memory performance. Gasbarri et al. (2008), examining short-term memory in the early (low estradiol and low progesterone) and late (high estradiol and low progesterone) follicular phases, found decrements in short-term memory performance during the high-estradiol phase. Two other studies showed that working memory (Man et al., 1999) and short-term memory (Schmitt et al., 2005) performance was worse in the mid-luteal phase compared with the follicular phase. Again, these findings could be attributed to changes in progesterone rather than estradiol, or an interaction of the two hormones.

Inconsistencies in estradiol effects are also observed in brain imaging studies. Estradiol enhances many aspects of global brain function, including brain activation, blood flow and glucose metabolism (Archer et al., 2006; Berga, 2007; Eberling et al., 2000; Maki and Resnick, 2001; Nevo et al., 2007; Rilling et al., 2008). Brain imaging studies of postmenopausal women have reported effects of hormone replacement therapy (HT) on brain activation in certain memory tasks (see Maki and Resnick, 2001 for a review). Among postmenopausal women, HT is associated with enhanced activation in task-related regions, including prefrontal activation on short-term (Smith et al., 2006) and working memory (Dumas et al., 2010) tasks. However, HT-induced decreases in activation, such as decreased inferior parietal activation for storage of non-verbal material (Shaywitz et al., 1999), have also been reported. Increases or decreases in activation are often not accompanied by changes in task performance, leading Maki and Resnick (2001; p. 797) to suggest that brain imaging may be more sensitive to effects of estradiol or other hormones than task performance. However, if performance does not change as a function of hormonal or cognitive processing manipulations, the increased or decreased activation may not necessarily reflect the cognitive operations engaged for a given behavioral task. Rather, the changes in activation may be due to some other factor not related to the task, such as global cerebrovascular changes with estradiol (Krejza et al., 2004; Maki and Resnick, 2001; Nevo et al., 2007). For this reason, it is more compelling to examine, and easier to interpret, brain activation changes that are related to task performance, working-memory specific cognitive operations and hormonal fluctuations.

Given the mixed findings on whether and how estradiol affects working memory performance and concomitant functional brain organization and activation magnitude, the present study used functional magnetic resonance imaging (fMRI) to examine associations among estradiol, behavioral performance on a verbal n-back task, a well-accepted working memory task, and brain activation. Although other studies have also examined brain activation patterns across the menstrual cycle in a variety of cognitive (Craig et al., 2008b; Dietrich et al., 2001; Fernandez et al., 2003; Schoning et al., 2007; Weis et al., 2008, 2010) and behavioral domains (Amin et al., 2006; de Leeuw et al., 2006; Dreher et al., 2007; Gizewski et al., 2006; Goldstein et al., 2005; Protopopescu et al., 2005), to our knowledge, no brain imaging study has examined the influence of estradiol on neural correlates of working memory across the menstrual cycle.

Normally cycling, healthy, pre-menopausal women underwent fMRI testing in the early (EF) and late follicular (LF) phases of the menstrual cycle. By focusing only on EF and LF phases, the goal was to isolate neural components of working memory that were associated with variations in estradiol levels specifically, apart from the effect of progesterone. Increases in brain activation under menstrual cycle phase conditions of high versus low estradiol are not easily interpretable unless directly linked to performance changes, working-memory specific task demands, or estradiol changes. Therefore, blood samples were collected to determine whether estradiol levels across the EF and LF phases were associated with brain activation and n-back task performance. If enhanced brain activation is associated with performance decrements and elevated estradiol levels, then it is possible to conclude that estradiol is associated with impairments in working memory. If greater activation is associated with performance enhancement and elevated estradiol levels, then estradiol has a facilitating influence.

1.2 Methods

1.2.1 Participants

Nineteen women enrolled in the study, but only eight completed both fMRI sessions (early follicular and late follicular sessions) and provided blood samples after both sessions. Two

other participants completed all sessions but did not provide a second blood sample. Nine participants withdrew after enrolling due to scheduling conflicts. Age of study completers ranged from 18 to 38 years ($M = 25$ years, $SD = 6.4$). All participants were right-handed, had normal vision, and reported no major medical, neurological or psychiatric conditions. Participants were not using contraceptives and reported no irregularities in their menstrual cycles.

1.2.2 Procedure

Participants completed three sessions. The first session involved informed consent and screening (e.g., assessing handedness, visual function, etc), and practice with the working memory task. During this session, each subject was given the Calendar of Premenstrual Experiences, (COPE; Mortola et al., 1990) to complete on a daily basis in order to monitor physical, emotional and physiological changes across their menstrual cycles and to estimate the first day of menses. After completing the COPE through one full menstrual cycle, participants were asked to call the lab to schedule a second session that occurred either during the early follicular phase (EF; Days 3–5 following menses) or the late follicular phase (LF; Days 10–12 following menses, as confirmed by estradiol and progesterone levels). The third session occurred during the phase of the menstrual cycle that was not tested in session 2. Half of the participants completed session 2 during the EF phase and half completed session 2 during the LF Phase. For sessions 2 and 3, the participants completed one fMRI session followed by blood collection. During the fMRI session, subjects completed a verbal working memory task and a spatial visualization task (mental rotation). Data from the spatial visualization task are not reported.

1.2.3 Hormone assays

To determine changes in hormone levels between EF and LF sessions, five ccs of blood were drawn into gold top tubes immediately after each session, centrifuged, and transported to the Reproductive Endocrinology Laboratory at the University of Kentucky. Serum was frozen until assayed. Estradiol, progesterone testosterone, LH and FSH were assayed by a solid-phase, competitive chemiluminescent enzyme immunoassay using an Immulite 1000 (Siemens Healthcare Diagnostics, Los Angeles, CA) according to the manufacturer's recommendations. Serum and alkaline phosphatase labeled hormone were added to antibody coated beads which were then incubated at 37 C for up to 70 minutes. Test units were washed after incubation, alkaline phosphatase substrate was added and the samples incubated at 37 C for 10 minutes. Counts per second (cps) for each sample were converted to analyte concentrations using stored master curves. The assay sensitivities were as follows: estradiol (15 pg/mL), progesterone (0.2 ng/mL), testosterone (15 ng/dL), LH (0.1 mIU/mL) and FSH (0.1 mIU/mL). The intra- and inter- assay coefficient of variation were routinely between 5–8% and 10–13% respectively.

1.2.4 Task and Design

For the fMRI sessions, an “n-back” working memory task was implemented as a block design with three levels of memory load: 0-back, 1-back and 2-back. The n-back task presented upper and lower case letters from the Roman alphabet at .25 Hz. The 0-back condition required detecting the presence of an “X” or “x.” The 1-back condition required detecting whether the current letter matched the letter presented previously (regardless of case). The 2-back condition required detecting whether the current letter matched the letter presented two time intervals previously (regardless of case). Each letter was presented for 500 msec followed by a fixation cross for 3500 msec. Participants could respond during the letter presentation or during presentation of the fixation cross. A response was required for every letter presentation; separate responses were required when there was a match and when there was no match. Subjects used the index and middle fingers of the right hand to

respond (with index finger indicating a match). Memory load was manipulated across six task blocks (lasting 72 seconds each) within a run in a pseudo-random order and alternating with seven baseline blocks (lasting 12 seconds each) that required visual fixation of a crosshair. Two runs were completed within each session with the order of runs counterbalanced across subjects and sessions (EF vs. LF). Four different versions of the runs were created so that a given subject never saw the same order of blocks or letters within a block across the experiment. Stimuli were projected onto a 83×82 cm screen using an high-resolution LCD projector connected to a Dell computer running E-prime 1.0 (Psychology Software Tools, Pittsburgh, PA). Participants viewed the stimuli (visual angle of 4.7 degrees) through a mirror attached to the head coil.

1.2.5 fMRI Data Acquisition

Data were collected using a Siemens Vision 1.5 Tesla magnet equipped with a quadrature head coil and T2*-weighted gradient echo sequence. Eighteen brain volumes per task block and three brain volumes per fixation block consisted of 46 axial slices acquired in ascending order to allow for whole brain coverage with 3.56 mm^3 voxels (TR = 4000 ms, TE = 40 ms, flip angle = 90° , FOV = 228×228 mm). High-resolution T1-weighted MP-RAGE anatomical scans (150 sagittal slices 1 mm thick, FOV = $256 \times 256 \text{ mm}^2$) were collected for each participant at the end of the first session.

1.2.6 Data Analysis

Behavioral data (reaction time, errors) were analyzed with SPSS (Chicago, IL) using a 3 (Load) $\times$ 2 (Phase) repeated measures ANOVA. Reaction time (RT) on each trial was log-transformed to satisfy the assumption of normality for the multivariate approach to repeated measures analyses. Individual RTs greater than three standard deviations of the group-averaged RTs were considered outliers and treated as missing values.

Using FMRIB's FSL package (<http://www.fmrib.ox.ac.uk/fsl>), functional brain images in each participant's time series were motion corrected and functional runs were discarded when uncorrected head motion exceeded half a voxel (1.7 mm). Images in the data series were spatially smoothed with a 3D Gaussian kernel (FWHM = 7.5 mm), and temporally smoothed using a high-pass filter (378 seconds). All 10 subjects who completed both fMRI sessions were included in the analysis. All subjects contributed two usable runs in the EF phase; one subject contributed only one usable run in the LF phase, but all other subjects had two usable runs.

Customized square waveforms (on/off) representing each of the three memory loads (0-, 1-, 2-back) were convolved with a double-gamma hemodynamic response function. Hemodynamic parameters were estimated for each explanatory variable (0-, 1-, 2-back) and statistical contrast maps of interest were generated. The main contrast of interest in the present study was 2 versus 0 back to isolate working memory processes while controlling for influences of visual stimulus presentation and response selection and execution. The six head movement parameters (3 rotation values in radian and 3 translation values in millimeter) were added as covariates of no interest to model the variance in the fMRI signal induced by the head motion. Contrast maps were normalized into common stereotaxic space before mixed-effects group analyses were performed. This involved registering the average EPI volume to the MP-RAGE volume, and the MP-RAGE volume to the ICBM152 T1 template, using FLIRT (FMRIB's Linear Image Registration Tool) module of FSL package. One mixed-effects group analysis was conducted for each session (EF and LF) using the spatially normalized contrast maps from individual participants. The main contrast of interest that is reported here is the 2- versus 0-back contrast. In addition, the Phase $\times$ Load interaction was examined by a group analysis directly contrasting the 2- versus 0-back

contrast across phase sessions. Functional regions-of-interest ROIs were defined as clusters of 43 or more contiguous voxels (Xiong et al., 1995) in which parameter estimate (PE) values for 2 versus 0-back activation differed significantly from zero.

In each ROI for each session, PE values were extracted for each level of memory load in each session. For example, in the ROIs isolated by the 2 versus 0-back contrast in the EF session six PE values were extracted based on the factorial combination of Load (0-, 1-, 2-back) $\times$ Phase (EF, LF). These PE values represented the magnitude of fMRI activation, which was the main dependent measure from the fMRI data. Using SPSS (Chicago, IL) we conducted a 3 (Load) $\times$ 2 (Phase) repeated measures ANOVA within each ROI. These repeated measures ANOVAs were needed because the 2- versus 0-back contrast used to isolate the ROIs did not consider all three levels of memory load, nor did this contrast test for interactions of memory load and phase. The scalar repeated-measures ANOVA conducted with SPSS, however, tested for all main effects and interactions in each ROI.

In addition to ANOVAs, two types of correlations were conducted for each region that was isolated by the 2- versus 0-back contrast in the LF phase and for the two regions isolated by the combined contrast of 2- versus 0-back for LF versus EF phases (i.e., the Phase $\times$ Load interaction). One set of correlations examined the association between *change* in fMRI signal magnitude (expressed as a difference score, LF 2-back PE value minus EF 2-back PE value) and *change* in 2-back performance (LF 2-back error rate minus EF 2-back error rate, or LF 2-back log-transformed RT minus EF 2-back log-transformed RT). A second set of correlations examined the association between *change* in fMRI signal magnitude (already described) and *change* in estradiol level (LF estradiol minus EF estradiol). Correlations between change in fMRI signal and change in performance or between change in fMRI signal and change in estradiol level addressed the theoretically relevant variation in estradiol across the two menstrual cycle phases. A positive correlation between change in fMRI signal and change in estradiol level indicates that estradiol is associated with greater activation in the LF phase. However, greater activation in the LF phase cannot be interpreted as facilitating or interfering with respect to behavior unless the correlations with performance are also considered. A positive correlation with error rate or RT in a particular region would indicate that greater activation in the LF phase was associated with poorer performance. A negative correlation with error rate or RT in a particular region would indicate that greater activation in the LF phase was associated with better performance. Non-parametric correlations (Spearman rank) were used due to the small sample size. In addition, a bootstrap procedure was used to construct confidence intervals for the Spearman correlations between change in fMRI signal and other measures (change in error rate, reaction time and estradiol concentration). For each test, 2500 bootstrap samples were drawn with replacement from the original sample. To correct for possible skewness in these resampled distributions a bias-corrected and accelerated bootstrap method (Efron 1987) was used to construct 95% confidence intervals. Correlation reliability was evaluated from the confidence interval coverage and exclusion of zero correlation.

3.1 Results

3.1.1 Hormonal analysis

A paired t-test comparing EF and LF sessions for each of five hormones (estradiol, progesterone, luteinizing hormone, follicle stimulating hormone, and testosterone) revealed that only estradiol levels increased from the EF ($M = 49.4$ pg/ml; $SD = 20.5$ pg/ml) to LF phase ($M = 110.5$ pg/ml; $SD = 65.7$ pg/ml), $t(7) = -2.7$, $p = .029$, in the 8 participants that provided both blood samples. The other hormones showed no significant difference ($p > .11$). Consequently, only estradiol effects were examined with subsequent analyses. The range of changes in estradiol from the EF to the LF phase was 4 to 149 pg/ml, indicating that

some women in our sample did not likely show a biologically significant change in estradiol across the two cycle phases. However, on average, the change for the group was significant.

3.1.2 Behavioral performance

Based on the 10 participants who completed both fMRI sessions, the 2-back condition led to more errors and slower responding than the 0- and 1-back conditions (Figure 1). The main effect of memory load was significant both for errors, $F(2, 18) = 6.2$, $p = .016$, and reaction time (RT), $F(2, 18) = 14.8$, $p = .0001$. However, neither errors nor RT changed as a function of menstrual cycle phase nor was there a Phase $\times$ Load interaction (all p 's $> .15$). Memory load remained significant when the two subjects who did not provide a second blood sample were removed from the dataset: $F(2, 14) = 4.3$, $p = .048$ for errors, $F(2, 14) = 11.0$, $p = .001$ for RT.

3.1.3 2-back versus 0-back Activation in the Early Follicular Phase

Many regions commonly reported to be activated during working memory task performance (Goldstein et al., 2005b; Speck et al., 2000) were activated during each phase for the 2-v-0-back contrast (Table 1; Figures 2 and 3, blue color scale), according to the voxel-wise analyses. Initial voxel-wise analyses were based on 10 subjects to maximize power to detect regions. However, subsequent analyses within ROIs (using SPSS) were performed on only the eight subjects that provided two blood samples for estradiol level determination. Regions that showed more activation for 2- than 0-back conditions included left inferior parietal and prefrontal cortex and right-hemisphere homologues of these regions. According to the scalar ANOVAs conducted in each ROI separately, all regions showed a significant effect of memory load such that increasing the demands in the n-back task induced a linear and monotonic increase in activation in these regions, giving more confidence that these regions indeed are related to working memory processing. Figure 1 (right panel) shows these memory load functions for left inferior parietal cortex as an illustration of this effect. The left and right cerebellum and tectum/pineal body showed greater activation in the EF than the LF phase. Two regions showed a significant Load $\times$ Phase interaction -- the cerebellar vermis and right insula (see Table 1). In these two regions, 2-back activation was greater during the EF than the LF phase ($p = .07$ for vermis; $p = .002$ for insula, according to a paired t-test) but activation was equated across phase for the 0- ($p = .52$ for vermis; $p = .45$ for insula) and 1-back ($p = .71$ for vermis; $p = .81$ for insula) conditions.

3.1.4 2-back versus 0-back Activation in the Late Follicular Phase

Many of the same regions were activated in the LF phase (Figures 2 and 3, red-yellow color scale) as in the EF phase (blue color scale). The ANOVAs in each region revealed a significant effect of memory load (Table 1). Again, the main effect of memory load indicated that increasing the demands in the n-back task induced a linear and monotonic increase in activation in these regions. The main effect of phase emerged in the left and right cerebellum, which showed less activation in the LF phase. No regions showed significant Load $\times$ Phase interactions.

Correlations between change in fMRI signal and change in estradiol revealed that an increase in estradiol from the EF to the LF phase was associated with greater recruitment of the left hemisphere insula ($\rho = .762$, $p = .028$, $n = 8$, Figure 3B) and precentral gyrus ($\rho = .833$, $p = .01$, $n = 8$, Figure 3C) regions in the LF compared to EF phase. The 95% confidence interval (CI) was .29 to 1 for the left hemisphere insula and $-.13$ to 1 for the left precentral gyrus. Correlations between change in fMRI signal and change in performance revealed that an increase in errors from the EF to the LF phase was associated with less recruitment of the right cerebellum ($\rho = -.97$, $p = .0001$, $n = 8$, CI = -1 to $-.35$; Figure 2A). In contrast, an increase in errors from the EF to LF phase was marginally associated

with more recruitment of the left middle frontal cortex ($\rho = .671$, $p = .069$, $n = 8$, $CI = -.34$ to $.98$; Figure 3A). Increase in RT from the EF to the LF phase was associated with less recruitment of the right hemisphere inferior frontal ($\rho = -.714$, $p = .047$, $n = 8$, $CI = -1$ to $.16$; Figure 2B) and middle frontal ($\rho = -.81$, $p = .015$, $n = 8$, $CI = -1$ to $.08$; Figure 2C) regions. The bootstrap analysis confirmed significance for the left insula and right lateral cerebellum and indicated marginal effects in the left precentral, right inferior frontal and right middle frontal cortex, but a non-significant effect in the left middle frontal gyrus. None of the correlations between changes in estradiol and performance was significant.

3.1.5 Phase $\times$ Memory Load Interaction

Regions that showed an effect of phase for the 2- versus 0-back contrast (according to the voxel-wise analysis) are listed in Table 1. The majority of the Phase $\times$ Memory Load interactions reflected more activation for the 2-back condition during the EF phase than during the LF phase. This interaction emerged primarily in subcortical structures: the bilateral hippocampus, vermis, brain stem and the right caudate nucleus. No regions showed more activation during the LF than EF phase for the 2-back condition. However, the increase in estradiol from the EF to the LF phase was associated with more recruitment of the left postcentral gyrus ($\rho = .81$, $p = .015$, $n = 8$; $CI = .09$ to 1 , indicating a significant effect).

4.1 Discussion

In this experiment, brain activation associated with verbal n-back performance was examined across early and late follicular phases of the menstrual cycle to isolate influences of estradiol on functional brain organization for working memory. The regions recruited in each menstrual cycle phase were similar. In fact, the only regions to show a magnitude difference between the two phases were the cerebellum and the tectum. Although the main effect of cycle phase was not predominant across all brain regions, correlations between change in fMRI signal and change in estradiol level or change in performance across the two phases revealed an influence of estradiol on functional brain organization for working memory.

The most striking pattern that emerged was that changes in estradiol had different associations with the two hemispheres. Specifically, greater activation in the left fronto-parietal network for working memory was associated with increased estradiol levels in the LF phase and poorer 2-back performance (i.e., an increase in errors in LF compared to EF phase), whereas greater activation in right prefrontal cortex and the right cerebellum in the LF phase was associated with improvements in performance (i.e. decreased reaction time or errors in LF compared to EF phase). Another way of thinking about the results is that improved performance in the LF phase was associated with relatively less activation in the left hemisphere (e.g., Figure 3a) and relatively more activation in the right hemisphere (e.g., Figure 2b) compared to the EF phase. Conversely, poorer performance in the LF phase was associated with relatively more activation in the left hemisphere and relatively less activation in the right hemisphere. Note that the associations with estradiol or performance are based solely on *changes* in activation levels from the EF to LF phase and not with *absolute* levels of fMRI signal magnitude. In fact, few of the regions that showed associations with estradiol or performance showed an overall fMRI signal magnitude change across the two phases (except the right lateral cerebellum), which is consistent with other studies (e.g., Weis et al., 2008). In other words, the changes observed from the EF to the LF phase in the present study reflect a subtle reallocation of resources across the two hemispheres in the high estradiol phase rather than large-magnitude changes in overall levels of activation in the two hemispheres. This subtle reallocation of hemispheric resources may be more advantageous in terms of memory performance, potentially because

recruitment of the non-dominant hemisphere can lead to more efficient processing in complex tasks (Belger and Banich, 1998).

Previous studies have shown that estradiol and progesterone can reduce functional cerebral asymmetries by modulating transcallosal communication of the two hemispheres (Hausmann, 2005). Hausmann et al. (2002) demonstrated that the degree to which the two cerebral hemispheres are recruited for a given task is modulated by changing hormone levels across the menstrual cycle. In particular, progesterone and estradiol levels were shown to reduce cerebral asymmetries for a task that is normally lateralized to a particular hemisphere (Hausmann, 2005; Hausmann et al., 2002). In cortex, pyramidal cells are the major receptor bearing neurons which likely support corticocortical connections (Kritzer, 2004). Hausmann and colleagues (2000, 2005) suggest that gonadal sex steroids can reduce corticocortical transmission via glutamatergic and gaba-ergic actions. In particular, in low-estradiol or low-progesterone states, the dominant hemisphere for a given cognitive task suppresses or inhibits activity in the non-dominant hemisphere via glutamatergically induced excitatory post-synaptic potentials. Higher estradiol or progesterone states will reduce the corticocortical transmission, which leads to reduced inhibition of the non-dominant hemisphere which essentially diminishes the degree of functional lateralization for a task. Two recent neuroimaging studies employing connectivity analyses have provided additional support for this mechanism (Weis et al., 2008, 2010). For example, Weis et al. (2008) used a left-lateralized word matching task and showed that during menses (low estradiol state) the left inferior frontal cortex exerted a stronger inhibitory influence on the homotopic right inferior frontal cortex than during the follicular phase (high estradiol state).

Although the present study did not test this mechanism directly, the finding that improved task performance in the LF phase was associated with a subtle reallocation of resources across the hemispheres may be consistent with the transcallosal communication / interhemispheric decoupling hypothesis proposed by Hausmann and Gunturkun (2000). On the other hand, changes in estradiol in the LF phase were only associated with activation changes in the left hemisphere and not the right hemisphere. Moreover, the present analyses were not able to demonstrate that activation in a given brain region was predicted by both estradiol and performance (or that a region's activation predicted performance). To make these kinds of conclusions we would need to employ multiple regression or mediation analyses. Given the sample size, however, we did not think these analyses would be appropriate.

It is important to note that the right lateral cerebellum is considered by some to strongly integrated with the language dominant left-hemisphere (Marian et al., 2001) and that cortico-cerebellar connections are contralateral. In this sense, the right lateral cerebellum should not necessarily be associated with right-hemisphere cortical areas (as shown in Figure 2) but associated with left-hemisphere cortical areas. Interestingly, activation in the right lateral cerebellum was associated with errors, similar to the left-hemisphere cortical areas, whereas right-hemisphere cortical areas were associated with reaction time. Taking this into consideration, the right lateral cerebellum, unlike the right-hemisphere prefrontal areas, may not necessarily be associated with better performance in the LF phase given that it was recruited significantly *less* in the LF phase (hence, the values in the scatterplot in Figure 2 are almost all negative). Nevertheless, the trend depicted in Figure 2 indicates that if the right lateral cerebellum were to be recruited more strongly in the LF than EF phase, it may be associated with improved performance. This suggestion is consistent with the idea that the cerebellum may be critically involved in working memory (Gottwald et al., 2004; Ziemus et al., 2007). Specifically, Desmond et al. (1997) suggested that the cerebellum may be associated with phonological rehearsal and motor control of articulation (albeit

subvocally), both of which were heavily involved in the present verbal working memory task.

One limitation of the present study was that the timing of sessions during the LF phase may not have coincided with maximal peak follicular levels of estradiol. Although average estradiol level during the LF phase was significantly higher than in the EF phase and was within the normal ranges for our laboratory, the average level was lower than peak follicular levels that have been reported elsewhere (Speroff et al., 1994). In fact, this was the motivation for examining the magnitude of change in estradiol levels from the EF to the LF phase, rather than absolute levels in each phase. In addition, absolute hormone levels vary among laboratories depending upon the analytic methodology employed for hormone determination (unpublished observations). Nevertheless, even with a sub-maximal change in estradiol, the present study isolated some interesting associations between estradiol and brain activation. It is unclear whether changes in brain activation would have been even greater at higher estradiol levels.

The present finding that a greater increase in activation in the left fronto-parietal network for working memory from the EF to LF phase was associated with increased estradiol levels and poorer 2-back performance from the EF to LF phase is consistent with some previous results. For example, in post-menopausal women, higher levels of estradiol are associated with performance decrements on working memory following estrogen-based treatment compared to performance prior to treatment (Grigороva and Sherwin, 2006). In addition, fluctuations in estradiol or estradiol plus progesterone across the menstrual cycle interfere with working memory or short term memory performance (Gasbarri et al., 2008; Man et al., 1999; Schmitt et al., 2005).

The finding that estradiol, progesterone, or both, can interfere with working memory can be contrasted with other published research showing that estrogen-based HT can improve *verbal* memory. Verbal memory is often assessed with paragraph recall or other memory tests that require the maintenance of information over a certain time period then retrieval of that information later. These tasks do not include the additional requirement to manipulate or update the information in memory as is required by working memory tasks (Daneman and Carpenter, 1980). Verbal memory and related tasks may rely on a hippocampal-dependent brain system (Scoville and Milner, 1957) whereas working memory may rely on a striatal-based system e.g., (Bertolino et al., 2010; Dodds et al., 2009; Landau et al., 2009; Lewis et al., 2004). These two systems may be influenced differently by estradiol. A study in rodents showed that higher levels of estrogen may facilitate hippocampal-dependent learning and memory (e.g., tasks that require retention of information as in verbal memory tasks) but lower levels of estrogen may facilitate striatal-dependent learning and memory (Davis et al., 2005). The implication is that higher levels of estrogen may interfere with striatal-dependent memory. This may explain why interfering influences of estradiol were observed in the present study whereas studies of verbal memory have shown that estradiol improves performance. However, the finding that estradiol can improve verbal memory comes largely from studies in post-menopausal women (Sherwin, 2003). Comparisons of the present results with findings in postmenopausal women are limited, however, by age and circulating estradiol levels, which will depend on the type and dose of HT and the period between menopause and initiation of HT. It is possible, for example, that estradiol has beneficial effects on working memory function in older postmenopausal women with low circulating estradiol levels but interferes with this function in younger premenopausal women experiencing menstrual cycle variations in estradiol levels.

The present study took an important step toward understanding the influence of estradiol on fMRI activation magnitude associated with working memory. By relating fMRI activation to

performance on the n-back task, we were able to demonstrate that increased activation in the left hemisphere from the EF to LF phase was associated with poorer n-back performance in the LF phase whereas increased activation in the right hemisphere from the EF to LF phase was associated with better n-back performance in the LF phase. At present, we cannot conclude that estradiol mediated this association because estradiol did not directly affect performance. Nevertheless, we hypothesize that the interfering effect of estradiol in the left-hemisphere in the LF phase may be attenuated with recruitment of the right hemisphere (possibly through a mechanism of reduced suppression of the non-dominant hemisphere, as proposed by Hausmann and Gunturkun, 2000). Right-hemisphere recruitment (and consequent improvements in performance) in the LF phase may vary across individuals, which could underlie the inconsistent findings across studies regarding whether estradiol improves or interferes with working or short-term memory. However, the small sample size of the present study did not afford a close examination of such individual differences, which should be addressed in future studies with a larger sample size using regression-based analyses. In addition, mechanisms of interhemispheric interaction could be addressed in future studies using psychophysiological interaction analysis (e.g., Weis et al., 2008, 2010) or dynamic causal modeling performed on fMRI time series data. The present findings also describe some interesting interactions (e.g., whether estradiol mediates the relation between task performance and fMRI signal magnitude or whether fMRI signal magnitude mediates the relation between estradiol and task performance) that could be further explored in future research with a larger sample size.

In summary, working memory is an essential underlying operation for many cognitive tasks, like mathematical computation (Wilson and Swanson, 2001). A better understanding of brain structure and function related to working memory is critical to developing interventions designed to treat and prevent age- and illness-related working memory impairment. The present study demonstrated that estradiol interfered with critical nodes of verbal working memory – left lateral prefrontal cortex and the left inferior parietal lobule. Consistent with studies demonstrating that higher levels of estradiol can reduce cerebral asymmetries for a task that is lateralized to the left hemisphere (Hausmann, 2005), the present findings suggest that the right hemisphere may be recruited for working memory during higher estradiol phases in order to compensate for the interference in the left-hemisphere. Further studies with larger sample sizes will be required to validate this important finding.

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Figure 1.

Error and reaction time (RT) performance in the EF phase (left panel) and LF phase (middle panel). Right panel: fMRI signal as a function of memory load and cycle phase in the left inferior parietal cortex. Error bars are standard errors of the mean (n=8).

Figure 2.

Right-hemisphere fMRI activation patterns (significant at $p < .0005$) for the 2-back versus 0-back contrast in the EF phase (blue color scale) and LF phase (red-yellow color scale). Overlaps of activation are depicted in purple. Correlations between fMRI signal change from EF to LF phase and task performance change from LF to EF phase are also shown for (A) Right lateral cerebellum, (B) Right inferior frontal gyrus, BA 44 (C) Right middle frontal gyrus, BA 8. In each graph, Montreal Neurological Institute (MNI) coordinates are shown for that region.

Figure 3.

Left-hemisphere fMRI activation patterns (significant at $p < .0005$) for the 2-back versus 0-back contrast in the EF phase (blue color scale) and LF phase (red-yellow color scale). Overlaps of activation are depicted in purple. Correlations between fMRI signal change from EF to LF phase and task performance change from LF to EF phase or estradiol change are also shown for (A) Left middle frontal gyrus, BA 46, (B) Left insula, BA 48, (C) Left precentral gyrus, BA 6. In each graph, MNI coordinates are shown for that region.

Regions isolated by various contrasts (all regions were significant at $p < .0005$ uncorrected), with F-values for main effects of Load and Phase and the Load $\times$ Phase interaction

Table 1

Phase Region	Size	MNI coordinates			Main effect of Phase of Load	Main Effect Interaction	Load $\times$
		x	y	z	BA	F(1, 9)	F(2, 18)
<i>2-back v. 0-back in the Early Follicular phase</i>							
L Superior Parietal	42	-20	-72	54	7	ns	24.9 ^a
L Inferior Parietal	784	-50	-44	42	40	ns	47.9 ^a
L Mid Cingulate	395	-2	26	38	24	ns	26.6 ^{a,e}
L Inferior Frontal	790	-42	10	30	44	ns	54.1 ^a
L Insula	385	-46	14	-2	48	ns	19.5 ^{a,e}
L Cerebellum-Crus I	303	-38	-62	-32	ns	53.7 ^a	ns
L Cerebellum-8	67	-38	-48	-48	8,2 ^c	29.5 ^a	4.2 ^{d,e}
Vermis	47	-2	-60	-32	ns	32.0 ^a	6.1 ^c
Tectum/Pineal body	468	2	-30	-2	6,4 ^c	16.4 ^{b,e}	ns
R Supramarginal	286	52	-44	44	40	ns	38.1 ^{a,e}
R Precentral	170	42	10	44	9	ns	11.5 ^{a,e}
R Angular	86	34	-58	44	7	ns	30.5 ^{a,e}
R Middle Frontal	304	30	38	20	46	ns	38.2 ^a
R Insula	464	36	22	0	47	ns	26.4 ^a
R Cerebellum-7b	430	40	-54	-44	17,6 ^b	39.0 ^{a,e}	3.4 ^d
<i>2-back v. 0-back in the Late Follicular phase</i>							
L Supp Motor Area	100	2	16	48	32	ns	35.1 ^{a,e}
L Inferior Parietal	2304	-32	-54	46	7	ns	81.7 ^a
L Precentral	1666	-40	2	38	6	ns	54.4 ^a
L Middle Frontal	153	-36	48	16	46	ns	9.9 ^{b,e}

Phase Region	Size	MNI coordinates				Main effect of Phase of Load	Main Effect Interaction	Load ×
		x	y	z	BA			
L Insula	68	-34	14	6	48	ns	F(1, 9)	F(2, 18)
L Cerebellum-7b	361	-36	-60	-44		5.1 ^d	24.5 ^a	ns
R Middle Frontal	43	34	8	58	8	ns	45.6 ^a	ns
R Inferior Frontal	64	48	28	28	44	ns	20.0 ^a	ns
R Cerebellum-8	64	32	-62	-46		6.9 ^c	34.5 ^{a,e}	ns
							38.2 ^a	ns
<i>2-back v. 0-back for Early v. Late Follicular phase</i>								
L Cerebellum-6	315	-14	-64	-20		ns	8.2 ^{c,e}	8.6 ^c
L Hippocampus	49	-28	-24	-6	20	ns	8.2 ^b	4.1 ^c
L Mid Orbitofrontal	140	-30	46	-8	47	ns	ns	ns
Midbrain	100	8	-22	-16		ns	16.7 ^a	6.6 ^c
Vermis	83	4	-42	-32		ns	24.4 ^{a,e}	20.4 ^{c,e}
Pons / Medulla	49	8	-28	-44		9.6 ^c	10.7 ^b	12.3 ^b
R Caudate	572	18	2	26		ns		13.6 ^a
	10.6 ^b							
R Ant Cingulate	292	14	40	18	32	ns	7.6 ^b	.ns
R Fusiform gyrus	100	30	-76	-2	19	ns	ns	8.5 ^{c,e}
R Hippocampus	106	32	-14	-14	20	ns	ns	7.1 ^{c,e}
R Middle Temporal	64	60	-14	-22	20	ns	4.9 ^{c,e}	ns
<i>2-back v. 0-back for Late v. Early Follicular phase</i>								
L Postcentral	180	-26	-38	66	2	ns		ns
	6.8 ^c							
R Superior Frontal	58	22	68	4	10	ns	ns	6.7 ^c

Note.

^a p < .0001,

^b p < .01,

^c p < .05,

$$d^2 p <= .064, \\ \epsilon^2_F(2, 8)$$

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