CLINICAL INVESTIGATION

# Effect of Estrogen on Brain Activation Patterns in Postmenopausal Women During Working Memory Tasks

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**Context** Preclinical studies suggest that estrogen affects neural structure and function in mature animals; clinical studies are less conclusive with many, but not all, studies showing a positive influence of estrogen on verbal memory in postmenopausal women.

**Objective** To investigate the effects of estrogen on brain activation patterns in postmenopausal women as they performed verbal and nonverbal working memory tasks.

**Design** Randomized, double-blind, placebo-controlled, crossover trial from 1996 through 1998.

**Setting** Community volunteers tested in a hospital setting.

**Patients** Forty-six postmenopausal women aged 33 to 61 years (mean [SD] age, 50.8 [4.7] years).

**Intervention** Twenty-one-day treatment with conjugated equine estrogens, 1.25 mg/d, randomly crossed over with identical placebo and a 14-day washout between treatments.

**Main Outcome Measures** Brain activation patterns measured using functional magnetic resonance imaging during tasks involving verbal and nonverbal working memory.

**Results** Treatment with estrogen increased activation in the inferior parietal lobule during storage of verbal material and decreased activation in the inferior parietal lobule during storage of nonverbal material. Estrogen also increased activation in the right superior frontal gyrus during retrieval tasks, accompanied by greater left-hemisphere activation during encoding. The latter pattern represents a sharpening of the hemisphere encoding/retrieval asymmetry (HERA) effect. Estrogen did not affect actual performance of the verbal and nonverbal memory tasks.

**Conclusions** Estrogen in a therapeutic dosage alters brain activation patterns in postmenopausal women in specific brain regions during the performance of the sorts of memory function that are called upon frequently during any given day. These results suggest that estrogen affects brain organization for memory in postmenopausal women.

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MENOPAUSE REPRESENTS, perhaps, the single most influential biological or health-related event for most middle-aged women, and it is estimated that the average woman will spend at least half of her adult life with decreased levels of circulating estrogen.[1,2] Decisions concerning hormone replacement therapy represent major concerns for postmenopausal women. Declining estrogen levels characterize menopause with effects on a range of systems including, in addition to the reproductive system, the cardiovascular and skeletal systems.[3] Furthermore, there is evidence that estrogen affects basic neural processes in mature animals.[4] Estrogen has also been shown to affect cognitive function in animals, for example, improving working memory in rats.[5]

Observational studies and clinical trials have examined the influence of estrogen on cognitive function, particu-

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larly memory, in postmenopausal women. Results are far from consistent.[2,3,6-8] In those studies showing a positive influence of estrogen on cognitive function, the effects are frequently observed on measures of verbal memory.[2] Recent advances in technology now permit the noninvasive measurement of brain function as individuals perform memory and other cognitive tasks. This technique, functional magnetic resonance imaging, exploits the differences in the magnetic properties of oxygenated compared with deoxygenated blood. In performing a cognitive task, such as working memory, blood flow and oxygen concentration are altered in those brain regions engaged by the task.

Neuroimaging studies examining the neural correlates of verbal memory have established a core set of expected patterns of functional activation observed at specific brain regions during the encoding, storage, and retrieval of to-be-remembered materials.[9] For example, storage (or maintenance) of verbal material in working memory is typically associated with activations at anterior brain regions in the frontal lobe and at a more posterior region in the parietal lobe.[10] With respect to encoding and retrieval, an almost universally obtained result is a relatively greater left-frontal hemisphere activation during encoding[11,12] and a relatively stronger right-frontal hemisphere activation during retrieval, a pattern designated as the hemispheric encoding/retrieval asymmetry (HERA) effect.[13] We used functional magnetic resonance imaging to determine whether estrogen treatment in postmenopausal women modified these expected brain activation patterns.

## METHODS

### Subjects

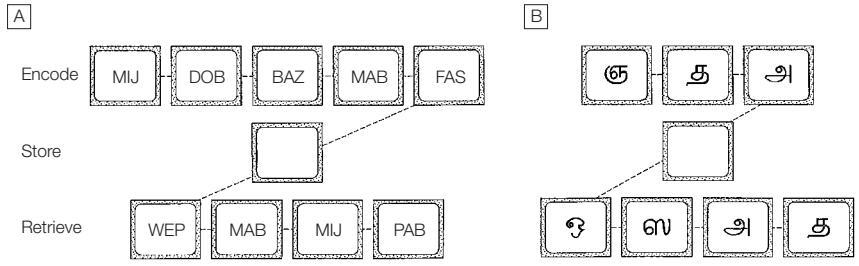
We studied 46 postmenopausal right-handed women between the ages of 33 and 61 years (mean [SD] age, 50.8 [4.7] years) in a randomized, double-blind, placebo-controlled, crossover trial. Women were recruited for a study examining "the role of estrogen in cognitive processes" through postings in libraries, letters to women's groups and physicians' offices, and newspaper advertisements. Informed consent was obtained from all subjects. Subjects were compensated $250 for their participation. Entry criteria consisted of having good general health, being right handed, having normal structural magnetic resonance imaging findings, having an IQ of at least 85, and having last menstrual period at least 5 months before entering the trial; exclusion criteria were having follicle-stimulating hormone levels of 45 IU/L or less and estradiol levels that were at least 128 pmol/L at baseline. Subjects had received no exogenous hormones for at least 3 months before entry.

### Intervention

Women were treated for 2 periods of 21 days each, 1 with conjugated equine estrogens (1.25 mg/d) and the other with identical placebo with 14 days of washout between treatments. Subjects were randomized to start treatment with estrogen or placebo; the randomization scheme was generated using a random number table in blocks of 4. Eligible participants were assigned the next available sequential randomized treatment assignment. The randomization scheme was in the sole possession of the Investigational Drug Service of the Yale-New Haven Hospital Pharmacy, New Haven, Conn; hence, study personnel and subjects remained blinded to treatment assignment throughout. Study medication, or placebo, consisted of 1 tablet daily containing conjugated estrogens, 1.25 mg, or identical-appearing white placebo tablets. Compliance was monitored by weekly contacts with the project nurse, pill counts at the termination of each phase, and serum samples at the end of each 21-day period for estrone, estradiol, equilin, and dihydroequilin.

Forty-seven women were randomized to the protocol; 1 subject was found to have a large cystic abnormality during the first imaging session. Although she completed the protocol, the structural brain abnormality precluded analysis of the functional data. Functional imaging data were thus available for 46 subjects. The primary analyses reported herein are on all 46 women, constituting a modified intention-to-treat analysis. The nature of the study mandated that the serum hormone levels not be disclosed until the study was complete. At that time, 10 subjects were identified as not meeting the inclusion or exclusion criteria because they were nonmenopausal based on their follicle-stimulating hormone and estradiol concentrations (n = 6, 1 of whom also had a low IQ), 1 was not healthy, based on abdominal surgery (laparoscopic cholecystectomy with anesthesia) during the 14-day washout period; and 3 were noncompliant based on serum equilin levels of less than 200 pg/mL during the estrogen phase. An additional analysis was performed on this subset of 36 sub-

**Figure 1.** Experimental Protocol for Verbal and Nonverbal Assessment of Working Memory




The components of each cycle, encode, store, retrieve (forced choice recognition), and rest, were each 20 seconds long. Each run alternated between verbal and nonverbal cycles. A, For the verbal cycle encode phase subjects saw 5 nonsense words sequentially for 4 seconds each, followed by a 20-second storage period with nothing on the screen. During the retrieval period, subjects saw 2 familiar nonsense words and 2 new nonsense words. B, For nonverbal cycles, subjects saw 3 Tamil characters for 6.67 seconds each, followed by a 20-second storage period. During the retrieval period, subjects saw 2 familiar characters and 2 new Tamil characters.

jects who satisfied inclusion and exclusion criteria.

### Imaging

Subjects underwent imaging in a 1.5-T Signa MR imaging system (General Electric, Waukesha, Wis) equipped with echo-planar imaging hardware (Advanced NMR, Wilmington, Mass). Women lay supine in the imaging system, looking up through a periscope at a screen that was attached to the gantry; stimuli were projected on the screen with a Macintosh laptop computer (Apple Computer, Cupertino, Calif). Stimuli for the verbal memory tasks were pronounceable nonsense words, and for the nonverbal memory tasks were Tamil letters (for non-Tamil speakers these characters are coded as complex geometric patterns). The protocol is shown in FIGURE 1.

### Image Analysis

We used 2 parallel types of data analyses, both with the goal of identifying brain areas showing estrogen effects and/or estrogen interactions with task (encode, store, retrieve) and stimulus-type (nonsense words or Tamil). In 1 approach, analyses were performed on a voxel-by-voxel basis. Effect sizes were computed using standard linear contrasts, which represent differences in mean activation levels between 1 set of experimental conditions and another set. The associated significance levels ($\alpha = .05$) were assessed using a nonparametric randomization test[14] and overlaid on the mean anatomic image for display; we refer to these maps of complex effects as contrast maps (FIGURE 2 and FIGURE 3). The other type of analysis, termed a *region of interest* analysis,[15-17] operates on relatively large brain areas and focuses on brain regions that previous research has implicated in memory, for example, superior frontal and parietal sites.

## RESULTS

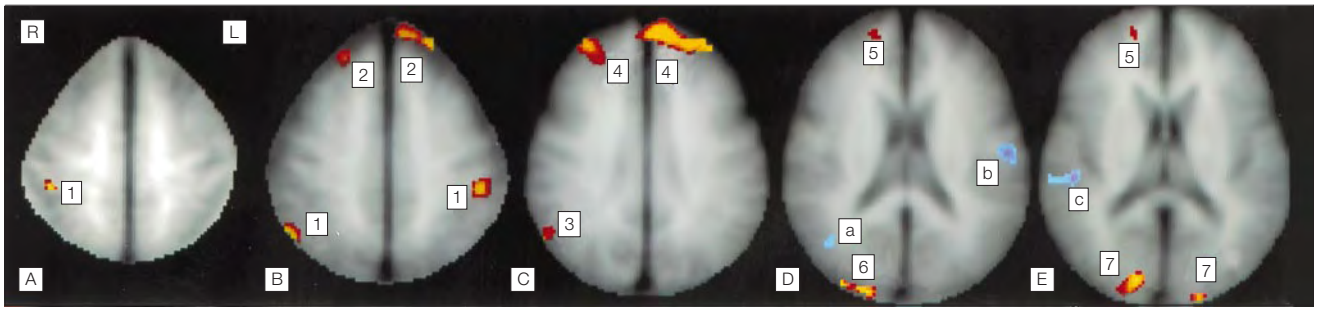
### Subjects

The 46 subjects had a mean IQ of 99.0 (range, 74.8-127), mean last menstrual period of 34.3 months (range, 5-168 months; median, 16.0 months), mean follicle-stimulating hormone levels of 78.6 IU/L (range, 4.1-150 IU/L), and mean estradiol levels of 108 pmol/L (range, 55.1-348.7 pmol/L). Thirty-five subjects (76%) were actively employed outside the home. Subjects had received no exogenous hormones for at least 3 months before entry.

### Brain Activation Patterns

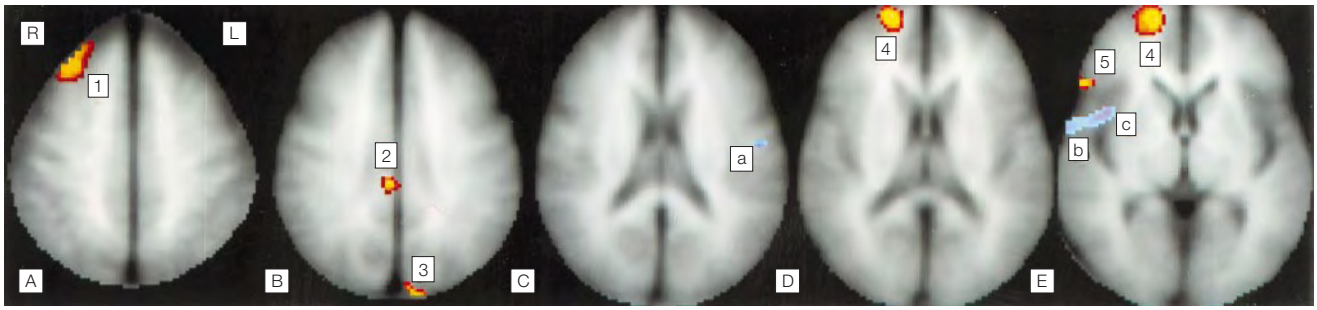
Estrogen produced significant modifications in expected brain activation pat-

**Figure 2.** Functional Magnetic Resonance Imaging Showing Effect of Estrogen on the Verbal Storage Component of Verbal Working Memory




Estrogen was associated with increased activation of the anterior, frontal lobe regions (superior [regions 2 and 4] and middle [region 5] frontal gyri) bilaterally. Of the posterior regions, estrogen was associated with increased activation of the inferior parietal lobule bilaterally (regions 1 and 3); and the superior (region 6) and middle (region 7) occipital gyri on the right. Sites with decreased activation on estrogen included regions around the inferior parietal lobule, as indicated by letter a, the left-central sulcus, as indicated by letter b, and the right superior temporal gyrus, as indicated by letter c. Letters under each image correspond to the following positions along the z-axis of the Talairach atlas. A indicates 50; B, 40; C, 32; D, 24; and E, 12.

**Figure 3.** Functional Magnetic Resonance Imaging Showing Effects of Estrogen on the Retrieval Component of Working Memory




Estrogen was associated with increased activation of the right anterior regions, such as the right superior (region 1), and the middle and inferior (regions 4 and 5) frontal gyri. Other areas of increased activation included posterior cingulate (region 2) and precuneus (region 3). Brain regions with decreased activation during retrieval included the superior temporal gyrus and insula on the right (b and c respectively), and the central sulcus region on the left (a). Letters under each image correspond to the following positions along the z-axis of the Talairach atlas: A indicates 40; B, 32; C, 24; D, 12; and E, 4.

terns in a number of brain regions. During the verbal store task (Figure 2), estrogen increased activation in the inferior parietal lobule and the superior frontal gyrus. Region of interest analyses confirm this pattern; significant condition × stimulus-type × task interactions were obtained for both the inferior parietal lobule ($F_{2,90} = 7.359$; $P<.025$) and the superior frontal gyrus ($F_{2,90} = 6.237$; $P<.01$). As illustrated for the inferior parietal lobule in FIGURE 4, increases in activation from the placebo to the estrogen condition were specific to the verbal store task.

Estrogen also produced a sharpening of the hemispheric encoding/retrieval asymmetry effect. For example, strong increases in activation were found in the right superior frontal gyrus during the retrieval tasks, both for verbal and nonverbal stimuli (Figure 3). Region of interest analyses were consistent and indicated that the left hemisphere showed greater activation than the right hemisphere during encoding, and the right hemisphere showed greater activation than the left hemisphere during retrieval, the hemispheric encoding/retrieval asymmetry effect. These results were further modified by significant 3-way interactions (condition × task × hemisphere interaction at the superior frontal gyrus, $F_{2,90} = 4.055$; $P<.025$), which demonstrated that the hemispheric encoding/retrieval asymmetry effect was much more pronounced in the estrogen condition (Figure 4).

The effects described above, both for the voxel-by-voxel and for the region of interest analyses, were also examined for the subset of subjects who satisfied inclusion and exclusion criteria and who were compliant (n = 36). The pattern of results did not change.

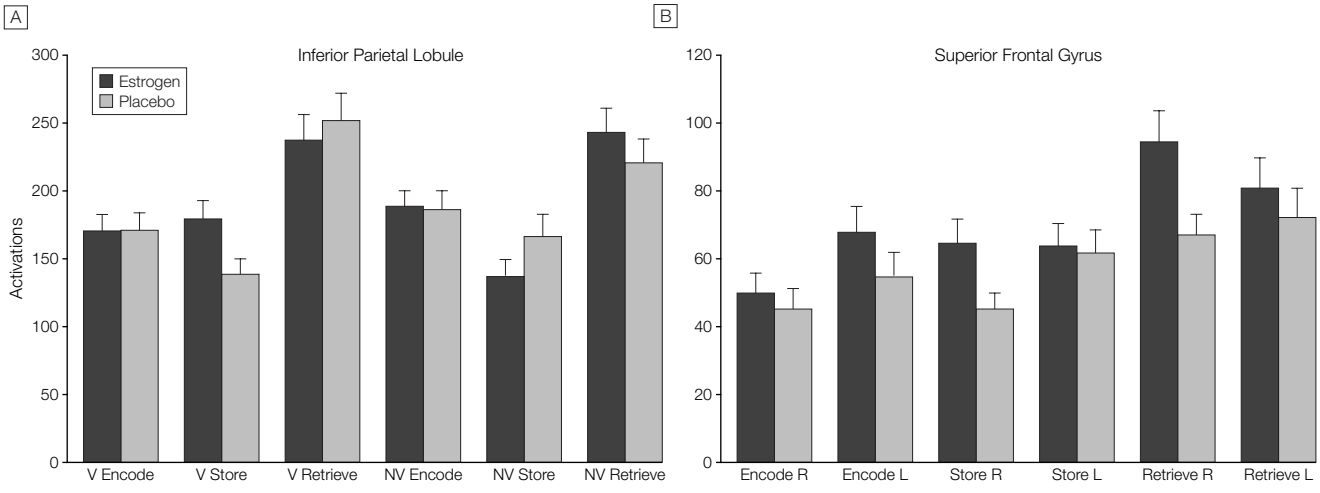
Accuracy of retrieval of information did not differ between the estrogen and the placebo condition for either the verbal or nonverbal stimuli ($F<1$; mean proportion correct was 0.912, 0.923, 0.914, and 0.930 for the verbal placebo, nonverbal placebo, verbal estrogen, and nonverbal estrogen, respectively).

## COMMENT

The results of this study indicate that estrogen in a traditionally prescribed therapeutic dose produces significant alterations in brain activation patterns in postmenopausal women as they perform working memory tasks. These data suggest that it may be possible to affect functional brain organization in older women; these alterations in brain activation patterns in subjects taking estrogen suggest functional plasticity of memory systems in mature women.

Our experimental study was theoretically driven, guided by our prior experience with studying the process of reading. Reading is known to rely on a component of language, phonologic processing, which relates to the sound structure of language.[18] A large body of research indicates that phonologic processes are also strongly involved in verbal working memory[19,20] and that verbal information is typically held in temporary storage in its phonologic form. We further observed that the components of language and memory often reported to be sensitive to the actions of estrogen (eg, verbal working memory, articulatory speed, and verbal fluency)[21,22] have in common a reliance on phonologic processing. Accordingly, we hypothesized that estrogen may exert a positive influence on language and memory through its

**Figure 4.** Effects of Estrogen in the Inferior Parietal Lobule and the Superior Frontal Gyrus




A, For the inferior parietal lobule, a significant condition × stimulus-type × task interaction was obtained ($F_{(2,90)} = 7.359$, $P<.025$). Of note, increases were significant with estrogen use during the verbal (V) store task (with corresponding decreases in the nonverbal [NV] store task). B, The superior frontal gyrus illustrates the sharpening of the hemisphere encoding/retrieval asymmetry (HERA) effect with estrogen. A significant 3-way interaction was obtained at the superior frontal gyrus (condition × task × hemisphere; $F_{(2,90)} = 4.055$; $P<.025$), indicating that the HERA effect was observed in the estrogen condition and not in the placebo condition. During estrogen use but not during placebo use, right-hemisphere activation is significantly greater than left-hemisphere activation during retrieval and left is significantly greater than right-hemisphere activation during encoding. Data are mean (SEM). R indicates right; L, left hemisphere.

actions on phonologic mechanisms and, for this study, we chose a set of verbal tasks that specifically engaged phonologic systems.

Women treated with estrogen demonstrated increased activation in the inferior parietal lobule during tasks requiring temporary storage of phonologically coded verbal materials (nonsense words). This response provides support for the hypothesis that estrogen mediates the short-term storage of phonologic material. Our findings in the inferior parietal lobule are reinforced by a recent report by Jonides et al,[10] who studied both men and women and found that activation in the inferior parietal region occurred during the short-term storage and retrieval of phonologic stimuli. The results support our hypothesis that estrogen effects may be mediated through its actions on neural sites serving phonologically coded materials.

However, our findings also indicate that the effects of estrogen are not limited to verbal memory. For example, we observed a sharpening of the HERA effect in the superior frontal gyrus that was present on nonverbal as well as verbal tasks. These findings of effects on nonverbal memory are consistent with the findings of Resnick and associates[23] that show effects of estrogen on a visual memory task. Although many studies of estrogen, either across the menstrual cycle[24] or in postmenopausal women,[25,26] demonstrate an effect on verbal memory, for the most part, these studies do not include nonverbal stimuli.[23] The notion that estrogen exerts an influence on nonverbal as well as verbal memory systems is consonant with observations that estrogen exerts its actions on neural systems distributed throughout the brain.[27,28]

An intriguing finding in the current study is that changes in brain activation patterns in frontal regions noted above for the estrogen-treated women—greater left-hemisphere activation during encoding and greater right-hemisphere activation during retrieval—appear similar to patterns observed in younger subjects compared with older ones in previous studies.[29,30] In addition, older subjects show increased activation in insula relative to younger subjects and in our study estrogen was associated with decreased activation in this region (Figure 2, B; Figure 3, C).

We note that despite the estrogen-induced differences in brain activation patterns, error rates on each task were comparable between conditions. Brain activation patterns have been shown to be more sensitive than behavioral measures in some conditions. For example, functional imaging may detect brain activation pattern differences in patients at high risk for Alzheimer disease before behavior deficits are evident,[31] and Cabeza and associates[29] found that older and younger subjects demonstrated age-related differences in brain activation patterns despite comparable behavioral performance. Based on our findings, we suggest that functional imaging techniques may detect effects of estrogen on the brain that are not yet demonstrable by behavioral measures themselves.

This study has many strengths, including the randomized, double-blind, placebo-controlled, crossover design, a large sample size for an imaging study, and tasks that assess verbal and nonverbal memory. We relied on a theoretic framework incorporating both phonologic processing and working memory to systematically assess the effects of estrogen on different components of both verbal and nonverbal working memory and incorporated nonsense words so that we were able to examine phonologic processes specifically. A limitation of this study was the relatively brief time that women were receiving either estrogen or placebo and the relatively short washout period between conditions. Although this treatment period may have been too short to produce significant behavioral effects, our findings suggest that it was sufficiently long to demonstrate an effect using functional imaging as a sensitive index of brain function. Furthermore, as indicated by the minimal error rates, the relative ease of performance of the memory tasks may have precluded detection of differences between the estrogen and placebo conditions ("ceiling" effect).

There are many considerations that enter into a woman's decision about whether to take hormone replacement therapy. Acknowledgment and understanding of the effects of estrogen on the skeletal and cardiac systems have progressed considerably, although new data continue to modify our knowledge.[31,32] The influence of estrogen on cognitive function has been much more difficult to establish. As Barrett-Connor[33] recently indicated, there is no question of the biological plausibility for a beneficial effect of estrogen on brain function, yet the studies to date in postmenopausal women are inconsistent. Lack of clarification of estrogen's role in cognition has been a source of particular frustration for postmenopausal women, in part because the symptoms are often subtle yet may have pervasive effects on the quality of life.

This current study demonstrates that estrogen alters brain activation patterns in postmenopausal women and its corollary that functional brain organization in mature women (and, we assume, men) is neither fixed nor immutable. These changes in brain activation patterns (1) are observed in specific brain regions associated with the sorts of memory function that are called on frequently during any given day (for example, trying to remember a telephone number that had been just looked up); and (2) appear to reinstate patterns typically observed in younger, but not older, subjects as they perform memory tasks. While we believe the changes in brain organization should predict accompanying improvements in performance of memory tasks, we caution that in this study we did not observe such changes during the study period. However, these data suggest that estrogen affects brain organization in postmenopausal women. In addition, functional imaging may provide a new tool to detect these effects of estrogen. These results are encouraging and suggest that the use of functional imaging together with protocols examining, for example, different

dosages, treatment lengths, and washout periods, may provide a new means to explore the effects of estrogen on cognitive function in postmenopausal women.

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**REFERENCES**

**1.** Seifer D, Naftolin F. Moving toward an earlier and better understanding of the perimenopause. *Fertil Steril*. 1998;69:387-388.
**2.** Sherwin B. Estrogen effects on cognition in menopausal women. *Neurology*. 1997;48(suppl 7):S21-S26.
**3.** Rice M, Graves A, McCurry S, Larson E. Estrogen replacement therapy and cognitive function in postmenopausal women without dementia. *Am J Med*. 1997;103(suppl 7):26S-35S.
**4.** Woolley C, McEwen B. Estradiol regulates hippocampal dendritic spine density via an *N*-methyl-D-aspartate receptor-dependent mechanism. *J Neurosci*. 1994;14:7680-7687.
**5.** O'Neal M, Means L, Poole M, Hamm R. Estrogen affects performance of ovariectomized rats in a two-choice water-escape working memory task. *Psychoneuroendocrinology*. 1996;21:51-65.
**6.** Sherwin B. Estrogen, the brain, and memory. *J North Am Menopause Soc*. 1996;3:97-105.
**7.** Haskell S, Richardson E, Horwitz R. The effect of estrogen replacement therapy on cognitive function in women: a critical review of the literature. *J Clin Epidemiol*. 1997;50:1249-1264.
**8.** Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA*. 1998;279:688-695.
**9.** Fletcher P, Frith C, Rugg M. The functional neuroanatomy of episodic memory. *Trends Neurosci*. 1997;20:213-218.
**10.** Jonides J, Schumacher E, Smith E, et al. The role of parietal cortex in verbal working memory. *J Neurosci*. 1998;18:5026-5034.
**11.** Fiez J, Raife E, Balota D, Schwarz J, Raichle M, Petersen S. A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci*. 1996;16:808-822.
**12.** Smith E, Jonides J. Working memory: a view from neuroimaging. *Cognit Psychol*. 1997;33:5-42.
**13.** Tulving E, Kapur S, Craik F, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A*. 1994;91:2016-2020.
**14.** Manly B. *Randomization, Bootstrap and Monte Carlo Methods in Biology*. London, England: Chapman & Hall; 1997.
**15.** Shaywitz BA, Shaywitz SE, Pugh KR, et al. Sex differences in the functional organization of the brain for language. *Nature*. 1995;373:607-609.
**16.** Pugh KR, Shaywitz BA, Shaywitz SE, et al. Cerebral organization of component processes in reading. *Brain*. 1996;119:1221-1238.
**17.** Shaywitz SE, Shaywitz BA, Pugh KR, et al. Functional disruption in the organization of the brain for reading in dyslexia. *Proc Natl Acad Sci U S A*. 1998;95:2636-2641.
**18.** Shaywitz S. Dyslexia. *Sci Am*. 1996;275:98-104.
**19.** Wagner R, Torgesen J. The nature of phonological processes and its causal role in the acquisition of reading skills. *Psychol Bull*. 1987;101:192-212.
**20.** Paulesu E, Frith CD, Frackowiak RSJ. The neural correlates of working memory. *Nature*. 1993;362:342-344.
**21.** Jacobs D, Tang M, Stern Y, et al. Cognitive function in nondemented older women who took estrogen after menopause. *Neurology*. 1998;50:368-373.
**22.** Hampson E. Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn*. 1990;14:26-43.
**23.** Resnick S, Metter E, Zonderman A. Estrogen replacement therapy and longitudinal decline in visual memory. *Neurology*. 1997;49:1491-1497.
**24.** Phillips S, Sherwin B. Variations in memory function and sex steroid hormones across the menstrual cycle. *Psychoneuroendocrinology*. 1992;17:497-506.
**25.** Kampen D, Sherwin B. Estrogen use and verbal memory in healthy postmenopausal women. *Obstet Gynecol*. 1994;83:979-983.
**26.** Phillips S, Sherwin B. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology*. 1992;17:485-495.
**27.** McEwen B, Alves S, Bulloch K, Weiland N. Ovarian steroids and the brain: implications for cognition and aging. *Neurology*. 1997;48(suppl 7):S8-S15.
**28.** Diano S, Naftolin F, Horvath T. Gonadal steroids target AMPA glutamate receptor-containing neurons in the rat hypothalamus, septum and amygdala: a morphological and biochemical study. *Endocrinology*. 1997;138:778-789.
**29.** Cabeza R, Grady C, Nyberg L, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci*. 1997;17:391-400.
**30.** Schacter D, Savage C, Alpert N, Rauch S, Albert M. The role of hippocampus and frontal cortex in age-related memory changes: a PET study. *Neuroreport*. 1996;7:1165-1169.
**31.** Kennedy A. Frackowiak R, Newman S, et al. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neuroscience Lettters*. 1995;186:17-20.
**32.** Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
**33.** Finkelstein J, Klibanski A, Arnold A, Toth T, Hornstein M, Neer R. Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34). *JAMA*. 1998;280:1067-1073.
**34.** Barrett-Connor E. Rethinking estrogen and the brain. *J Am Geriatr Soc*. 1998;46:918-920.