Behav Neurosci. Author manuscript; available in PMC 2016 April 20.

Published in final edited form as:
Behav Neurosci. 2012 February ; 126(1): 123–127. doi:10.1037/a0025539.

Estrogen and Cognitive Functioning in Women: Lessons We Have Learned

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Abstract

Extant research findings allow several conclusions regarding the relationship between estrogen and cognitive functioning across the female life span. First, performance on tests of verbal memory fluctuates in concert with physiological changes in ovarian hormone production during the menstrual cycle and during pregnancy and the postpartum period. Estrogen therapy (ET) prevents the decrease in verbal memory when administered immediately following the surgical removal of both ovaries in premenopausal women. Some, but relatively little evidence is available to support the idea that ET, initiated at the time of a natural or a surgical menopause for a few years, may protect against cognitive decline 30 years later and more research in this area is urgently needed. Finally, the evidence to date strongly suggests that the initiation of ET decades after the menopause has occurred does not protect against cognitive decline or dementia. Taken together, these findings support the so-called "window of opportunity" hypothesis which holds that ET will be neuroprotective only when administered closely in time to a natural or surgical menopause.

Keywords

estrogen; cognitive functioning; pregnancy; postmenopause

The considerable volume of research findings on the impact of estrogen on brain structure and function and its consequent influence on aspects of cognitive functioning in both animals and humans during the past two and a half decades has provided important and intriguing but often conflicting evidence. Although some of the inconsistency in the human literature could be explained by methodological differences between studies, such as the characteristics of the populations enrolled, the dose, drug, and their routes of administration, and methodological issues, to name a few, these differences failed to convincingly explain discrepancies between studies in this area. During the past decade, one differentiating factor, the age of women at the time of the initiation of estrogen therapy (ET), has garnered considerable validity and led to the formulation of the critical period hypothesis, or the "window of opportunity" maxim that, to this point, provides guidelines for the necessary and sufficient conditions for the neuroprotective effects of estrogen on cognitive functioning in women. Since numerous recent comprehensive reviews of the area are available (Sherwin & Henry, 2008; Maki & Sundermann, 2009), this article will instead focus on what the extant

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evidence tells us, and the directions it provides for potentially fruitful avenues for future investigation.

I. Performance on Tests of Some Aspects of Cognitive Functioning Fluctuate in Concert With Physiological Changes in Sex Hormone Production During Reproductive Events in Premenopausal Women

Considerable information is available to support the idea that women's performance on tests of specific cognitive domains fluctuates during the normal menstrual cycle. For example, women performed better on cognitive tests favoring females (e.g., verbal fluency, fine motor skills, perceptual speed) during the midluteal phase of the cycle when levels of estradiol (E_2) were high as compared with the menstrual phase of the cycle, and they performed better on cognitive skills favoring males (e.g., spatial ability) during the menstrual phase of the cycle when E_2 levels were low (Hampson, 1990). Lower scores on a test of visual memory occurred during the menstrual phase of the cycle, whereas scores on a test of verbal memory correlated positively with verbal memory scores during the midluteal phase (Phillips & Sherwin, 1992). Similarly, E_2 levels correlated positively with verbal fluency and negatively with scores on a test of spatial ability in young, cycling women (Maki, Rich, & Rosenbaum, 2002). Others have found that higher scores on a test of verbal working memory were associated with high E_2 levels at midcycle (Rosenberg & Park, 2002). These findings serve to underline the fact that modifications in brain plasticity induced by high levels of sex-hormone production can occur within a timeframe of several days, as evidenced by the cognitive changes observed from one menstrual cycle phase to the next. They also establish that E_2 enhances performance on tasks in which females typically excel, whereas the relative absence of E_2 results in an enhancement in cognitive skills in which males typically excel, as the literature on sex differences in cognitive functioning implies (Halpern, 1992). Therefore, extant human evidence strongly supports the view that, in young, reproductive-aged women, changes in the quantities of ovarian sex hormones during a normal menstrual cycle influence performance on cognitive tests although the magnitude of the changes reported in the majority of studies suggests that these changes would not be clinically significant.

There is also evidence that modifications in aspects of cognitive function occur under the influence of the drastic changes in the hormonal milieu during pregnancy and the postpartum period. Impairments in verbal free recall, in working memory (Henry & Rendell, 2007; Janes, Casey, Huntsdale, & Angus, 1999), in word fluency, and in word list learning (de Groot, Hornstra, Roozendaal, & Jolles, 2003) in performance on priming tasks and incidental learning tasks (Sharp, Brindle, Brown, & Turner, 1993) occur in pregnant women, as compared with nonpregnant controls. During the third trimester and the early postpartum period, women performed more poorly on a task of verbal recall as compared with nonpregnant controls (Glynn, 2010) and, in a longitudinal study, pregnant women performed worse than nonpregnant controls on two tests of verbal memory, on a visuospatial task, and on a task of processing speed (Henry & Sherwin, 2011). These findings support the view that changes in sex hormone production within the physiological range that occur during reproductive events modify performance on a variety of cognitive functions.

Investigations on the pharmacological suppression of ovarian function in young, cycling women treated with a gonadotropin releasing-hormone analog (GnRH-a) provide further support. When cycling women were treated with a GnRH-a, levels of E_2 decreased significantly in concert with a significant decrease in scores on tests of verbal memory and learning (Sherwin & Tulandi, 1996) and on scores on tests of working memory (Grigorova & Sherwin, 2006). In both studies, the cognitive deficit was reversed only in the group that randomly received add-back conjugated equine estrogen (CEE) plus the GnRH-a while scores of those who received add-back placebo plus the GnRH-a remained depressed indicating that E_2 was the critical ovarian hormone responsible for the maintenance of verbal and working memory in these young women.

II. ET Protects Aspects of Cognitive Function in Surgically Menopausal Women Treated Immediately After Their Surgery

Because surgical menopause (the removal of the uterus and both ovaries) is frequently undertaken for benign gynecological disorders in premenopausal women, it is of interest to ask whether depriving women of several years of estrogen exposure has any influence on cognition in either the short or long term. In the earliest, prospective, randomized, controlled trial (RCT) of surgically menopausal women who had been premenopausal prior to their surgery for benign conditions, standardized neuropsychological tests were used to investigate whether estrogen and/or androgen influenced aspects of cognition in postmenopausal women (Sherwin, 1988). In this crossover design, women who received any of the active hormonal drugs maintained their performance on a test of verbal memory, whereas scores decreased significantly in those who had received a placebo. Moreover, it was determined that the estrogenic protection of verbal memory in the women did not occur secondary to the alleviation of hot flashes. In a replication of that study, in which a more comprehensive battery of neuropsychological tests were used, surgically menopausal women who randomly received E_2 valerate, 10 mg intramuscularly every 4 weeks following the surgical removal of their ovaries had significantly higher scores on tests of short-and long-term verbal memory as compared with women who had received placebo (Phillips & Sherwin, 1992). In both studies, there was a specificity of the estrogenic effect on verbal memory; in neither study did ET enhance performance on tests of visual memory or spatial abilities. In 65-year-old postmenopausal women who had never been treated with ET, those who received 7.8 mg E_2 per week transdermally for 3 weeks experienced a selective improvement in performance on tasks of visual learning and memory (Duka, Tasker, & McGowan, 2000). No tests of verbal memory were administered in that study. This evidence underlines the observation that declines in verbal memory shortly following the surgical removal of both ovaries in a premenopausal woman can be obviated by the administration of ET.

On the other hand, several RCTs failed to find an effect of ET on cognitive functioning When 62 midlife women 47 to 65 years of age were treated with transdermal E_2 for 12 weeks versus placebo, no effect of hormonal treatment was evident (Pola–Kantola et al., 1998) but verbal episodic memory was not assessed. Similarly, 53-year-old women who were treated with CEE several years following their surgical menopause did not perform

better than placebo-treated women on tests of attention, the only neuropsychological tests administered in that study.

Because impairments in cognition associated with normal aging accelerate after the age of 60 years (Hedden & Gabrielli, 2004), a critical issue is whether its benefits would be enduring following the discontinuation of treatment. In a prospective longitudinal study, the outcome measures included the Telephone Interview for Cognitive Status-modified and a brief dementia questionnaire also administered by telephone (Rocca et al., 2007). Women who had undergone bilateral oophorectomy prior to the onset of their natural menopause, and had been untreated, had an increased risk of cognitive impairment or dementia 30 years later as compared with referent women [hazard ratio (HR) = 1.46; 95% confidence interval (CI) 1.13 to 1.90]; however, those who had been administered ET until at least the age of 50 years (approximate time of a natural menopause) had no increased risk of cognitive impairment or dementia as compared with naturally menopausal women 30 years later. These results extend the findings from the surgical menopause studies that showed a benefit of ET in the short term (Sherwin, 1988; Phillips & Sherwin, 1992) by demonstrating that the neuroprotective effect on cognitive functioning of ET initiated immediately following a surgical menopause for several years is enduring 30 years later.

Only one study is available to support the possibility that, when initiated closely in time to the natural menopause, ET also has a neuroprotective effect. In a series of RCTs undertaken to determine whether ET protected against osteoporosis, 479 women had been randomly assigned to treatment with E_2 or placebo for 2 or 3 years and participated in follow-up cognitive testing 5–15 years later (Bagger, Tanko, Alexandersen, Qin, & Christiansen, 2005). Women who had originally been randomized to hormone therapy—HT; (estrogen [E] + progesterone [P])—for 2 to 3 years and then stopped treatment (past-users) had a 64% decreased risk of cognitive impairment 5–15 years later, as compared with those who had originally been randomized to placebo and never took HT (never-users; OR: 0.36, 95% CI, 0.15–0.90, $p = .03$). Moreover, women who had been randomly assigned to HT and who continued to take it (long-term users) had a 66% decreased risk of cognitive impairment 5–15 years later (OR: 0.36, 95% CI, 0.16–0.80; $p = .01$). The finding that 2 to 3 years of HT, initiated closely in time to the menopause, was equally as protective against the risk of cognitive impairment, relative to long-term treatment, suggests that 2 to 3 years of ET may endow enduring cognitive protection when initiated at the time of menopause Because of the important clinical implications of this finding, it urgently needs to be replicated in both animal and human studies.

The clinical requirement to coadminister progesterone (P) or a synthetic progestin (HT) along with E to naturally postmenopausal women to protect the uterus against the stimulatory effects of E has been frequently overlooked in analyses of the findings. Numerous, chemically different progestins (synthetic P) were used in studies on naturally menopausal women that investigated cognition. Although a micronized P preparation which more closely resembles endogenous P is currently available, most studies on E + P and cognition in postmenopausal women coadministered a synthetic P along with E, the most common being medroxyprogesterone acetate (MPA). There is reason to believe that progestins, and MPA in particular, might have an independent negative effect on cognition

and/or may attenuate the beneficial effect of the coadministered estrogen. For example, the decrease in apical dendritic spine density in the CA 1 area of the hippocampus that occurs during the estrus phase of the rat cycle was prevented by the administration of RU-486, a P receptor antagonist, suggesting that P causes the decrease in spine density (Gould, Woolley, Frankfurt, & McEwen, 1990). Such oppositional effects of MPA to E_2 have also been documented in humans. Whereas scores on a global measure of cognitive functioning improved over time in a longitudinal study of elderly women taking unopposed ET, cognitive scores actually worsened during the same timeframe in those treated with E_2 + MPA (Rice et al., 2000). Finally, in a recent single photon emission computerized tomography (SPECT) study, the duration of ET correlated positively with the density of cortical cholinergic terminal concentrations, but the effect was attenuated in women who were also taking a progestin along with estrogen, suggesting that, in women, progestins may adversely influence neuronal integrity (Smith, Jonides, Marshuetz, & Koeppe, 1998). These findings emphasize the importance of analyzing separately studies using E-alone and those using E + P.

III. ET Initiated in Surgically or in Naturally Menopausal Women One or More Decades Following Their Menopause Does Not Protect Against Cognitive Decline With Aging

The Women's Health Initiative Memory Study, an ancillary study to the Women's Health Initiative (WHI), was the largest RCT designed to examine the effects of the continuous administration of E-alone or E + P on cognitive functioning. Seventy-two-year-old surgically menopausal women free of probable dementia were randomized to receive either CEE 0.625 mg daily or placebo for approximately five years until the study was terminated (Espeland et al., 2004). Global cognitive function was measured annually with the Modified Mini-Mental State Examination (3MSE). Mean 3MSE scores in the CEE group were significantly lower than those given placebo ($p = .04$). When data from nonadherent women were censored, the difference was no longer significant.

In the treatment arms of the approximately 72-year-old naturally menopausal women in the WHIMS, there was a significantly higher risk of probable, all-cause dementia in the active group compared with placebo (HR = 2.05, 95% CI = 1.21–3.48) but no difference between the groups in the incidence of mild cognitive impairment, thought to be a precursor to Alzheimer's disease Shumaker et al., 2003). Also, naturally menopausal women who had been randomly assigned to CEE + MPA for 4 years had a small increased risk in cognitive decline, as compared with women who had received placebo ($p = .008$) (Rapp et al., 2003). Therefore, the findings from the largest RCT undertaken on women approximately 72 years of age at the time of enrollment, failed to confirm previous evidence from smaller RCTs, from longitudinal, and from cross-sectional studies that estrogen protected against cognitive aging in postmenopausal women.

On the other hand, a preliminary reanalysis of the WHIMS data by age found that women who took ET before the age of 65 years (prior to their enrollment in the WHI) were 50% less likely to develop all-cause dementia as compared with nonusers (Henderson, Espeland,

Hogan, Rapp, & Stefanick, 2007). However, the finding was not affected by timing, by age at prior hormone initiation, or by the duration or recentness of use. This supports the notion that ET has neuroprotective effects when taken by women younger than 65 years of age and has no effects, or may even cause harm, when initiated in older women. These findings are consistent with the so-called “healthy cell bias” of estrogen action, which proposes that there is a beneficial effect of estrogen on the survival of neurons that are healthy at the time of their exposure to this sex hormone, but that an exacerbation of neurological demise occurs if exposure to estrogen occurred in previously compromised neurons (Chen, Nilsen, & Brinton, 2006). Other possible reasons for the neutral or harmful effect of ET initiated decades after the menopause have been discussed comprehensively (Sherwin & Henry, 2008).

IV. ET Initiated Following a Diagnosis of Alzheimer’s Disease (AD) Does Not Have Beneficial Effects on Cognitive Functioning

Two RCTs investigated whether ET would improve the memory impairments in women with probable AD. There were no significant posttreatment differences between 78-year-old women with AD randomly treated with CEE 1.25 mg daily for 16 weeks, as compared with those given placebo on several tests of cognitive function (Henderson et al., 2000). In the second RCT, 120 women diagnosed with mild-to-moderate AD received either CEE 0.625 mg/day, CEE 1.25 mg/day of a placebo daily for 12 months (Mulnard et al., 2000). Consistent with the natural course of this degenerative disease, the cognitive function of all women deteriorated somewhat over the year and no differences were apparent between groups. One small 8-week treatment RCT using transdermal E_2 found improvements in verbal and in visual memory compared to placebo in women with probable AD (Asthana et al., 2001).

Summary and Future Directions

The extant evidence from basic neuroscience, from animal, and from human studies provides compelling evidence that neuroprotection for optimal cognitive functioning in older women is in line with the so-called “critical window of opportunity.” That is, there is reason to believe that women who take ET at the time of menopause for several years, thereby seamlessly extending the number of years their brains are exposed to E_2, will have less cognitive decline with aging and, possibly, a lower risk of AD. However, there is a paucity of data from human studies available to allow the conclusion that if ET is initiated at the time of menopause and terminated after a few years, the neuroprotective effects will endure when cognitive aging begins to accelerate in individuals above the age of 60 years. Although a 30-year RCT to test this hypothesis would be definitive, logistical, ethical, and financial issues associated with such a study make it very unlikely it will ever be undertaken. Therefore, it is hoped that the development of animal models and creative ways of asking this question in humans will provide some answers in the future.

Finally, because all drugs have side effects, it would be important to understand the risk/benefit ratio for postmenopausal women who take ET. Recently, the data from the WHI E-alone arm was reanalyzed according to the age of the participants at the time of the initiation

of ET. These reanalyses show that surgically menopausal women who were between 50 and 59 years of age when they were enrolled in the WHI, who received CEE for approximately 6 years, and were followed for an additional 4.7 years subsequent to the cessation of the clinical trial, had neither an increased nor a decreased risk of coronary heart disease, deep vein thrombosis, stroke, hip fracture, colorectal cancer, and total mortality as compared with the women who had randomly received placebo (LaCroix et al., 2011). It was also the case that women treated with CEE had a significantly lower incidence of breast cancer than placebo-treated women at follow-up. Moreover, the increase in risk of stroke and venous thromboembolism observed in women randomized to CEE during the intervention period of the trial dissipated during the follow-up period. However, these findings cannot be generalized to the efficacy of combined estrogen + progestin hormone regimens for the treatment of naturally menopausal women with an intact uterus. It would therefore seem that ET, initiated soon after the menopause for a few years, has no enduring negative effects on a variety of organ systems while protecting cognitive function. On the other hand, this conclusion is tempered by the paucity of evidence that ET, given to perimenopausal women for a few years and then discontinued, will have enduring protective effects 15 years later when cognitive aging becomes manifest. Possibly the most critical issue for this area is to gather data that tests this hypothesis.

Acknowledgments

The preparation of this article was supported by a grant from the Canadian Institutes of Health Research, MOP-89960, awarded to B.B. Sherwin.

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