Hormones and Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Postmenopausal hormone therapy and cognition

Anna C. McCarrey *, Susan M. Resnick *

Laboratory of Behavioral Neuroscience, National Institute on Aging, NIH, Baltimore, MD, 21224, USA

ARTICLE INFO

Available online xxxx

Keywords:
Hormone therapy
Estrogen
Cognition
Aging
Menopause

ABSTRACT

This article is part of a Special Issue "Estradiol and cognition".

Prior to the publication of findings from the Women's Health Initiative (WHI) in 2002, estrogen-containing hormone therapy (HT) was used to prevent age-related disease, especially cardiovascular disease, and to treat menopausal symptoms such as hot flushes and sleep disruptions. Some observational studies of HT in midlife and aging women suggested that HT might also benefit cognitive function, but randomized clinical trials have produced mixed findings in terms of health and cognitive outcomes. This review focuses on hormone effects on cognition and risk for dementia in naturally menopausal women as well as surgically induced menopause, and highlights findings from the large-scale WHI Memory Study (WHIMS) which, contrary to expectation, showed increased dementia risk and poorer cognitive outcomes in older postmenopausal women randomized to HT versus placebo. We consider the 'critical window hypothesis', which suggests that a window of opportunity may exist shortly after menopause during which estrogen treatments are most effective. In addition, we highlight emerging evidence that potential adverse effects of HT on cognition are most pronounced in women who have other health risks, such as lower global cognition or diabetes. Lastly, we point towards implications for future research and clinical treatments.

Published by Elsevier Inc.

Effects of menopause on cognition

Menopause refers to the time in a women's life when her ovaries begin producing less estrogen and progesterone, and she becomes infertile. This transition period can last up to 5 years and in some cases longer (Harlow and Paramsothy, 2011), with the current median age of menopause at 52.5 years, defined as 12 months following cessation of menses (Gold et al., 2013). The cessation of menstrual cycles results in a number of physiological changes that can affect emotion and cognitive processes. Importantly, women born in the USA from the 1950s onwards can expect to live more than one-third of their lives with depleted ovarian hormones ("Population and Vital Statistics", 2007). To alleviate common menopausal symptoms such as hot flushes, night sweats, and sleep disruptions (Dennerstein et al., 2000; Obermeyer et al., 2007; Ribowsky, 2011), some women opt to artificially replace hormones and boost levels through estrogen-containing postmenopausal hormone therapy (HT).

Prior research indicates that the cumulative estrogen exposure a women encounters over her lifespan influences late life cognitive ability. These accumulations stem from age at menses and at menopause, duration of breastfeeding if child-bearing, duration of HT in hormone users and time since menopause (Hesson, 2012). Additionally, experiencing menopause at younger ages has been associated with reduced cognitive performance in older adulthood (Hogervorst, 2012; Hogervorst et al., 2011; Ryan et al., 2014), as well as greater mortality risk (Nelson et al., 2012). Several studies describe cognitive reductions in women during the menopausal transition (Mitchell and Woods, 2011; Schaafsma et al., 2010; Weber et al., 2013), particularly in cognitive domains such as working memory and attention (Greendale et al., 2009; Keenan et al., 2001; Kimura, 2002; Wroolie et al., 2011). Nonetheless, the literature is inconclusive with respect to the link between menopause and cognition, with some reviews indicating no substantial changes in cognitive functioning (Henderson and Sherwin, 2007), or none of clinical relevance (Henderson et al., 2003). Other studies have reported only short-lasting cognitive decline with menopause (Greendale et al., 2009) or that only limited cognitive domains are effected such as verbal fluency (Fuh et al., 2006). A 2011 review of endogenous and exogenous estrogen exposures in mid- and late-life women reported no reliable association with episodic memory or executive functions (Henderson and Popat, 2011). Potential explanations for the inconsistency in findings may include differences in the timing of menopause studied, ages of women and the effects of cognitive aging in women at retirement age (e.g. 65+ years) or other covariates not measured (Shanmugan and Epperson, 2012). Moreover, teasing apart age effects from those of menopause becomes increasingly difficult

* Corresponding authors at: Intramural Research Program, National Institute on Aging, 251 Bayview Blvd., Baltimore, MD 21224-6825, USA.
E-mail addresses: anna.mccarrey@nih.gov (A.C. McCarrey), resnicks@mail.nih.gov (S.M. Resnick).

http://dx.doi.org/10.1016/j.yhbeh.2015.04.018
0018-506X/Published by Elsevier Inc.

when it is considered that the menopausal transition is a period in life marked by increased intra- and inter-individual variability in physiology, and in cognitive and affective response to that variability. The Penn Ovarian Aging Study, which aimed to determine whether the menopausal transition is associated with age-independent cognitive decline, found that verbal fluency but not psychomotor speed is linked to reproductive senescence independent of age (Epperson et al., 2013).

Hormone therapy

Observational studies

Although the primary indication for HT is to alleviate uncomfortable symptoms of menopause such as night sweats and insomnia, early observational studies reported supplementary health gains such as decreased risk for coronary heart disease and hip fracture (Grady et al., 1992). Investigations conducted by our group and others found that in comparison to non-HT users, individuals undergoing estrogenic treatment performed significantly better on tests of working memory (see LeBlanc et al., 2001; Maki and Hogervorst, 2003; Sherwin, 2006 for review), verbal memory (Maki et al., 2001) and visual memory (Resnick, Metter, & Zonderman, 1997).

Additionally, observational studies suggested that estrogen-based HT offered protection against risk for dementia (Birge and Mortel, 1997; Haines, 1998; Henderson, 1997; Hogervorst et al., 2000; LeBlanc et al., 2001; Melton, 1999; Panidis et al., 2001; Zandi et al., 2002) and some prospective studies indicated a 50% reduction in Alzheimer's disease (AD) risk in those using HT compared with non-users (Kawas et al., 1997; Paganini-Hill and Henderson, 1996; Zandi et al., 2002). However, women who opted to use HT were inclined to be healthier overall, so that probable unadjusted confounders impacted the outcomes of such studies. Thus, despite attempts to control for possible confounds known to influence cognitive abilities including age, education and socioeconomic status, the "healthy user" bias continues to be a critical confound in observational studies. Similarly, other methodological issues inherent to observational studies include the different types and doses of hormones administered, the varying durations of HT, fluctuations in temporal proximity relative to menopause, and the route of treatment delivery, including cyclic versus continuous administration. Lastly, menopausal women who have a uterus take adjuvant progesterone for protection against endometrial hyperplasia (Froom, 1991), and a number of synthetic progestins have been administered for this purpose. Thus, the varying formulations of progestins likely differ in regard to their impact on cognition and health indices, and little is known about these effects.

Intervention Studies and the Women's Health Initiative

Randomized controlled trials are designed to overcome the limiting factors inherent in the observational studies described above. That is, by randomly assigning women to HT and placebo groups, not only is the healthy-user bias eliminated, but the dosage, hormone preparation, route of delivery and timing factors can be strictly controlled. Unlike the beneficial effects of HT reported in observational studies, randomized controlled trials in older menopausal women have produced more mixed findings. Despite some studies describing improvements in cognitive ability in HT compared with placebo groups (Haskell et al., 1997; Sherwin, 2006; Zec and Trivedi, 2002), especially in younger surgically menopausal women, findings from the Women's Health Initiative (WHI) reported in 2003, did not support a protective effect of HT in older postmenopausal women.

The WHI was a randomized controlled trial designed to study the effects of HT on health outcomes in postmenopausal women. The study's main objective was to test the popular assertion that postmenopausal HT had a protective effect against cardiovascular disease, an important public health concern. The WHI HT trial was comprised of two parallel placebo controlled trials of conjugated equine estrogen (CEE)-based HT regimens. Enrollees were 50 to 79 years of age and postmenopausal. Active therapies consisted of 0.625 mg/day CEE in women post-hysterectomy and 0.625 g/day CEE combined with 2.5 mg/day medroxyprogesterone acetate (MPA) in women with a uterus. Although study medications were terminated in 2002 (women without prior hysterectomy) and 2004 (women with prior hysterectomy), women continue to be followed. Results were unexpected, in that a protective effect against cardiovascular disease was not found (Anderson et al., 2004; Rossouw et al., 2002). Moreover, both the CEE Alone and CEE + MPA treatments were found to increase risk for stroke and blood clots in the leg and lungs, while the CEE + MPA trial was linked to an increased risk of breast cancer.

In addition to the primary and secondary outcomes tested in the main WHI trial, two inter-related ancillary intervention studies investigated the effects of HT on cognitive outcomes in postmenopausal women. The WHI Memory Study (WHIMS) (Shumaker et al., 1998) enrolled 7429 women 65 years of age and older to evaluate effects of HT on risk and progression of dementia, and global cognitive function. The WHI Study of Cognitive Aging (WHISCA) (Resnick et al., 2004) study enrolled 2302 WHIMS participants without dementia to provide information on the effects of HT on a larger battery of specific cognitive functions, including verbal, visual, and working memory, attention, verbal fluency, and spatial ability. While WHIMS began in parallel with the main WHI trial, WHISCA was initiated on average 3 years after randomization to the HT.

Findings from the WHIMS and WHISCA studies were also unexpected in that the predicted cognitive advantages and decrease in risk for dementia in the HT groups were not found. Rather, the WHIMS study reported that in women aged 65 years and older an *increase* in risk for dementia was found in both active treatment groups. This association was significant in the combination CEE + MPA group (HR = 2.05 [1.21, 3.48]; $p = 0.01$) (Shumaker et al., 2003), but failed to reach significance in the CEE Alone trials (HR = 1.51 [0.83, 2.74]; $p = 0.18$) (Shumaker et al., 2004). Moreover, significant decreases in global cognitive function over time were reported for both active treatment arms (Espeland et al., 2004; Rapp et al., 2003b), the effects of which were found to persist after treatment termination (Espeland et al., 2010).

Findings from the WHISCA study demonstrated that in comparison to placebo, older postmenopausal women randomized to the combination CEE + MPA group had lower verbal learning and memory scores over an average time period of 4 to 5 years (Resnick et al., 2006). No other cognitive abilities measured were affected. (Note: see Singh and Su, 2013, for a review of possible confounds that may have impacted findings such as the neurobiological differences between synthetic medroxyprogesterone acetate used in the combined trials compared to endogenous progesterone). For the CEE Alone trial, the WHISCA results demonstrated no significant advantageous nor detrimental effects on age-related change in specific cognitive functions (Resnick et al., 2009a). Furthermore, neither the CEE + MPA nor CEE Alone treatment significantly impacted measures of affect or depressive symptoms (Resnick et al., 2006, 2009a).

In their review of estrogen effects on AD, Henderson and Brinton (2010) speculated that in addition to the healthy-user bias, results from the WHI trials also may differ from observational findings due to differences in the age at which hormone initiation occurred. While HT use is most often initiated during or shortly after the menopausal transition in women enrolled in observational studies, the initial WHIMS studies focused on older postmenopausal women, age 65 years or older.

Critical period hypothesis

The use of HT as a remedy for menopausal symptoms was reduced globally in the wake of the findings from the WHI (Ettinger et al., 2012). Nonetheless, HT continues to be highly effective in relieving distressing menopausal symptoms such as night sweats and hot flushes. As mentioned, HT in the WHIMS and WHISCA studies was initiated in

Please cite this article as: McCarrey, A.C., Resnick, S.M., Postmenopausal hormone therapy and cognition, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.04.018

women aged 65 years and older, and treatment initiated at an earlier time may have produced different results. This is known as the "critical period" (Resnick and Henderson, 2002) or "window of opportunity" hypothesis, whereby cognitive benefit attributable to HT may be limited to treatment close in temporal proximity to menopause (Henderson, 2013; Maki, 2013; Sherwin and Henry, 2008).

Observational studies

Many observational studies lend support for the critical period hypothesis. For example, an Australian study of 428 women >60 years old found that those who had initiated HT early postmenopause performed significantly better in tests of psychomotor speed, verbal fluency and global cognition (MacLennan et al., 2006). Another large scale study of 343 postmenopausal Danish women found similar advantages of early HT on cognitive outcomes (Bagger et al., 2005). Lastly, in a large epidemiological study in Cache County, investigators reported that in comparison to current users of HT, former users (that is, more likely to have initiated HT at menopause onset), had a reduction in risk for AD (Zandi et al., 2002). This reduction was also associated with duration of HT use.

Intervention studies

To test the "critical period" hypothesis directly, two recent intervention studies were conducted examining the effects of HT initiation soon after menopause on cognitive function. Firstly, the WHIMS-Young (WHIMS-Y) study investigated 1326 women who had taken part in the WHI CEE-based randomized controlled trials when aged 50–55 years. An average of 14.2 years after randomization to treatment and 7.2 years after treatment discontinuation, when the women were approximately 67.2 years of age, a battery of cognitive tests were administered via a telephone interview (Espeland et al., 2013). This study addressed the critically important question of whether cognition is impacted years later when women undergo HT during early menopause. Contrary to the initial WHI results, these data indicated neither harm nor benefit to cognitive ability in women initiating HT early in menopause.

A second large scale randomized controlled clinical trial examined the relationship between estrogenic treatment during early menopause and cognition and mood (Wharton et al., 2013). In the Kronos Early Estrogen Prevention Study (KEEPS), 728 women, with a mean baseline age of 53 years and with a 4 year follow up period, were randomized during early menopause to one of three groups: lower dose CEE (0.45 mg/day); transdermal estradiol (50 μg/day); or placebo (Harman et al., 2005). In addressing a methodological shortcoming of prior studies, participants in the active estrogen arms were administered oral progesterone (200 mg), as opposed to the synthetic progestin used in WHI, for 12 days each month. The parent KEEPS study's primary endpoints were cardiac health measures, however, an ancillary study (KEEPS-Cog) was designed to examine several cognitive domains such as memory, attention and mood in 571 of the KEEPS women (Wharton et al., 2014). As with the WHIMS-Y results, there were neither advantageous nor harmful effects of HT on measures of memory or other cognitive functions. Interestingly, the KEEPS investigators did find an improvement in symptoms of depression and anxiety in women randomized to oral CEE. Taken together, women who are considering the health benefits and risks of initiating HT for the relief of menopausal symptoms can take some comfort in these findings, and they are in keeping with prior findings in older WHIMS participants that healthier women are less susceptible to any deleterious effects of HT (Resnick et al., 2009b).

Estrogens and surgical menopause

Surgical menopause is a type of medically induced menopause where both ovaries are surgically removed by bilateral oophorectomy. The most common indications for this type of surgery in premenopausal women are cervical, endometrial and ovarian cancer (Novetsky et al., 2011; Shuster et al., 2008). As the main producers of estrogen, surgical removal of the ovaries results in a sharp withdrawal of these steroid hormones, whereas naturally menopausal women encounter a more gradual reduction in ovarian hormone production over a number of years.

Observational studies

From a cognitive standpoint, younger age at surgical menopause has been linked to an increased risk of cognitive dysfunction and dementia (Bove et al., 2014; Nappi et al., 1999; Phung et al., 2010; Rocca et al., 2007, 2012). Observational results from longitudinal studies of surgical menopause indicate that both young and old women who have undergone bilateral oophorectomy carry an increased risk of cognitive impairment and dementia (Rocca et al., 2007, 2008), as well as reductions in global cognition and memory. Additionally, such cognitive changes have been observed as soon as 3–6 months following surgery. On the other hand, some studies have described no or negligible effects of surgical menopause on cognitive abilities in middle-aged (Kok et al., 2006; Vearncombe and Pachana, 2009) and older women (Bove et al., 2014; Kritz-Silverstein and Barrett-Connor, 2002). In general, observational studies examining the effects of HT use following surgical menopause have described cognitive benefits (Bove et al., 2014; Rocca et al., 2007). One study reporting the combined results from two different longitudinal cohorts of older women (average age 78 years) found that HT undergone within 5 years of surgery, and for a minimum of 10 years, was associated with a reduced decline in global cognitive function (Bove et al., 2014).

Intervention studies

Barbara Sherwin and her colleagues performed a series of studies in the late 1980s and early 1990s examining the effects of HT in younger surgically menopausal women. The first intervention study tracked 50 pre-operative patients who were randomly assigned to hormone (estrogen–androgen, estrogen or androgen) treatment or placebo control groups. Following 1 month of baseline observation where four tests of cognition were administered, the patients underwent surgery. Results showed that in comparison to the active hormone group, significantly lower scores for the placebo group post-surgery were found for logical reasoning and short- and long-term memory (Sherwin, 1988). A later intervention study followed 19 women before and after bilateral oophorectomy and hysterectomy surgery, tested on a variety of memory measures (Phillips and Sherwin, 1992). Again, the women were randomly assigned to HT or placebo groups. There was a significant group by time interaction in that HT prevented the decline in immediate and delayed verbal memory associated with surgical menopause. However, the beneficial effect of HT was domain specific as immediate and delayed recall of visual material and digit span scores were not subject to hormonal effects in this small trial. These studies highlight that hormone treatments in younger women appear to protect against post-surgery cognitive decline, and may be especially beneficial to verbal memory performance.

Overall these studies combined suggest that with surgically induced menopause, the temporal proximity and duration of HT play a critical role in its neuroprotective efficacy. Clinical studies also lend support for the idea that cognitive function is negatively affected by surgical menopause and that women undergoing this procedure may experience greater benefit from HT (Farrag et al., 2002; Henderson and Sherwin, 2007). Nonetheless, findings are still mixed and the literature is generally inconsistent in its conclusions (Maki and Hogervorst, 2003). Furthermore, there is a lack of both observational and intervention studies where surgical menopause is clearly defined and objective cognitive deficits, in contrast to cognitive symptoms, are assessed.

Please cite this article as: McCarrey, A.C., Resnick, S.M., Postmenopausal hormone therapy and cognition, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.04.018

Estrogenic treatment and the vulnerable brain

As mentioned, there is reason to believe that from a cognitive standpoint, HT in older women may have variable effects in naturally menopausal women, and that this variation may be linked to health status. WHIMS-MRI was conducted to better understand the mechanism contributing to the deleterious effects of HT on cognitive outcomes as well as dementia risk (Coker et al., 2009, 2014; Resnick et al., 2009b). As HT increases risk for stroke and thromboembolic events, it was hypothesized that increases in ischemic burden might explain the adverse effect of HT on cognition. In addition, WHIMS-MRI examined potential effects of HT on variations in regional brain volumes, including hippocampal and frontal regions. Ischemic lesion burden and regional brain volumes were investigated in 1403 women from the WHIMS study randomly assigned to CEE + MPA, CEE Alone (on average 3.0 and 1.4 years after cessation of treatment, respectively) or placebo groups. Contrary to prediction, HT versus placebo groups did not differ significantly with respect to ischemic lesion burden (Coker et al., 2009). In contrast, results showed a decline in total brain, frontal and hippocampal volumes in women formerly assigned to HT versus placebo. Furthermore, the original WHIMS study found that baseline mental status at enrollment, as measured by a modified Mini-Mental State Exam (3MSE), was a significant factor moderating the deleterious cognitive effects of HT (Espeland et al., 2004). That is, the women with lower 3MSE scores at baseline had significantly greater HT-related cognitive reductions than the women with higher 3MSE scores at baseline. Analogous to these findings, WHIMS-MRI also demonstrated that the deleterious cognitive effects of HT on brain volumes were most marked in women with the lowest 3MSE scores at study commencement in the WHI, as well as those with the highest burden of white matter lesion volumes (Resnick et al., 2009b). These data suggest that poorer cognitive health at HT initiation may increase vulnerability to adverse effects of estrogens on the postmenopausal brain. Consistent with these findings, recent results from the Three Cities study indicated an interaction between diabetes and endogenous estradiol levels on risk for dementia. In women with diabetes, higher estradiol levels were associated with a marked increase in risk for dementia in older women (HR = 14.2 [1.6,123]), with a more modest increase in women without diabetes (HR = 3.4 [0.1,147]) (Carcaillon et al., 2014).

Research with more basic science models has provided insights into mechanisms that may explain disparate findings between the generally positive impacts of estrogenic action in the brain in animal models (Luine, 2014) and the adverse consequences of therapeutic human interventions. For example, Brinton (2005, 2008) has proposed the 'healthy cell bias of estrogen action', based on the premise that exposure of healthy neurons to estrogens invokes a neuroprotective response that promotes both neurological function and cognition. On the other hand, in compromised or diseased cells, estrogenic treatment over time will exacerbate neurodegeneration, pointing to a vulnerability in certain brains for HT. These findings are consistent with in vitro analyses of estrogen treatment of hippocampal neurons prior to, or after amyloid-β insult, which show neuroprotective outcomes versus no benefit or worsened degeneration, respectively (Morrison et al., 2006). Taken together, these findings suggest that women who are less neurologically healthy, including older women, may be most vulnerable to any deleterious cognitive effects of HT, and in contrast, that HT may confer neuroprotective benefits on healthy brains.

In addition, studies in animal models suggest that specific regimens of HT may influence cognitive outcomes. In contrast to the WHI findings in older women where continuous hormone supplementation was administered, research in aged surgically menopausal rhesus monkeys showed that a cyclic regimen of HT (21 days via injection) compared to vehicle-injection is sufficient to preserve prefrontal cortex-dependent cognition, measured by spatial working memory (Rapp et al., 2003a). The large effect found on delayed response performance implicates the dorsolateral prefrontal cortex as the potential target of estradiol treatment (Morrison and Baxter, 2012). Thus, optimal HT regimens to maximize brain health and cognitive outcomes remain a subject of ongoing research (Baxter et al., 2013).

Concluding remarks

This article provides an overview of the current literature concerning the effects of postmenopausal hormone treatments on cognitive function. We review the relationships between sex steroid hormones and cognitive functioning, highlighting variation in potential HT effects in relation to age, hormone regimen, timing of treatment relative to menopause, and baseline cognitive and brain integrity. Although observational studies suggested that HT would benefit cognitive function and reduce the incidence of cognitive impairment, including dementia, results of the WHIMS randomized clinical trials in older postmenopausal women did not support the observational findings and showed poorer cognitive outcomes in women randomized to HT. The "critical period" hypothesis (Resnick and Henderson, 2002) posits that early treatment of younger postmenopausal women, closer to the menopausal transition, might be more beneficial to cognition. However, two recent randomized trials (WHIMS-Y and KEEP-Cog) testing this hypothesis showed neither harm nor benefit of HT interventions closer to menopause. Although the lack of cognitive benefit in these trials is disappointing, the absence of short- and long-term harm to cognitive function should reassure women who choose to use HT for treatment of menopausal symptoms. Lastly, MRI (Resnick et al., 2009b) and cellular studies (Brinton, 2005, 2008) point towards a greater adverse effect of postmenopausal estrogens on a vulnerable brain, whereby women who are less healthy, either cognitively or neurologically, seem to be at greater risk of having an adverse response.

In summary, investigations of hormone treatments in menopausal women have produced many inconsistent findings. The literature is vast and diverse with long-term cognitive outcomes still being realized. However, moving forward, results from more recent clinical intervention trials can help inform clinical practice with regards cognitive function as well as other important late-life outcomes such as risk for dementia. Ongoing research can build on the wealth of information from both the basic sciences and human studies to inform the types and timing of treatments that best serve menopausal women in the future.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Institute on Aging.

References

Anderson, G.L., Limacher, M., Assaf, A.R., Bassford, T., Beresford, S.A., Black, H., et al., 2004. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291 (14), 1701–1712. http://dx.doi.org/10.1001/jama.291.14.1701.

Bagger, Y.Z., Tankó, L.B., Alexandersen, P., Qin, G., Christiansen, C., Group, P.S., 2005. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. Menopause 12 (1), 12–17.

Baxter, M.G., Roberts, M.T., Gee, N.A., Lasley, B.L., Morrison, J.H., Rapp, P.R., 2013. Multiple clinically relevant hormone therapy regimens fail to improve cognitive function in aged ovariectomized rhesus monkeys. Neurobiol. Aging 34 (7), 1882–1890.

Birge, S.J., Mortel, K.F., 1997. Estrogen and the treatment of Alzheimer's disease. Am. J. Med. 103 (3, Supplement 1), 36S–45S.

Bove, R., Secor, E., Chibnik, L.B., Barnes, L.L., Schneider, J.A., Bennett, D.A., et al., 2014. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 82 (3), 222–229. http://dx.doi.org/10.1212/wnl.0000000000000033.

Brinton, R.D., 2005. Investigative models for determining hormone therapy-induced outcomes in brain: evidence in support of a healthy cell bias of estrogen action. Ann. N. Y. Acad. Sci. 1052 (1), 57–74. http://dx.doi.org/10.1196/annals.1347.005.

Brinton, R.D., 2008. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends Neurosci. 31 (10), 529–537.

Please cite this article as: McCarrey, A.C., Resnick, S.M., Postmenopausal hormone therapy and cognition, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.04.018

Carcaillon, L., Brailly-Tabard, S., Ancelin, M.-L., Rouaud, O., Dartigues, J.-F., Guiochon-Mantel, A., et al., 2014. High plasma estradiol interacts with diabetes on risk of dementia in older postmenopausal women. Neurology 82 (6), 504–511.

Coker, L.H., Hogan, P.E., Bryan, N.R., Kuller, L.H., Margolis, K.L., Bettermann, K., et al., 2009. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. Neurology 72 (2), 125–134. http://dx.doi.org/10.1212/01.wnl.0000339036.88842.9e.

Coker, L.H., Espeland, M.A., Hogan, P.E., Resnick, S.M., Bryan, R.N., Robinson, J.G., et al., 2014. Change in brain and lesion volumes after CEE therapies The WHIMS-MRI studies. Neurology 82 (5), 427–434.

Dennerstein, L., Dudley, E.C., Hopper, J.L., Guthrie, J.R., Burger, H.G., 2000. A prospective population-based study of menopausal symptoms. Obstet. Gynecol. 96 (3), 351–358.

Epperson, C.N., Sammel, M.D., Freeman, E.W., 2013. Menopause effects on verbal memory: findings from a longitudinal community cohort. J. Clin. Endocrinol. Metab. 98 (9), 3829–3838.

Espeland, M.A., Rapp, S.R., Shumaker, S.A., Brunner, R., Manson, J.E., Sherwin, B.B., et al., 2004. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291 (24), 2959–2968.

Espeland, M.A., Brunner, R.L., Hogan, P.E., Rapp, S.R., Coker, L.H., Legault, C., et al., 2010. Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative study of cognitive aging extension. J. Am. Geriatr. Soc. 58 (7), 1263–1271. http://dx.doi.org/10.1111/j.1532-5415.2010.02953.x.

Espeland, M.A., Shumaker, S.A., Leng, I., Manson, J.E., Brown, C.M., LeBlanc, E.S., et al., 2013. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern. Med. 173 (15), 1429–1436. http://dx.doi.org/10.1001/jamainternmed.2013.7727.

Ettinger, B., Wang, S.M., Leslie, R.S., Patel, B.V., Boulware, M.J., Mann, M.E., et al., 2012. Evolution of postmenopausal hormone therapy between 2002 and 2009. Menopause 19 (6), 610–615.

Farrag, A.-k.F., Khedr, E.M., Abdel-Aleem, H., Rageh, T.A., 2002. Effect of surgical menopause on cognitive functions. Dement. Geriatr. Cogn. Disord. 13 (3), 193–198.

Froom, J., 1991. Selections from current literature: hormone therapy in postmenopausal women. Fam. Pract. 8 (3), 288–292.

Fuh, J.-L., Wang, S.-J., Lee, S.-J., Lu, S.-R., Juang, K.-D., 2006. A longitudinal study of cognition change during early menopausal transition in a rural community. Maturitas 53 (4), 447–453.

Gold, E.B., Crawford, S.L., Avis, N.E., Crandall, C.J., Matthews, K.A., Waetjen, L.E., et al., 2013. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am. J. Epidemiol. 178 (1), 70–83.

Grady, D., Rubin, S.M., Petitti, D.B., Fox, C.S., Black, D., Ettinger, B., et al., 1992. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann. Intern. Med. 117 (12), 1016–1037. http://dx.doi.org/10.7326/0003-4819-117-12-1016.

Greendale, G.A., Huang, M.H., Wight, R.G., Seeman, T., Luetters, C., Avis, N.E., et al., 2009. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 72 (21), 1850–1857. http://dx.doi.org/10.1212/WNL.0b013e3181a71193.

Haines, C.J., 1998. Oestrogen and alzheimer's disease. Curr. Obstet. Gynaecol. 8 (1), 49–53.

Harlow, S.D., Paramsothy, P., 2011. Menstruation and the menopause transition. Obstet. Gynecol. Clin. N. Am. 38 (3), 595–607. http://dx.doi.org/10.1016/j.ogc.2011.05.010.

Harman, S., Brinton, E., Cedars, M., Lobo, R., Manson, J., Merriam, G., et al., 2005. KEEPS: the Kronos early estrogen prevention study. Climacteric 8 (1), 3–12.

Haskell, S.G., Richardson, E.D., Horwitz, R.I., 1997. The effect of estrogen replacement therapy on cognitive function in women: a critical review of the literature. J. Clin. Epidemiol. 50 (11), 1249–1264.

Henderson, V.W., 1997. Estrogen, cognition, and a woman's risk of Alzheimer's disease. Am. J. Med. 103 (3, Supplement 1), 11S–18S.

Henderson, V.W., 2013. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. J. Steroid Biochem. Mol. Biol. http://dx.doi.org/10.1016/j.jsbmb.2013.05.010.

Henderson, V.W., Brinton, R.D., 2010. Menopause and mitochondria: windows into estrogen effects on Alzheimer's disease risk and therapy. Prog. Brain Res. 182, 77–96. http://dx.doi.org/10.1016/s0079-6123(10)82003-5.

Henderson, V.W., Popat, R.A., 2011. Effects of endogenous and exogenous estrogen exposures in midlife and late-life women on episodic memory and executive functions. Neuroscience 191, 129–138. http://dx.doi.org/10.1016/j.neuroscience.2011.05.059.

Henderson, V.W., Sherwin, B.B., 2007. Surgical versus natural menopause: cognitive issues. Menopause 14 (3), 572–579. http://dx.doi.org/10.1097/gme.1090b1013e31803df31849c.

Henderson, V., Guthrie, J., Dudley, E., Burger, H., Dennerstein, L., 2003. Estrogen exposures and memory at midlife A population-based study of women. Neurology 60 (8), 1369–1371.

Hesson, J., 2012. Cumulative estrogen exposure and prospective memory in older women. Brain Cogn. 80 (1), 89–95.

Hogervorst, E., 2012. Prevention of dementia with sex hormones: a focus on testosterone and cognition in women. Minerva Med. 103 (5), 353–359.

Hogervorst, E., Williams, J., Budge, M., Riedel, W., Jolles, J., 2000. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in postmenopausal women: a meta-analysis. Neuroscience 101 (3), 485–512.

Hogervorst, E., Kusdhany, L., Rahardjo, T.B., 2011. An early age at menopause could accelerate age-related cognitive decline. In: Society, I.M. (Ed.), Menopause: state of the art. Edizioni Internazionali, Rome.

Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., et al., 1997. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 48 (6), 1517–1521.

Keenan, P.A., Ezzat, W.H., Ginsburg, K., Moore, G.J., 2001. Prefrontal cortex as the site of estrogen's effect on cognition. Psychoneuroendocrinology 26 (6), 577–590.

Kimura, D., 2002. Sex hormones influence human cognitive pattern. Neuro Endocrinol. Lett. 23, 67.

Kok, H.S., Kuh, D., Cooper, R., van der Schouw, Y.T., Grobbee, D.E., Michael, E., et al., 2006. Cognitive function across the life course and the menopausal transition in a British birth cohort. Menopause 13 (1), 19–27.

Kritz-Silverstein, D., Barrett-Connor, E., 2002. Hysterectomy, oophorectomy, and cognitive function in older women. J. Am. Geriatr. Soc. 50 (1), 55–61.

LeBlanc, E.S., Janowsky, J., Chan, B.K., Nelson, H.D., 2001. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 285 (11), 1489–1499.

Luine, V.N., 2014. Estradiol and cognitive function: past, present and future. Horm. Behav. 66 (4), 602–618.

MacLennan, A.H., Henderson, V.W., Paine, B.J., Mathias, J., Ramsay, E.N., Ryan, P., et al., 2006. Hormone therapy, timing of initiation, and cognition in women aged older than 60 years: the REMEMBER pilot study. Menopause 13 (1), 28–36.

Maki, P.M., 2013. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause 20 (6), 695–709. http://dx.doi.org/10.1097/GME.0b013e3182960cf8.

Maki, P., Hogervorst, E., 2003. HRT and cognitive decline. Best Pract. Res. Clin. Endocrinol. Metab. 17 (1), 105–122.

Maki, P.M., Zonderman, A.B., Resnick, S.M., 2001. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am. J. Psychiatr. 158 (2), 227–233.

Melton, L., 1999. Oestrogen shields brain from ageing. Lancet 354 (9184), 1101.

Mitchell, E.S., Woods, N.F., 2011. Cognitive symptoms during the menopausal transition and early postmenopause. Climacteric 14 (2), 252–261.

Morrison, J.H., Baxter, M.G., 2012. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat. Rev. Neurosci. 13 (4), 240–250.

Morrison, J.H., Brinton, R.D., Schmidt, P.J., Gore, A.C., 2006. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. J. Neurosci. 26 (41), 10332–10348.

Nappi, R., Sinforiani, E., Mauri, M., Bono, G., Polatti, F., Nappi, G., 1999. Memory functioning at menopause: impact of age in ovariectomized women. Gynecol. Obstet. Investig. 47 (1), 29–36.

Nelson, H.D., Walker, M., Zakher, B., Mitchell, J., 2012. Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the US Preventive Services Task Force recommendations. Ann. Intern. Med. 157 (2), 104–113.

Novetsky, A.P., Boyd, L.R., Curtin, J.P., 2011. Trends in bilateral oophorectomy at the time of hysterectomy for benign disease. Obstet. Gynecol. 118 (6), 1280–1286.

Obermeyer, C.M., Reher, D., Saliba, M., 2007. Symptoms, menopause status, and country differences: a comparative analysis from DAMES. Menopause 14 (4), 788–797.

Paganini-Hill, A., Henderson, V.W., 1996. EStrogen replacement therapy and risk of alzheimer disease. Arch. Intern. Med. 156 (19), 2213–2217. http://dx.doi.org/10.1001/archinte.1996.00440180075009.

Panidis, D.K., Matalliotakis, I.M., Rousso, D.H., Kourtis, A.I., Koumantakis, E.E., 2001. The role of estrogen replacement therapy in Alzheimer's disease. Eur. J. Obstet. Gynecol. Reprod. Biol. 95 (1), 86–91.

Phillips, S.M., Sherwin, B.B., 1992. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 17 (5), 485–495.

Phung, T.K.T., Waltoft, B.L., Laursen, T.M., Settnes, A., Kessing, L.V., Mortensen, P.B., et al., 2010. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement. Geriatr. Cogn. Disord. 30 (1), 43–50.

Rapp, P.R., Morrison, J.H., Roberts, J.A., 2003a. Cyclic estrogen replacement improves cognitive function in aged ovariectomized rhesus monkeys. J. Neurosci. 23 (13), 5708–5714.

Rapp, S.R., Espeland, M.A., Shumaker, S.A., Henderson, V.W., Brunner, R.L., Manson, J.E., et al., 2003b. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289 (20), 2663–2672.

Resnick, S.M., Henderson, V.W., 2002. Hormone therapy and risk of Alzheimer disease. JAMA 288 (17), 2170–2172.

Resnick, S.M., Metter, E.J., Zonderman, A.B., 1997. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? Neurology 12, 1491–1497.

Resnick, S.M., Coker, L.H., Maki, P.M., Rapp, S.R., Espeland, M.A., Shumaker, S.A., 2004. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. Clin. Trials 1 (5), 440–450.

Resnick, S.M., Maki, P.M., Rapp, S.R., Espeland, M.A., Brunner, R., Coker, L.H., et al., 2006. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J. Clin. Endocrinol. Metab. 91 (5), 1802–1810.

Resnick, S.M., Espeland, M.A., An, Y., Maki, P.M., Coker, L.H., Jackson, R., et al., 2009a. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J. Clin. Endocrinol. Metab. 94 (11), 4152–4161.

Resnick, S.M., Espeland, M.A., Jaramillo, S.A., Hirsch, C., Stefanick, M.L., Murray, A.M., et al., 2009b. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. Neurology 72 (2), 135–142. http://dx.doi.org/10.1212/01.wnl.0000339037.76336.cf.

Ribowsky, J., 2011. Hormone Therapy for menopause: a concise update of the benefits and risks. Adv. NPs PAs 2 (8), 19–22 (quiz 23).

Rocca, W., Bower, J., Maraganore, D., Ahlskog, J., Grossardt, B., De Andrade, M., et al., 2007. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 69 (11), 1074–1083.

Please cite this article as: McCarrey, A.C., Resnick, S.M., Postmenopausal hormone therapy and cognition, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.04.018

Rocca, W.A., Grossardt, B.R., Maraganore, D.M., 2008. The long-term effects of oophorectomy on cognitive and motor aging are age dependent. Neurodegener. Dis. 5 (3-4), 257–260. http://dx.doi.org/10.1159/000113718.

Rocca, W.A., Grossardt, B.R., Shuster, L.T., Stewart, E.A., 2012. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. Neurodegener. Dis. 10 (1-4), 175–178. http://dx.doi.org/10.1159/000334764.

Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M., et al., 2002. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288 (3), 321–333.

Ryan, J., Scali, J., Carrière, I., Amieva, H., Rouaud, O., Berr, C., et al., 2014. Impact of a premature menopause on cognitive function in later life. BJOG 121 (13), 1729–1739.

Schaafsma, M., Homewood, J., Taylor, A., 2010. Subjective cognitive complaints at menopause associated with declines in performance of verbal memory and attentional processes. Climacteric 13 (1), 84–98.

Shanmugan, S., Epperson, C.N., 2012. Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition. Hum. Brain Mapp. 35, 847–865.

Sherwin, B.B., 1988. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 13 (4), 345–357.

Sherwin, B.B., 2006. Estrogen and cognitive aging in women. Neuroscience 138 (3), 1021–1026.

Sherwin, B.B., Henry, J.F., 2008. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. Front. Neuroendocrinol. 29 (1), 88–113. http://dx.doi.org/10.1016/j.yfrne.2007.08.002.

Shumaker, S.A., Reboussin, B.A., Espeland, M.A., Rapp, S.R., McBee, W.L., Dailey, M., et al., 1998. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control. Clin. Trials 19 (6), 604–621.

Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., et al., 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289 (20), 2651–2662.

Shumaker, S.A., Legault, C., Kuller, L., Rapp, S.R., Thal, L., Lane, D.S., et al., 2004. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291 (24), 2947–2958.

Shuster, L.T., Gostout, B.S., Grossardt, B.R., Rocca, W.A., 2008. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int. 14 (3), 111–116.

Singh, M., Su, C., 2013. Progesterone and neuroprotection. Horm. Behav. 63 (2), 284–290.

United Nations Department of Economic and Social Affairs PD, d. Population and Vital Statistics Report. Table 3 2007. Retrieved January 15, 2015, from http://unstats.un.org/UNSD/demographic/sconcerns/mortality/mort2.htm.

Vearncombe, K.J., Pachana, N.A., 2009. Is cognitive functioning detrimentally affected after early, induced menopause? Menopause 16 (1), 188–198. http://dx.doi.org/10.1097/gme.1090b1013e3181775eb3181774.

Weber, M.T., Maki, P.M., McDermott, M.P., 2013. Cognition and mood in perimenopause: a systematic review and meta-analysis. J. Steroid Biochem. Mol. Biol. http://dx.doi.org/10.1016/j.jsbmb.2013.06.001.

Wharton, W., Gleason, C.E., Miller, V.M., Asthana, S., 2013. Rationale and design of the Kronos Early Estrogen Prevention Study (KEEPS) and the KEEPS cognitive and affective sub study (KEEPS Cog). Brain Res. 1514, 12–17.

Wharton, W., Gleason, C.E., Dowling, N.M., Carlsson, C.M., Brinton, E.A., Santoro, M.N., et al., 2014. The KEEPS-cognitive and affective study: baseline associations between vascular risk factors and cognition. J. Alzheimers Dis. 40 (2), 331–341. http://dx.doi.org/10.3233/jad-130245.

Wroolie, T.E., Kenna, H.A., Williams, K.E., Powers, B.N., Holcomb, M., Khaylis, A., et al., 2011. Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17β-estradiol versus conjugated equine estrogens. Am. J. Geriatr. Psychiatr. 19 (9), 792.

Zandi, P.P., Carlson, M.C., Plassman, B.L., Welsh-Bohmer, K.A., Mayer, L.S., Steffens, D.C., et al., 2002. Hormone replacement therapy and incidence of Alzheimer disease in older women. JAMA 288 (17), 2123–2129.

Zec, R., Trivedi, M., 2002. The effects of estrogen replacement therapy on neuropsychological functioning in postmenopausal women with and without dementia: a critical and theoretical review. Neuropsychol. Rev. 12 (2), 65–109.

Please cite this article as: McCarrey, A.C., Resnick, S.M., Postmenopausal hormone therapy and cognition, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.04.018