CHAPTER

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Sex Hormones and Cognitive Aging

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INTRODUCTION

Sex steroid hormones influence cognition and affect at many points in life. Steroid hormones have organizational effects during the prenatal and neonatal periods. They have maturational effects during various stages of development, including activational effects at puberty, variation during the menstrual cycle and across seasons, and possibly effects at menopause and beyond. In this chapter, we will focus on hormone effects on behavior during adulthood. We begin with a discussion of menstrual cycle variation effects on cognition, affect, and neural activity. We next discuss the major focus of this chapter, that is, effects of estrogen in relation to age-related cognitive decline and risk for dementia in postmenopausal women, followed by a brief discussion of the more limited information on testosterone effects on cognition, emphasizing effects in older men. Finally, we highlight several important areas for future research.

EFFECTS OF ESTROGEN AND TESTOSTERONE IN YOUNG ADULTS

Variation in Cognition across the Menstrual Cycle

Much of the research examining the effects of hormonal fluctuations across the menstrual cycle has investigated fluctuations in verbal and spatial abilities. One reason for this emphasis is the finding that men, with naturally high levels of testosterone and relatively lower levels of estrogen and progesterone, tend to perform better on visuospatial (classically male) tasks, while women, with naturally high levels of estrogen and progesterone and lower levels of testosterone, tend to perform better on verbal (classically female) tasks (Hampson & Kimura, 1992; Maki & Resnick, 2001). This sex difference is evidenced early in life and persists to old age.

Reviews (Craig & Murphy, 2007; Gasbarri, Tavares, Rodrigues, Tomaz, & Pompili, 2012; Hampson & Kimura, 1992; Maki & Resnick, 2001) and early studies (Hampson, 1990; Hampson & Kimura, 1988; Maki, Rich, & Rosenbaum, 2002; Rosenberg & Park, 2002) examining the effects of hormonal fluctuations on cognitive processing across the menstrual cycle emphasized findings where high estrogen and progesterone levels were associated with better performance on verbal measures (verbal articulation, fluency) and fine motor skills and poorer performance on visuospatial tasks. More recent studies have yielded less consistent findings. For example, Pletzer and colleagues found higher error rates in verbal numerical processing in women during the follicular phase (low estrogen and progesterone) and higher error rates in spatial numerical processing during the luteal phase (high estrogen and progesterone) (Pletzer, Kronbichler, Ladurner, Nuerk, & Kerschbaum, 2011). Although Maki et al. (2002) found women performed better on tasks of verbal fluency and motor skills and poorer on a 3-D visuospatial task (mental rotations) during high estrogen and progesterone phases of the menstrual cycle (midluteal phase: ML) compared with low estrogen and progesterone (early follicular phase: EF), they did not find menstrual cycle effects on an explicit memory category-cued recall task. In contrast, Mordecai and colleagues found no differences on tasks of verbal fluency, verbal or visuospatial memory, 3-D visuospatial abilities or attention for EF versus ML (Mordecai, Rubin, & Maki, 2008). In other studies, estrogen and progesterone effects, based on menstrual cycle phase, were also not observed for semantic decision making, perceptual letter-matching tasks (Fernandez et al., 2003), reaction time (RT) using a decision-making monetary incentive delay task (Ossewaarde et al., 2011), spatial rotation (Rosenberg & Park, 2002) and 3-D visuospatial abilities (Schöning et al., 2007). Interestingly, practice on mental rotation tasks

may impact observations of hormone associations, with one study finding associations between low estrogen and better performance during initial testing but not after repeated exposure (Courvoisier et al., 2013).

Results from studies examining working memory across the menstrual cycle have also been inconsistent. Rosenberg and Park (2002) found that higher levels of estrogen or progesterone (late follicular: LF; ovulation: OV; ML) were associated with better verbal working memory accuracy than lower estrogen and progesterone (menses: MN). In contrast, no significant differences in accuracy or RT were found on an N-back task across low (EF) and high estrogen (LF) phases, although comparison of 2-back with 0-back performance revealed an increase in errors during high-estrogen versus low-estrogen phases (Joseph, Swearingen, Corbly, Curry Jr, & Kelly, 2012).

Menstrual Cycle Fluctuations in Neural Activity

Neuroimaging studies have increased exponentially since Maki and Resnick (2001) reported the dearth of research into brain activation pattern changes across the menstrual cycle. Early studies found varying results depending on the type of behavioral tasks and neuroimaging procedure used, as well as the type of investigation (within-subject studies across the menstrual cycle, hormone-suppressing and -activating interventions) (Berman et al., 1997; Dietrich et al., 2001; Reiman, Armstrong, Matt, & Mattox, 1996; Veltman, Friston, Sanders, & Price, 2000). More recent studies using functional magnetic resonance imaging (fMRI) to investigate variation in brain function across the menstrual cycle report menstrual cycle variation in neural activation both in conjunction with performance differences and even in the absence of behavioral performance differences.

Several investigations have demonstrated menstrual cycle variation in both neural activation and task performance. For example, Derntl et al. found better facial emotional recognition performance was associated with greater amygdala activation during the follicular phase compared to the luteal phase of the menstrual cycle (Derntl et al., 2008). Investigating cortical activation with spatial and verbal numerical processing in the follicular versus the luteal phase, Pletzer et al. (2011) found higher errors rates and greater bilateral inferior parietal lobule and medial prefrontal cortex deactivation in the luteal phase for spatial versus verbal numerical processing. In addition, differential right and left frontal activation associated with working memory performance has also been associated with cyclic variation across the menstrual cycle (Joseph, Swearingen, Corbly, Curry, & Kelly, 2012).

There are also a number of studies reporting hormonal effects on neural activation in the absence of behavioral performance variability across the menstrual cycle. For example, Fernandez et al. (2003) found no estrogen-related behavioral effects in either a semantic decision-making task or perceptual letter-matching task, yet they found that higher levels of both estrogen and progesterone were associated with medial superior frontal activation and higher progesterone level was associated with bilateral superior temporal activation during the semantic task. Craig et al. found that higher estrogen was correlated with magnitude of left inferior frontal gyrus (LIFG) activation even though estrogen level was not associated with verbal recall (Craig et al., 2008c), and Schoning et al. (2007) found differences in brain activation in specific frontal, temporal and parietal regions across high- and low-estrogen phases during a 3-D mental rotation task despite the absence of menstrual cycle performance differences. In the latter study, higher estrogen during the ML phase correlated with increased bilateral activation in superior parietal, frontal gyrus, and right inferior parietal regions.

In an effort to systematically examine the effects of hormonal fluctuations on cognitive performance and brain functions, some studies have simulated menstrual cycle hormone level fluctuations using estrogen-lowering medications, specifically gonadotropin-releasing hormone agonists (GnRHa). A series of studies by Craig and colleagues (Craig et al., 2007, 2008a, 2008b) examined the effect of estrogen suppression after 8 weeks of GnRHa administered in a group of women awaiting fibroid surgery. Visual recognition accuracy using a Delayed Match to Sample task (Craig et al., 2008a) did not vary based on estrogen level (LF vs. estrogen suppression), yet recognition RT decreased across the two testing phases, and women had decreased activation during visual encoding in the middle temporal and left parahippocampal gyrus, precuneus, posterior cingulate, and paracentral lobule. In a similar study investigating verbal encoding and recognition memory, Craig et al. (2007) found no effects of 8 weeks of GnRHa administration on encoding performance but found reduced recognition discrimination after GnRHa administration. There were no activation effects during recognition, yet there were activation attenuations in the left prefrontal cortex, medial frontal gyrus and anterior cingulate during verbal encoding. Additionally, Craig et al. (2008b) found that adding back estrogen after estrogen suppression returned decreased activation in the LIFG to previous levels during encoding and reversed the decrease in verbal recognition performance to prior levels of discrimination.

Variation in Affect across the Menstrual Cycle

Early investigations (Brooks-Gunn & Warren, 1989; Warren & Brooks-Gunn, 1989) and anecdotal reports indicate that mood varies across the menstrual cycle. However, more recent results of menstrual cycle variation in affect are less evident. Maki et al. (2002) and Mordecai et al. (2008), investigated variation in affect using the Positive and Negative Affect Scale (PANAS) and depressive symptoms using the Center for Epidemiological Studies Depression Scale (CESD), and Hampson et al. employed the Profile of Mood States (POMS) (Hampson, Finestone, & Levy, 2005). No significant estrogen-related variation was observed. Additionally, Hausmann (2005) found no differences in cheerfulness, seriousness or bad mood based on hormonal fluctuations across the menstrual cycle. The detection of menstrual cycle variation in affect may be hindered by large individual differences and conditions such as pre-menstrual syndrome.

In summary, the variability in behavioral and functional activation findings across studies of menstrual cycle hormonal fluctuations may reflect differences across studies related to both assessment of hormone status and behavioral domains. Factors related to assessment of hormone status include measurement of hormone status (e.g., types of assays of estrogen and progesterone, saliva versus plasma, self-report), phases of the menstrual cycle when testing occurred, and hormonal fluctuations depending on day of testing. Similarly, results are dependent on the specific cognitive and affective domains assessed. Although menstrual cycle variation in neural activation is more consistently reported, these results also vary according to the time of testing and brain areas investigated. Future research should systematically investigate menstrual cycle variation using standardized measures of hormone status and cognitive function, and the examination of specific task-related brain regions in activation studies.

EFFECTS OF MENOPAUSE AND HORMONE LEVELS ON COGNITION IN OLDER WOMEN

Menopause is the time in a women's life in which her menstrual cycle ends, and she no

longer has reproductive capacity. The timing of menopause is defined as 12 months from the final menstrual period, with a median age of 52.5 years (Gold et al., 2013). The depletion of ovarian hormones such as estrogen, progesterone, and testosterone during the menopausal transition results in a number of physiological changes, including effects on the central nervous system. Importantly, with increased longevity in recent years, women now spend more than one-third of their lives with depleted ovarian hormones. Common menopausal symptoms include hot flashes, night sweats, and urogenital problems among others (Dennerstein, Dudley, Hopper, Guthrie, & Burger, 2000; Obermeyer, Reher, & Saliba, 2007; Ribowsky, 2011). Artificially replacing hormones and boosting levels through hormone therapy (HT) alleviates many of these physiologic symptoms, and early observational and epidemiological studies suggested that HT had a number of health benefits, including decreased rate of coronary heart disease and mortality (Grodstein & Stampfer, 1995; Grodstein et al., 1997,2000; Henderson, Paganini-Hill, & Ross, 1991; Shlipak et al., 2000).

From a psychological perspective, observational studies suggested that the cumulative lifetime exposure to estrogen a women experiences impacts her cognitive functioning later in life. Factors influencing cumulative estrogen exposure include age at menses and at menopause, duration of HT in hormone users, duration of breastfeeding if child-bearing and time since menopause (Hesson, 2012). Menopause earlier in life has been linked to lower cognition in later adulthood (Hogervorst, 2012; Hogervorst, Kusdhany, & Rahardjo, 2011), as well as increased risk of overall mortality (Nelson, Walker, Zakher, & Mitchell, 2012). A number of studies report cognitive decline in women undergoing the menopausal transition (Mitchell & Woods, 2011; Schaafsma, Homewood, & Taylor, 2010; Weber, Maki, & McDermott, 2013), especially in particular cognitive domains, such as working memory and attention (Greendale et al., 2009; Keenan, Ezzat, Ginsburg, & Moore, 2001; Kimura, 2002; Wroolie et al., 2011). However, findings are mixed, and some reviews of observational studies point to no substantial changes to cognition occurring during the natural menopausal process (Henderson & Sherwin, 2007) or none of clinical relevance (Henderson, Guthrie, Dudley, Burger, & Dennerstein, 2003). Other studies describe findings whereby cognitive impairments are temporary (Greendale et al., 2009) or that only very specific cognitive domains are impacted, such as verbal fluency (Fuh, Wang, Lee, Lu, & Juang, 2006). In reviewing this literature, Henderson and Popat (2011) found no consistent links between serum estrogen levels and episodic memory or executive functions at midlife or in older naturally menopausal women. The inconsistent behavioral findings may be explained in part by the stage of menopause examined, the effects of brain aging in older women (aged 65+ years) and other covariates not considered (Shanmugan & Epperson, 2012). In addition, it is difficult to distinguish effects of menopause from age, and the menopausal transition is a time marked by greater intra- and inter-individual variability in physiology, and in cognitive and affective response to that variability.

Estrogens and Menopausal HT in Women—Observational Studies

As mentioned, in addition to relieving menopausal symptoms such as hot flashes and vaginal dryness, HT was thought to have a number of benefits to health, which included prevention of cognitive decline during the menopausal transition and beyond. Basic science investigations, including those using cell culture and animal models, indicated that estrogens, particularly estradiol, promote cholinergic activity, enhance synaptic plasticity, and offer

neuroprotection against beta-amyloid-induced neurotoxicity (Brinton, Chen, Montoya, Hsieh, & Minaya, 2000; Smith, Minoshima, Kuhl, & Zubieta, 2001; Tinkler, Tobin, & Voytko, 2004; Zec & Trivedi, 2002b). Early observational studies suggested that estrogen-based HT protected against risk for Alzheimer's disease (AD), with several prospective studies suggesting more than a 50% reduction in risk in women who had used HT compared with non-users (Kawas et al., 1997; Paganini-Hill & Henderson, 1996; Zandi et al., 2002). Similarly, a number of observational studies in postmenopausal women, including those performed by our group, found that HT users performed significantly better than non-users on tests of cognition including visual memory (Resnick, Metter, & Zonderman, 1997), verbal memory (Maki, Zonderman, & Resnick, 2001), and working memory (see LeBlanc, Janowsky, Chan, & Nelson, 2001; Maki & Hogervorst, 2003; Sherwin, 2006 for reviews). Although these studies attempted to adjust for potential confounds known to impact cognitive performance, such as age, education and socioeconomic status, the "healthy user" bias remains an important confound in observational studies. Women who chose HT tended to be healthier overall, and it is likely that unadjusted confounders might still influence the results of these studies. In addition, the observational studies often included women taking different types and doses of hormone preparations at different times relative to menopause and for different durations. Furthermore, women who go through natural menopause and still have a uterus must take adjuvant progesterone to protect against estrogen-induced endometrial hyperplasia and cancer. In addition to progesterone, a variety of synthetic progestins have been used for this purpose, and the different formulations likely vary with respect to their effects on cognition and health outcomes.

Estrogens and Menopausal HT in Women—Effects of Surgical Menopause and Intervention in Younger and Older Women

Surgical menopause refers to the surgical removal of both ovaries, bilateral oophorectomy, in women still undergoing menstrual cycles. Indications for this type of procedure include malignant or benign ovarian or metastatic disease that cannot be treated medically, and ovarian or breast cancer risk reduction (Novetsky, Boyd, & Curtin, 2011; Shuster, Gostout, Grossardt, & Rocca, 2008). Unlike the natural menopausal process, where women experience a gradual decrease in ovarian hormone production over several years, surgical menopause brings about an abrupt and immediate withdrawal of these steroid hormones.

Observational results from The Mayo Clinic Cohort Study of Oophorectomy and Aging, a large-scale, long-term longitudinal study, suggested that surgical menopause in both young and old women carries an increased risk of cognitive impairment and dementia (Rocca et al., 2007; Rocca, Grossardt, & Maraganore, 2008). In another longitudinal study spanning 2 years, global cognition scores (Mini Mental State Exam) and two Wechsler Memory subscores were reduced in the surgical compared with age-, education- and weight-matched premenopausal controls (Farrag, Khedr, Abdel-Aleem, & Rageh, 2002). Moreover, these changes appeared early, at 3–6 months following surgery. Additionally, an earlier age of surgical menopause has been associated with an increased risk of cognitive dysfunction and dementia (Bove et al., 2014; Nappi et al., 1999; Phung et al., 2010; Rocca et al., 2007; Rocca, Grossardt, Shuster, & Stewart, 2012). Some researchers however, have reported negligible or no effect of surgical menopause on cognitive

functioning in middle-aged (Kok et al., 2006; Vearncombe & Pachana, 2009) and older women (Bove et al., 2014; Kritz-Silverstein & Barrett-Connor, 2002).

Interest in the effects of HT on cognition was reinvigorated by a series of studies in younger surgically menopausal women conducted by Barbara Sherwin and her colleagues in the late 1980s and early 1990s. Sherwin (1988) and Phillips and Sherwin (1992) found beneficial effects of HT on cognitive function, especially verbal memory performance, in younger women who had undergone surgical menopause. Phillips and Sherwin (1992) tracked 19 women before and after bilateral oophorectomy and hysterectomy surgery, and who had been randomly assigned to estrogen-replacement therapy or a placebo group on varying memory measures. The group by time interaction was significant in that HT prevented the surgical-menopause-associated decline in immediate and delayed verbal memory. This HT effect was domain-specific as digit span scores and the immediate and delayed recall of visual material were not subject to hormonal effects. In another study examining HT use after surgical menopause, the same group reported significantly lower scores in tests of short- and long-term memory and logical reasoning for the placebo group post-surgery (Sherwin, 1988). In general, hormone treatments appeared to protect against post-surgery cognitive decline.

Observational studies have reported similar cognitive benefits for HT use after surgical menopause (Bove et al., 2014; Rocca et al., 2007). For example, Bove et al. (2014) combined the results from two longitudinal cohorts of older women (mean age 78 years), and found that HT use for at least 10 years, and within 5 years of surgery, was linked to a decreased decline in global cognitive functioning. This suggests that the length and timing of HT use may affect its neuroprotective effect in surgically induced menopause. Not all studies, however, have found such effects (Maki & Hogervorst, 2003), and there is a paucity of research studies where surgical menopause is clearly defined and objective cognitive deficits, as opposed to cognitive symptoms, are measured. Nevertheless, clinical data support the assertion that cognitive functioning may be impacted by early surgical menopause (Farrag et al., 2002; Henderson & Sherwin, 2007) and that HT may be of greater benefit to women having undergone surgical menopause.

Estrogens and Menopausal HT in Women—Intervention Studies in Older Postmenopausal Women

In contrast to the beneficial effects of estrogen therapy in younger women following surgical menopause, results of randomized controlled trials in older, naturally menopausal women have yielded more mixed results. Although some studies have reported cognitive improvements when comparing HT to placebo groups (Haskell, Richardson, & Horwitz, 1997; Sherwin, 2006; Zec & Trivedi, 2002a), the majority of recent intervention studies do not support a beneficial effect of HT in older postmenopausal women. A number of factors may contribute to mixed results, including the type of hormones used, the dosage, the timing of treatment, and the way in which the treatment was administered, including cyclic versus continuous. Additionally, results vary depending on the specific cognitive functions. Some have argued that verbal memory is the cognitive domain most affected by HT (e.g., Sherwin) whereas others have argued that working memory and prefrontal function may be more affected than delayed memory and hippocampal-dependent tasks (Krug, Born, & Rasch, 2006). This is in keeping with a study

from Voytko and colleagues (2009), who found greater prefrontal effects of preserved executive functions in the form of Wisconsin Card Sorting performance and shifting visuospatial attention in a sample of menopausal monkeys administered HT.

Results from the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative Study of Cognitive Aging (WHISCA)

The WHIMS (Shumaker et al., 1998) and WHISCA (Resnick et al., 2004) studies have been conducted as ancillary studies to the Women's Health Initiative (WHI) randomized controlled trial of the effects of HT on health outcomes in postmenopausal women. The WHI HT trial was comprised of two parallel placebo controlled trials of conjugated equine estrogen (CEE)-based HT regimens. Enrollees were 50–79 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. The WHIMS ancillary study enrolled 7429 women 65 years of age and older to evaluate effects of HT on risk and progression of dementia. The WHISCA study enrolled women without dementia to evaluate effects of HT on memory and other cognitive abilities and was initiated on average 3 years after randomization to the HT trial. In 2008, WHI clinic visits ceased and WHIMS transitioned to an annual telephone-administered cognitive assessment battery (described below), for the WHIMS Epidemiology of Cognitive Health Outcomes (ECHO), which combines the WHIMS and WHISCA studies.

Although the choice of CEE and combined CEE + MPA interventions, rather than estradiol-based HT, has been questioned by basic and clinical scientists, it is important to remember that these preparations were the most widely used types of postmenopausal HT treatments in the United States. Until findings from the WHI in 2003, HT was widely reported in observational studies to deliver additional health benefits such as decreased risk for coronary heart disease, hip fracture (Grady et al., 1992), and dementia (Birge & Mortel, 1997; Haines, 1998; Henderson, 1997; Hogervorst, Williams, Budge, Riedel, & Jolles, 2000; LeBlanc et al., 2001; Melton, 1999; Panidis, Matalliotakis, Rousso, Kourtis, & Koumantakis, 2001; Zandi et al., 2002). The primary goal of the WHI HT trials was to test the widely held belief that postmenopausal HT would prevent heart disease in postmenopausal women (and the primary adverse event expected was increased breast cancer), a critical public health issue. The expected benefit for cardiovascular disease was not supported by the main WHI HT trial results (Anderson et al., 2004; Rossouw et al., 2002). While results varied for the CEE + MPA versus the CEE alone HT trials, CEE + MPA was associated with an increased risk of breast cancer and both treatments increased risk for stroke and blood clots in the leg and lungs.

Results of the WHIMS and WHISCA studies also yielded findings that were contrary to the predicted reduction in risk for dementia and benefit to cognitive function. Instead, both active treatment groups showed an increase in dementia risk. Randomization to combination CEE + MPA compared with placebo was associated with a significant increase in risk of dementia in women aged 65 years and older (Shumaker et al., 2003) and with poorer global cognitive function over time (Espeland et al., 2004). Randomization to CEE alone versus placebo also resulted in an increased risk for dementia, albeit not-reaching the $P = 0.05$ significance level (Shumaker et al., 2004), and

was associated with significantly lower performance on a measure of global cognitive function (Espeland et al., 2004). The deleterious effects of both forms of HT on cognitive function persisted after treatment cessation (Espeland et al., 2010).

In addition to the WHIMS studies of dementia risk and global cognitive function, the WHISCA study of 2302 WHIMS participants provided 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, in women without dementia. Again, contrary to expectation, Resnick et al. (2006) found that older postmenopausal women randomized to combination CEE + MPA had poorer verbal learning and memory scores over time (average 4–5 years) compared to placebo controls. However, no other cognitive functions measured were impacted. (See Singh and Su (2013) for a discussion of the neurobiological differences between endogenous progesterone and synthetic MPA that may have influenced these findings.) In women randomized to CEE alone, results from the WHISCA study showed no significant benefits or harm to age changes in specific cognitive functions (Resnick, Espeland, An et al., 2009). Neither treatment, combination CEE + MPA nor CEE alone, significantly influenced measures of affect and depressive symptoms (Resnick et al., 2006; Resnick, Espeland, An et al., 2009).

To better understand the mechanism leading to the adverse effects of these HT treatments on dementia risk and some measures of cognitive function, an MRI study of brain structure was performed in 1403 women in the WHIMS study an average of 3.0 and 1.4 years after the termination of study medications for CEE + MPA and CEE alone, respectively (Resnick, Espeland, Jaramillo et al., 2009). In view of the documented increase in risk for stroke and thromboembolic events, WHIMS investigators hypothesized that the adverse effects of HT on dementia risk and cognition might be due to an increase in vascular disease. The WHIMS-MRI study evaluated the effect of HT on ischemic lesion volumes (primary endpoint), as a measure of increased vascular disease, and total brain, frontal and hippocampal volumes (secondary endpoints), as measures of neurodegeneration. Contrary to prediction, there was no increase in MRI-assessed vascular abnormalities in HT versus placebo (Coker et al., 2009) but there was a reduction in total brain, frontal and hippocampal volumes in women previously randomized to HT versus placebo. Moreover, the adverse effects of HT on brain volumes were most pronounced in women with the lowest cognitive function at enrollment in WHI, and those with the highest white matter lesion volumes on MRI. These findings suggest that women who are less healthy may be most vulnerable to adverse effects of HT, and conversely, that HT could have different effects on a healthy brain.

Following the highly influential findings from the WHI in 2003 there ensued dramatic reduction worldwide in the use of HT after menopause (Ettinger et al., 2012). However, HT remains a highly effective treatment for relief of menopausal symptoms, including hot flashes and vaginal dryness. In addition, many investigators argued that the WHIMS results were influenced by the fact that treatment was initiated years after the cessation of menopause in women 65 years of age and older, and that treatment initiated early in menopause might yield different findings. According to this "critical period" (Resnick & Henderson, 2002) or "window of opportunity" hypothesis, the cognitive benefits of postmenopausal HT might only be observed when HT is initiated in early menopause (Henderson, 2013; Maki, 2013; Sherwin & Henry, 2008). Several observational studies offered some support for this notion. In results from the large epidemiological Cache County study, Zandi et al. (2002) found that former users (more likely to have used HT closer

to menopause), especially those with more than 10 years' duration, but not current users of HT, had reduced risk for AD. In a large sample of 428 Australian women older than 60 years, benefits were found for tests of global cognition, psychomotor speed and verbal fluency in women who had initiated HT early post-menopause (MacLennan et al., 2006). Another large-scale study, where 343 postmenopausal Danish women were followed in order to assess the long-term effect of early hormonal treatment on cognitive function, found similar results (Bagger et al., 2005).

Two recent intervention studies tested the hypothesis that early initiation of menopausal HT would benefit cognition. In the WHIMS-Young (WHIMS-Y) Study, 1326 women who had been randomized to CEE with or without adjuvant MPA when aged 50–55 years were administered a validated battery of cognitive tests during a telephone interview conducted approximately 14.2 years after randomization to treatment and 7.2 years after treatment discontinuation (Espeland et al., 2013). The WHIMS-Y women were 67.2 years of age on average when tested. Given the Federal Drug Administration's recommendation of short duration/low-dose treatment when necessary for treatment of menopausal symptoms, this study provides an important test of the clinically relevant question: what happens to cognitive function years later when women receive HT during early menopause and then cease treatment? Findings from the WHIMS-Y study showed that early treatment of younger postmenopausal women resulted in neither harm nor benefit to cognitive function. From a cognitive perspective, these findings should offer some reassurance to women who find it necessary to use HT for relief of menopausal symptoms, and are consistent with earlier findings in older WHIMS participants that the healthiest women were less vulnerable to adverse effects of HT (Resnick, Espeland, Jaramillo et al., 2009).

Preliminary findings have also been reported from another randomized controlled clinical trial of HT during the early menopause (http://www.keepstudy.org/news/keeps_ceo.cfm). In the Kronos Early Estrogen Prevention Study (KEEPS), 727 women 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). Importantly, women on active estrogens were administered oral progesterone (200 mg), rather than the synthetic progestin used in WHI, for 12 days each month. Women were an average age of 53 years at baseline and were followed over a 4-year period. Although cardiovascular endpoints were the primary outcomes, a sub-study (KEEPS-Cog) evaluated a number of cognitive domains, including memory, in 571 of the KEEPS women (Wharton et al., 2014). The results of the cognitive study indicated that women randomized to oral CEE showed improvement in symptoms of depression and anxiety. However, similar to the WHIMS-Y results, HT in KEEPS had neither benefit nor harm to measures of memory and other cognitive functions.

Testosterone and Progesterone

While most of the literature on effects of hormones on cognitive function in older women focuses on effects of estrogens, the menopausal transition is also associated with declining levels of circulating testosterone and progesterone. Testosterone-based therapy has been used for several decades to treat low libido, however, lower levels of this hormone may also contribute to menopausal symptoms including cognitive variability (Singh & Su, 2013). For example, in a large sample of postmenopausal women not using HT, Ryan et al. (2012) reported that longitudinally, lower testosterone levels were correlated with better verbal episodic memory 2 years later, whereas higher total and free endogenous estradiol levels were

associated with better semantic memory. The authors concluded that the specific testosterone/estradiol ratio affects different aspects of memory. In a mini-review article focusing on testosterone and cognition in women, Hogervorst (2012) summarized that in observational studies where a representative sample of older women over a wide age range were included (i.e., women not selected for optimal health), testosterone levels had a negative relationship with verbal memory. Conversely, studies that included very healthy older cohorts over a wide age range found that testosterone has a positive impact on verbal memory performance. Finally, in a randomized controlled trial of 200 healthy, naturally menopausal women assigned to 4 weeks of testosterone undecanoate or placebo treatment, Kocoska-Maras et al. (2011) found no effect of testosterone on verbal fluency, verbal memory, or spatial ability. In comparison to estrogen-based assessments, studies examining testosterone levels are far fewer and there is a critical need for efficacy and safety studies of testosterone or testosterone-containing treatments in older women.

As mentioned, women undergoing HT are typically prescribed progesterone or progestin (progesterone-like medication) alongside estrogen to prevent endometrial hyperplasia and decrease the risk of uterine cancer (Froom, 1991). Therefore, basic science and clinical studies have investigated effects of progesterone, as well as estrogen and testosterone. Studies examining central nervous system effects of progesterone have found neuroprotective impacts in animal models of stroke, traumatic brain injury and spinal cord injury (Singh & Su, 2013). Human studies assessing the link between progesterone and cognition indicate associations between short-term progesterone therapy and benefits on some measures of speed of processing, but not on tests of attention or verbal memory (Schüssler et al., 2008). In sum, the literature documenting the effects of sex hormones other than estrogens on cognitive outcomes in older women is limited and results are inconsistent. Testosterone has been reported as beneficial, harmful and inconsequential, whilst progesterone appears to be linked to more basic cognitive functions, such as processing speed.

Estrogens and Menopausal HT in Older Women—Associations with Brain Structure and Function

Adverse effects of estrogen-containing HT on brain volumes in older postmenopausal women in WHIMS were noted above (Resnick, Espeland, Jaramillo et al., 2009). Nevertheless, there were many reasons to believe that estrogen-containing HT would have beneficial effects on brain structure and function. Estrogen receptors in the brain are known to be clustered in structures imperative to memory and learning such as the hippocampus and the prefrontal cortex (McEwen, Akama, Spencer-Segal, Milner, & Waters, 2012). This is important given that the hippocampus is one of the first brain structures to be affected by AD, with hippocampal atrophy one of the hallmarks of the disease (Apostolova et al., 2012; Jack et al., 2000). Moreover, animal models show that estradiol influences hippocampal function and animal learning (Spencer et al., 2008).

In human brains, estrogens impact structural anatomy in some of the same brain regions. For example, hippocampal and dorsal basal ganglia gray matter volumes within young healthy women have been shown to exhibit fluctuations throughout the menstrual cycle when concentrations of endogenous estradiol vary (Protopopescu et al., 2008). However, whether higher estradiol concentrations are linked to advantageous effects on brain structure remains unclear (Wnuk, Korol, & Erickson, 2012). Some studies that investigate the connection between estrogens and brain morphology report smaller volumes (Greenberg et al., 2006) and in particular the hippocampus (Lord, Engert, Lupien, & Pruessner, 2010), including findings in older

women randomized to CEE-based HT in the WHIMS study (Resnick, Espeland, Jaramillo et al., 2009). A cross-sectional finding from the Rotterdam Scan study (den Heijer et al., 2003) indicated that higher total estradiol levels were linked to lower hippocampal volumes and poorer memory performance in a large sample of older women. A follow-up study from a portion of the same sample found no association with total baseline estradiol levels and hippocampal volumes (den Heijer, van der Lijn, Niessen, & Breteler, 2009), although women in the lowest tertile at baseline had the largest decline in hippocampal volume over 3 years.

Other studies have found no association between HT and brain structure (Low et al., 2006; Sullivan, Marsh, & Pfefferbaum, 2005). Specifically, Resnick and Maki (2001) found no differences between menopausal HT users and non-users in measures of total brain volume, gray or white matter, or ventricular volumes. On the other hand, several studies that investigated the connection between estrogens and brain morphology reported *larger* volumes, especially in women receiving HT. For example, Lord, Buss, Lupien, and Pruessner (2008) found that compared to previous and non-users, current HT users had larger right hippocampal volumes, but that there was a significant negative relationship between HT duration and hippocampal volume in the current HT-users group. Larger hippocampal volumes have also been reported in HT users in other studies (Eberling et al., 2003; Erickson, Voss, Prakash, Chaddock, & Kramer, 2010; Hu et al., 2006; Yue et al., 2007). Erickson et al. (2007) reported spared gray matter prefrontal integrity and better executive control in women who received HT for up to 10 years, with both effects reversing when treatment persisted beyond this time. The same group has reported the timing of HT from menopause to be a factor, with larger hippocampal volumes reported for women who initiated treatment early postmenopause (Erickson et al., 2010). As with cognitive findings, the timing and duration of estrogen-based HT may play a role in its potential neuroprotective properties as evidenced by hippocampal and prefrontal volumes.

Sex hormones such as estrogen and progesterone may also alter functional brain networks (Mander, 2001). For example, using an fMRI visual working memory task, Berent-Spillson and colleagues showed that compared with never users, current users or women that had previously used HT exhibited increased activation in several regions critical for visual working memory including the frontal and parietal cortices and the hippocampus (Berent-Spillson et al., 2010). Additionally, a significant positive correlation between functional activation and task performance was found. Maki et al. showed that women who had undergone HT during perimenopause performed better than never-users on a verbal memory task, and that distinct patterns of hippocampal and parahippocampal activation were associated with better performance (Maki et al., 2011). Other studies have found similar increased patterns of neural activity during tasks in women receiving HT including bilateral prefrontal cortex (Persad et al., 2009; Smith et al., 2006). Taken together, these studies suggest that hormones such as estrogen can functionally alter neural systems subservient to (visual and verbal) working memory.

Using positron emission tomography (PET) scans in conjunction with HT both cross-sectionally and longitudinally over a 2-year time period, Resnick and Maki (2001) found HT-related increased patterns of brain activation in regions subservient to memory processes. Lastly, using event-related potentials (ERPs) to study HT effects in postmenopausal, age-related cognitive decline, Anderer et al. (2005) found a significant improvement of P300 latency in the HT-users group as compared with the placebo group. In sum, as with fMRI findings, PET and ERP studies suggest that hormonal treatment may modulate neural processes in postmenopausal women.

TESTOSTERONE AND COGNITIVE AGING IN MEN

Observational Studies of Circulating Levels of Testosterone and Cognitive Function

More detailed reviews of the literature on endogenous testosterone and cognitive function can be found in Yonker, Eriksson, Nilsson, and Herlitz (2006) and Thilers, Macdonald, and Herlitz (2006). Similar to studies of the associations between endogenous estradiol levels and cognitive function in women, results of studies of circulating testosterone and specific cognitive functions in both men and women yield inconsistent findings. In samples combined across younger men and women, curvilinear associations between endogenous testosterone and spatial ability have been reported. This association reflects a negative association between testosterone and spatial ability in young women in combination with a positive association in young men (Moffat & Hampson, 1996). In older men, when positive relationships are reported, they also tend to demonstrate associations between higher testosterone and higher visuospatial function, cognitive measures which often show male advantages on average. In contrast to findings with respect to visuospatial function, few positive associations have been reported for episodic memory and verbal fluency (e.g., Table 1 in Thilers et al., 2006). However, in a large population-based study (The Betula Study) of men and women aged 35–90 years, higher free (unbound and therefore metabolically active) testosterone was associated with better visuospatial abilities, verbal fluency and episodic memory in men but was negatively associated with verbal fluency in women (Thilers et al., 2006). In our earlier study in the Baltimore Longitudinal Study of Aging, which was restricted to men aged 50 years and older, free testosterone levels, measured by the free testosterone index, showed stronger associations than total testosterone with specific cognitive functions, including visuospatial abilities (Moffat et al., 2002). In addition, higher free testosterone levels were associated with a decreased risk for AD (Moffat et al., 2004). However, in the Florey Adelaide Male Ageing Study of 1046 men aged 35–80 years, higher total and free testosterone levels were associated with poorer verbal memory and executive function but faster psychomotor speed (Martin, Wittert, Burns, Haren, & Sugarman, 2007). In a smaller study of 96 men, aged 38–69 years, Martin et al. found no overall main effect of free testosterone levels on spatial abilities or other cognitive measures in the sample as a whole (Martin, Wittert, Burns, & McPherson, 2008). However, in men over age 50 years, higher total and free testosterone were associated with poorer processing speed and executive function. In a large sample of 3369 men aged 40–79 years, from the European Male Ageing Study, Lee et al. found no significant relationships between testosterone and performance on the Rey-Osterrieth Complex Figure, Digit Symbol Substitution Test, and a recognition memory test after adjusting for covariates (Lee et al., 2010). Similarly, there was no relationship between circulating testosterone and global cognition or executive function after adjustment for important covariates in 1602 men participating in The Osteoporotic Fractures in Men Study (MrOS) study (LeBlanc et al., 2010). The lack of consistent findings may reflect variation in study samples, both with respect to age and sex, specific cognitive abilities evaluated, and methods of measuring both free and total testosterone.

Intervention Studies of Testosterone Supplementation

In contrast to the more abrupt changes in ovarian steroid hormone levels experienced by postmenopausal women, men show gradual declines in testosterone from age 20 years

and older (Harman, Metter, Tobin, Pearson, & Blackman, 2001). Compared to young men, 30% of men over age 70 years have low total testosterone and 70% have low free testosterone concentrations that would be considered hypogonadal. Thus, there has been substantial interest in the use of testosterone supplements in older men to improve sexual function, motor function, energy, memory, and other cognitive functions. Marketing and use of testosterone supplements are widespread in the United States. Although improvement in bone density, muscle mass, sexual and motor function, as well as energy, has been demonstrated in young hypogonadal men (Snyder et al., 2000), the efficacy of testosterone supplementation in older men is unclear. It is also important to note that effects of testosterone supplementation may reflect changes in estrogens as well as androgens. In addition to effects mediated through the androgen receptor, testosterone is also aromatized to estradiol and can have estrogen-mediated effects.

A number of small randomized trials in young and older men suggest that testosterone may improve memory in older men, though not all studies find such benefits (see Driscoll & Resnick, 2007 for a review). However, in a carefully designed series of studies, Cherrier and colleagues found beneficial effects of testosterone supplementation in eugonadal young and older men with normal cognition. These studies used intramuscular injections of testosterone enanthate (weekly intramuscular injections of 100 mg) in young men aged 21–46 years (Cherrier et al., 2002) and older men aged 50–80 years (Cherrier et al., 2001, 2004, 2005). In young men, co-administration of testosterone restored the reduced verbal memory performance associated with suppression of gonadotropin and testosterone secretion. In older men, men receiving 6–8 weeks of testosterone treatment showed greater improvement on tests of verbal memory, spatial memory and spatial ability compared with placebo. Beneficial effects of weekly testosterone enanthate were also evident in hypogonadal men (Cherrier, Craft, & Matsumoto, 2003) and men with cognitive impairment (Cherrier et al., 2005). Importantly, in a separate intervention study using three doses, the beneficial effects of testosterone were evident only at moderate doses and were not evident at low- or high-dose treatments (Cherrier et al., 2007). This finding may shed light on the negative effect of testosterone enanthate (200 mg/biweekly for 90 days) on verbal memory in eugonadal older men who received cognitive testing when circulating testosterone was high (Maki et al., 2007). One small study of testosterone gel supplementation showed no benefit of treatment for cognitive function in men with cognitive impairment or normal memory functioning (Lu et al., 2006), and a second small study of testosterone gel in combination with gonadotrophin and testosterone suppression showed no acute effects on cognitive function in young and older individuals with normal cognition (Young, Neiss, Samuels, Roselli, & Janowsky, 2010). Lastly, in the largest study of testosterone treatment to date, 237 men between the ages of 60 and 80 years with low-normal testosterone levels were randomized to receive 80 mg of testosterone undecenoate or matching placebo twice daily for 6 months. Although lean body mass increased and fat mass decreased, there were no significant effects of treatment on functional mobility, bone mineral density or cognitive function, including measures of verbal memory, spatial ability, and executive function (Emmelot-Vonk et al., 2008). Variation across studies may reflect the type and dose of testosterone treatment, as well as timing of cognitive assessment relative to the timing of administration in the case of non-gel formulations.

As the majority of prior intervention trials have involved small study samples or have not included clearly hypogonadal men, the potential of testosterone supplementation to improve health outcomes, including cognitive function,

in older men remains uncertain. A large-scale multi-site study of the efficacy of testosterone gel in improving health outcomes in hypogonadal symptomatic men is ongoing (Snyder et al., 2014). The Testosterone Trials are a coordinated series of seven trials of the effects of 1% testosterone gel, titrated with a target range of 500–800 ng/dL, for 1 year on motor function, sexual function, vitality, cognition, anemia, bone, and cardiovascular outcomes and enrolled 789 men at 12 clinical sites. All study participants receive a brief cognitive battery at baseline, 6 months and 12 months, assessing memory complaints, verbal and visual memory, attention and executive function, and spatial ability. In addition, global cognitive function is assessed at baseline and at 12 months. All participants have been enrolled and study results are expected in 2015.

CONCLUSIONS AND AREAS FOR FUTURE RESEARCH

In this chapter, we provide an update of the literature investigating the relationship between sex steroid hormones and cognitive functioning, emphasizing the state of knowledge with respect to the influence of hormonal changes on cognitive aging in older adults. Although there is great interest in the potential of hormone treatments to prevent or reverse age-related cognitive decline, there is limited evidence in support of benefits in well-controlled clinical trials to date. With respect to estrogen treatment in older women, the WHIMS and its related studies have demonstrated that hormone treatment should not be initiated in older postmenopausal women aged 65 years and older. In older postmenopausal women, CEE-based treatments increased risk for dementia (Shumaker et al., 2004), had detrimental effects on global cognition (Rapp et al., 2003), and had adverse effects on brain volumes measured by MRI (Resnick et al., 2009b). Although hormone treatment may benefit younger women undergoing surgical menopause, studies of middle-aged women treated close to the menopausal transition showed neither harm nor benefit based on recent results from the WHIMS-Y and KEEPS-Cog studies. These findings in combination provide some reassurance that short-term use of HT for treatment of menopausal symptoms poses little risk to cognitive function.

In contrast to studies of estrogens and cognitive function in older women, there is comparatively less information from clinical trials of the cognitive effects of testosterone supplements in older men. Trials conducted to date have involved small samples of men with normal testosterone levels and have included a variety of testosterone regimens administered over different timeframes. The Testosterone Trials, which will conclude by Fall 2014, will provide important information on a sample of more than 789 hypogonadal older men administered testosterone gel over a 1-year period. Should efficacy, including cognitive benefit, be established in this trial, long-term follow-up studies will be necessary to better establish the safety profile of this treatment. Testosterone treatment is known to increase prostate-specific antigen and thus, may lead to more biopsies and detection of prostate cancers. Testosterone also may have other adverse health effects, with several recent studies suggesting potential cardiovascular risks (Basaria et al., 2010; Finkle et al., 2014).

In conclusion, there are many inconsistent findings from investigations of the contributions of age-related declines in sex steroid levels to cognitive aging. However, findings from recent clinical trials are beginning to inform clinical practice with respect to cognitive function as well as other aspects of physical and behavioral health. There is much to learn from future studies that can be guided by the wealth of information in the basic sciences to inform the types and timing of treatments that should be tested in future studies.

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