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An update on the cognitive impact of clinically-used hormone therapies in the female rat: models, mazes, and mechanisms

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Abstract

In women, ovarian hormone loss associated with menopause has been associated with cognitive decline. Hormone therapy (HT) may ameliorate some of these changes. Understanding the cognitive impact of female steroids, including estrogens, progestogens, and androgens, is key to discovering treatments that promote brain health in women. The preclinical literature has presented elegant and methodical experiments allowing a better understanding of parameters driving the cognitive consequences of ovarian hormone loss and HT. Animal models have been a valuable tool in this regard, and will be vital to future discoveries. Here, we provide an update on the literature evaluating the impact of female steroid hormones on cognition, and the putative mechanisms mediating these effects. We focus on preclinical work that was done with an eye toward clinical realities. Parameters that govern the cognitive efficacy of HT, from what we know thus far, include but are not limited to: type, dose, duration, and route of HT, age at HT initiation, timing of HT relative to ovarian hormone loss, memory type examined, menopause history, and hormone receptor status. Researchers have identified intricate relationships between some of these factors by studying their individual effects on cognition. As of late, there is increased focus on studying interactions between these variables as well as multiple hormone types when administered concomitantly. This is key to translating preclinical data to the clinic, wherein women typically have concurrent exposure to endogenous ovarian hormones as well as exogenous combination HTs, which include both estrogens and progestins. Gains in understanding the parameters of HT effects on cognition provide exciting novel avenues that can inform clinical treatments, eventually expanding the window of opportunity to optimally enhance cognition and brain health in aging women.

Ovarian Hormones and Cognition in the Rodent: Historical Context and Clinical Implications

In 1927, A.S. Parkes published a monograph in The Proceedings of the Royal Society of Medicine entitled "Internal Secretions of the Ovary", in which it is stated that, "The solution of the type of problem found in studying the internal secretions of the ovary is most satisfactorily sought by experiment, and since the lower mammals have to be used for this

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type of work, it is on their reactions that our knowledge of ovarian activity mainly depends. At the same time, however, ovarian activity in the human subject must obey similar laws, and with the aid of clinical observations, experimental work on the lower mammals may be made to throw much light on the problems associated with the human species" (Parkes, 1927, page 45). It is notable that even now, some eight decades later, researchers studying "internal secretions of the ovary" employ similar tenets of utilizing rodent models to understand the multiple effects that these hormones have on body systems and functions. Today we typically refer to "internal secretions of the ovary" as ovarian steroid hormones. Early researchers seeking to learn the functions of the internal secretions of the ovary observed, via experimental evaluations, that the ovary is essential for development of accessory reproductive organs, the estrous cycle, sustaining pregnancy, and mammary gland development (Parkes and Bellerby, 1926). Other studies led to the discovery that these secretions are involved in more than reproductive-related morphology and function; they are also involved in reproductive behaviors (Beach, 1947). Subsequent research has now shown that gonadal steroids impact many non-reproductive actions and functions in the brain as well, including learning and memory, and several of its postulated mechanisms. For many researchers, the hope is to translate findings to a genuine clinical impact on women's health.

In animal models and humans, the female steroids estrogens, progestogens and androgens have each been shown to impact cognition. To evaluate the cognitive effects of female steroid hormones in humans, researchers have been creative in their assessments and have reported effects across menopause transition stages (Luetters et al., 2007), with sex-change operations and concomitant sex hormone treatment (Gomez-Gil et al., 2009), and with hormone therapy before versus after treatment in surgically menopausal women (Sherwin, 2006). Animal models have been used to test the cognitive effects of steroid hormones. In animal models, the traditional procedure is to remove the major source of endogenous synthesis and release, the testes in the male (gonadectomy, or GDX) or the ovaries in the female (ovariectomy, or Ovx), then administer the exogenous steroid of question as a treatment regimen after surgery. Notably, within the last decade, research in both the animal and human literature evaluating the potential influence of gonadal hormones on brain health and function during aging has increased in breadth and depth. Much of this elevated interest is largely because of the recent discussion and debate about whether hormone therapies impact normal aging and/or Alzheimer's disease (AD). These reports include, but are not limited to: a meta-analysis showing that estrogen-containing hormone therapies decreased the risk of AD by 29% (Yaffe et al., 1998); placebo-controlled studies showing estrogens enhanced memory or improved dementia scores in female AD patients (Asthana et al., 1999; Asthana et al., 2001; Ohkura et al., 1994; Ohkura et al., 1995); a study showing that menopause exacerbated age-related cognitive changes in several domains, including visuospatial abilities (Halbreich et al., 1995); and then more recently, the outcome of the Women's Health Initiative studies showing null or detrimental effects on cognition or dementia from the most commonly used hormone therapies (for discussion, see Coker et al., 2010; Henderson, 2008; Maki and Henderson, 2012; Sherwin and Henry, 2008).

A major factor propelling research in women's health is that the life expectancy of women has significantly increased from an average of 54 years, to about 80 years (Singh et al., 1996). Since women are living longer, but age of spontaneous menopause has remained stable, women are now living approximately one-third of their lives in a hypo-estrogenic menopausal state (Amundsen and Diers, 1970; Amundsen and Diers, 1973; Sherwin, 2003). This realization has resulted in an increased interest in understanding the effects of ovarian hormone loss and subsequent hormone therapy administration. Emerging findings are now indicating that multiple parameters impact the extent, and even in some cases the direction, of cognitive effects of hormone loss and administration. Findings show the broad impact of

gonadal hormone effects on brain functions such as learning and memory, and underscore the rich effects that ovarian hormones have on brain plasticity.

Here, we review recent findings on the impact of gonadal hormones during cognitive aging. We discuss this work in the context of landmark gonadal hormone-related discoveries that have provided the framework to guide a path to healthy cognitive aging. Evidence regarding hormone loss and parameters involving treatment optimization has emerged from both preclinical and clinical realms. Preclinical animal models have been widely used because they allow methodical experimental control of factors likely influencing outcome in clinical studies such as age, duration of hormone loss or treatment, specific type and dose of hormone manipulated, socioeconomic status and education. Here, we review literature focusing on the female, spanning the activational effects of estrogens, progestogens, and androgens. We discuss effects on cognition, brain health, and the neuromechanisms possibly mediating these effects. Further, because spatial cognition has been the focus of the majority of the preclinical research in this area, we will focus on spatial cognition, and review the mnemonic memory types most commonly measured. In this review we will discuss ovarian hormones, as well as synthetic and naturally-derived hormones included in various hormone therapy regimens. Ovarian hormones are endogenous and originating from the ovaries of the organism, and hormones from hormone therapies are exogenous and originating from outside of the organism. Thus, the term “ovarian hormone” does not accurately encompass hormones that are exogenously administered and not released endogenously, such as many of those in hormone therapies. For parsimonious discussion, we refer collectively to both endogenous ovarian-derived hormones from the subject, and administered hormone therapy hormones, as “female steroid hormones”.

Operationally Defining and Testing Memory Effects of Female Steroids in the Preclinical Setting

When studying learning and memory in the rodent model, it is vital to acknowledge the multiple parameters involved in the process of quantifying cognitive scores in order to properly interpret data. Within the specific domain of spatial navigation, rodents learn to navigate through a novel environment so that routes to the target eventually become familiar, and associations are formed from cues in the environment to aid overall navigation. Spatial learning and memory involves the ability to navigate effectively through an environment, acquiring, integrating and retaining environmental features such as landmarks and other prominent cues; spatial abilities depend upon medial temporal lobe structures such as the hippocampus (Barnes, 1998).

Being able to differentiate and test various types of spatial memory is vital to successful translational research. Many experimental tests of rodent spatial memory aim to assess spatial working memory, a form of short-term memory which requires a subject to retain spatial information which must be updated and is useful for only a short period of time (trial-specific information, Baddeley and Hitch, 1974). Working memory requires manipulation of information kept “on-line”; in fact, the late Dr. Patricia Goldman-Rakic cleverly and accurately referred to working memory as “working with memory” (Goldman-Rakic, 1987). Working memory is affected by normal aging, revealing a memory decline that becomes more severe as task difficulty increases (Balota et al., 2000). In animals, age-related spatial deficits become more pronounced as memory demand increases as well. This has been shown for age-associated interference-related deficits (Lebrun et al., 1990) and for memory capacity deficits (Aggleton et al., 1989; Bimonte-Nelson et al., 2003; Bimonte-Nelson et al., 2004b; Bimonte et al., 2003). In general, working memory is distinguished from reference memory, which is necessary to remember information that remains constant over time (task-specific information, for discussion see Olton et al., 1979).

Activational versus Organizational Effects of Hormones: Perspectives For Discussion Herein

Gonadal steroid hormone actions are traditionally referred to as having *organizational effects*, operationally defined in the traditional sense as occurring early in development and having permanence, or as having *activational effects* which occur later in development, are transitory, and therefore depend on presence of the hormone at the time of assessment. For example, sex differences in neuroanatomy have been traditionally thought to reflect the permanent organizing effects of steroids present during early development. Activational effects have been thought to activate the underlying organized neural substrate. The expression of many sexually dimorphic behaviors (for example, sexual behaviors in rodents) depend on the presence of circulating hormones; indeed, exogenous administration of sex steroids can induce these behaviors as long as the hormone remains present. Notably, organizational and activational effects work together; as an example, while early hormonal exposure plays a significant role in organizing brain substrates underlying sexually differentiated behaviors, most of these effects are realized only when activational exposure ensues (e.g., Beatty, 1992). Endogenous gonadal hormones or exogenous hormone administration in adulthood can therefore impact behavioral phenomena that were organized early in development. This interactive model demonstrates that activating (or circulating) hormones are acting upon a neural substrate that has been differentiated, and therefore, a “male” versus “female” brain is unlikely to respond to the same circulating hormones in the same way (e.g., Beatty and Beatty, 1970). Accumulating evidence has, however, blurred this traditional organizational/activational dichotomy, with the temporal distinction being called into question. For example, estrogenic activation of sexual behavior in female rat pups has been seen as young as 6 days of age (Williams, 1987), and non-transient changes in brain morphology following post-pubertal hormone manipulations have been noted (Bimonte et al., 2000a; Bimonte et al., 2000b; Bimonte et al., 2000c; Bloch and Gorski, 1988; Pappas et al., 1979; Rodriguez-Sierra, 1986). It has therefore been suggested that the newer organizational/activational distinction should primarily depend on whether the induced effects are permanent or transient, regardless of when they occur during the lifespan (e.g., see Arnold and Breedlove, 1985; Fitch and Denenberg, 1998; Stewart and Kolb, 1988 for discussion).

How do we discuss new findings of ovarian hormone effects on the brain and its function within the context of the organizational/activational dichotomy? While defining these effects as organizational or activational does not necessarily change how we interpret the resulting experimental data per se, it is ideal (and some hormone researchers may say, necessary) to acknowledge the findings within the context of this long-held tenet. There is rich neurophysiological and neurochemical plasticity in the female brain, including brain regions known to subserve learning and memory, suggesting that cognitive brain regions are sensitive to ovarian hormone fluctuation (Becker and Cha, 1989; Frankfurt et al., 1990; Gibbs, 1996; Woolley et al., 1990). These effects are transient and may not necessarily be considered “permanent features,” but nevertheless constitute a part of what makes the female brain distinct from the male brain. Females clearly have an inherent “permanently cyclic” and dynamic neural landscape that modifies along with the reproductive cycle (Fitch and Denenberg, 1998). Moreover, these "permanently cyclic" features have potentially important relevance to cognitive aging since gonadal hormones can impact memory, and gonadal hormone levels change with age (Bimonte-Nelson et al., 2010; Conrad and Bimonte-Nelson, 2010). For the remainder of this review, we focus on the activational effects of female steroid hormones on cognitive function and brain health during aging in females, defining these effects as transient and depending on the presence of hormone.

Menopause Etiology

Studies have shown that ovarian hormone loss negatively impacts cognition in women, and that these effects correspond to the associated estrogen deficiency (Farrag et al., 2002; Phillips and Sherwin, 1992; Sherwin, 1988). Others have shown modest, statistically significant declines in cognitive performance in women after surgical menopause, but express that the effects were small and not likely to be of clinical significance (Kritz-Silverstein and Barrett-Connor, 2002). In numerous studies, cognitive decline has been seen in women after surgical menopause (Farrag et al., 2002; Phillips and Sherwin, 1992; Sherwin, 1988). For example, surgical menopause negatively impacted performance on tests of global cognitive function by three months after surgical ovarian hormone loss, an effect that persisted six months post-surgery (Farrag et al., 2002). Further, surgically menopausal women demonstrated lower memory scores relative to naturally menopausal women, and age of oophorectomy (surgical ovary removal) and greater years since surgery correlated with poorer performance (Nappi et al., 1999). A recent longitudinal study evaluating 1903 women from 2000–2006 found decreased cognitive processing speed in women during late perimenopause, effects not attributed to depression, anxiety, sleep irregularities, or vasomotor symptoms (Greendale et al., 2010). Memory complaints were also associated with poorer memory encoding in women transitioning into menopause, and this was predicted by estrogen levels (Weber and Mapstone, 2009). Moreover, a recent elegantly performed study evaluated cognitive change across time in postmenopausal women, controlling for age and education (Thilers et al., 2010). Results showed a decline in verbal fluency with postmenopause, as well as declines in visuospatial ability and episodic memory measures; the latter effects were greater in women with a body mass index over 25, as compared to those with a lower body mass index considered within the normal range (18.5–25; Thilers et al., 2010). Together, results in women support the hypothesis that decreases in endogenous estrogen levels concordant with postmenopause have a negative influence on cognitive abilities, although this effect is modest in some studies, and may depend on several factors including women's stage of the menopause transition, time since menopause induction if surgical, and body mass index. Age may be another factor, as increased risk of cognitive impairments was found in surgically menopausal women, and risk increased with younger age at surgery (Rocca et al., 2007).

Preclinical evaluations in rats also provide evidence that ovarian hormone loss impacts cognition. Because these preclinical studies allow methodical manipulation of factors that could impact outcome, the results from these studies can systematically demonstrate that hormone effects depend on many factors, including age (Bimonte-Nelson et al., 2003; Bimonte-Nelson et al., 2004b; Bimonte et al., 2003; Markowska and Savonenko, 2002; Savonenko and Markowska, 2003; Talboom et al., 2008). Indeed, cognitive decrements on spatial and non-spatial tasks have been observed in young adult rats in response to surgical menopause (Ovx) (Bimonte and Denenberg, 1999; Daniel et al., 1999; El-Bakri et al., 2004; Feng et al., 2004; Gibbs and Johnson, 2008; Singh et al., 1994; Talboom et al., 2010; Wallace et al., 2006). In contrast, Ovx in aged rats may be beneficial to cognition. Our laboratory showed that Ovx impaired working memory on the water radial arm maze in young animals (Bimonte and Denenberg, 1999), yet, initially to our surprise, years later we found Ovx-induced cognitive enhancements on the same task with aged Ovx animals performing better than ovary-intact age-matched sham animals (Bimonte-Nelson et al., 2003). Moreover, we have replicated this finding multiple times, and our research indicates that the Ovx-induced enhancements are likely due to removal of elevated progesterone levels seen with estropause in the rat (Bimonte-Nelson et al., 2003; Bimonte-Nelson et al., 2004b; Braden et al., 2010). At this point then, we know that Ovx in young animals is detrimental, and Ovx in aged animals is beneficial, for water radial arm maze working memory scores. The next question is, "when during aging does Ovx transition from

detrimental to beneficial for the rat?". The cognitive effects of Ovx during middle age are less clear, as only a few studies have evaluated Ovx effects on maze learning and memory in middle-aged rats (Acosta et al., 2009a; Bimonte-Nelson et al., 2006; Markowska and Savonenko, 2002; Savonenko and Markowska, 2003; Talboom et al., 2008). In middle-aged females 12–16 months-old, Ovx did not impact spatial reference memory (Acosta et al., 2009a; Bimonte-Nelson et al., 2006; Markowska and Savonenko, 2002; Talboom et al., 2008) or spatial working memory (Acosta et al., 2009a; Markowska and Savonenko, 2002; Savonenko and Markowska, 2003), as well as tasks on which either a spatial or non-spatial strategy can be used for successful performance (Markowska and Savonenko, 2002; Savonenko and Markowska, 2003). Deficits in spatial working memory were, however, detected in 17 month old Ovx rats following high-demand time delayed memory retention tests (Markowska and Savonenko, 2002). Thus, Ovx-related memory changes during middle-age may become evident when working memory demands are more challenging. In this regard, we previously demonstrated that the cognitive effects of Ovx in both young and old rats were more pronounced as working memory load increased (Bimonte-Nelson et al., 2003; Bimonte-Nelson et al., 2004b; Bimonte and Denenberg, 1999; Braden et al., 2010). Hence, increasing the working memory demand, either by extending time delays to challenge retention, or by increasing the number of items to remember, facilitates a broader scope of evaluations to realize Ovx-induced memory changes across the ages. A study methodically testing the effects of Ovx at different ages ranging from young adulthood to old age is necessary to determine the age at which Ovx transitions from detrimental to beneficial. Determining brain changes associated with this transition are not only important for clarifying mechanisms of menopause-related learning and memory alterations, but could also yield valuable information on underlying mechanisms of cognitive aging and potential mechanisms of hormone therapy-induced enhancements.

Preclinical research in rats has yielded much insight regarding the cognitive impact of Ovx effects across the life-span. Of note, the majority of women undergo menopause as a transitional loss of ovarian hormones due to age-related alterations of the hypothalamus, pituitary, and ovary, ultimately resulting in ovarian follicular depletion, rather than an abrupt loss of ovarian hormones via oophorectomy (Quirion et al., 1995). In addition, there are distinct differences in the mechanism and hormone profile of senescent female rats and women that preclude the use of the ovary-intact aging female rat as the sole and optimal model for menopause. In women, menopause occurs at about the fifth decade of life and is characterized by loss of ovarian-derived circulating hormones, including estrogen and progesterone (Quirion et al., 1995). For both women and female rats, neuronal changes in the hypothalamus are hypothesized to initiate the transition into reproductive decline, leading to reproductive senescence (Downs and Wise, 2009). However, the ultimate hormone profile of ovary-intact reproductively senescent female rats and woman differ, limiting the use of the normally aging female rat as an optimal model of human menopause. Nonetheless, the rodent model provides insights into mechanisms of menopause since there are some commonalities in reproductive physiology (Downs and Wise, 2009). In women, as aging ensues, estrogen and progesterone decline due to decreased ovarian follicular reserves (Quirion et al., 1995). Thus, menopause is the cessation of ovarian cyclicity, ultimately caused by ovarian follicular depletion. In contrast, the aging rat undergoes estropause, a persistent estrus state due to chronic anovulation rendering intermediate estrogen levels, or a pseudopregnant/persistent diestrus state characterized by high progesterone levels due to increased ovulation and corpora lutea (Meites and Lu, 1994). These changes in ovarian-derived hormone release in the rat are primarily due to hypothalamic/pituitary axis alterations (Downs and Wise, 2009; Meites and Lu, 1994). Thus, the primary mechanism that ultimately results in reproductive senescence and circulating hormone alterations in the woman is ovarian follicular depletion, while in the rat it is the hypothalamic-pituitary axis.

Transitional hormone loss can be induced in rodents via administration of the industrial chemical 4-vinylcyclohexene diepoxide (VCD) (Mayer et al., 2002; Mayer et al., 2004; Springer et al., 1996). VCD produces follicular depletion by selectively destroying primordial and primary follicles via acceleration of the natural process of atresia, resulting in hormone profiles in rodents that are more similar to naturally menopausal women as compared to Ovx (Mayer et al., 2002; Mayer et al., 2004; Springer et al., 1996; Timaras et al., 1995). We recently showed that VCD-induced transitional menopause impaired learning of a spatial recent memory task (Acosta et al., 2009a). We also demonstrated that rats undergoing transitional menopause before Ovx was better for spatial memory than an abrupt loss of hormones via Ovx without the prior transition (Acosta et al., 2009a). Nappi et al. (1999) showed that in women poorer cognitive scores corresponded with a longer duration of hormone deprivation from oopherectomy. It is of note that in that study, surgically menopausal women were younger at menopause than naturally menopausal women. Therefore, it is plausible that those surgically menopausal women did not undergo an extended period of transitional menopause before surgical menopause, and thus did not have benefits due to a transitional hormone decline prior to oophorectomy. In fact, Rocca et al. (2007) found that women that had undergone oophorectomy prior to menopause onset showed an elevated risk of cognitive impairment as compared to age-matched women without oopherectomy. In addition, risk of cognitive impairment increased as age at oopherectomy decreased, which presumably limited the duration of transitional menopause. Further evaluations of women receiving oopherectomy before, versus after, transitional menopause will better discern whether history of transitional menopause before surgical ovarian removal affects subsequent cognitive change. It is possible that an as yet undetermined duration of transitional menopause before oopherectomy is optimal for cognitive outcome, a tenet supported by the animal literature; indeed, this would obviate the abrupt ovarian hormone loss associated with oopherectomy.

Estrogens

Estrogens are a class of hormones including 17β-estradiol, estrone, and estriol. 17β-estradiol is the most potent naturally-circulating estrogen, followed by estrone and estriol, in order of receptor affinity (Kuhl, 2005; Sitruk-Ware, 2002). Since the first controlled clinical evaluation showing that 17β-estradiol injections enhanced memory in 75 year-old women (Caldwell and Watson, 1952), numerous studies have demonstrated cognitive decline after ovarian hormone loss, and enhancement after treatment with various types of estrogen-containing preparations, in menopausal women (for a review see Sherwin, 2006). Conjugated equine estrogens (CEE; tradename Premarin), is the most commonly prescribed hormone therapy given to women (Hersh et al., 2004). CEE contains the sulfates of at least ten estrogens, is over 50% estrone sulfate, 20–25% equilin sulfate, and has only trace amounts of 17β-estradiol. After CEE is metabolized, the resulting primary circulating hormones are estrone and, after estrone's conversion, 17β-estradiol, as well as equilin (Bhavnani, 2003; Sitruk-Ware, 2002). It is hypothesized that these three metabolites are primarily responsible for the estrogenic effects of CEE (Sitruk-Ware, 2002), although there are other estrogens and related metabolites that could initiate effects on their own; these hormones include, but are not limited to equilin, $\Delta^{8,9}$ dehydroestrone, dihydroequilin-17β, and equilenin (Kuhl, 2005).

The cognitive effects of CEE are mixed. CEE-containing therapy improves memory in studies of women utilizing self-report (Campbell and Whitehead, 1977), case studies (Ohkura et al., 1995) and randomized psychometric evaluations (Kantor et al., 1973). Yet, findings evaluating global cognitive function in the large placebo-controlled Women's health Initiative (WHI) Memory Study (WHIMS) demonstrated an increase in probable dementia risk and no effect on mild cognitive impairment in women 65 years or older taking

the combination therapy CEE + the progestin, medroxyprogesterone acetate (MPA, Shumaker et al., 2003). CEE alone showed a non-significant increase in incidence of probable dementia and mild cognitive impairment (Espeland et al., 2004; Shumaker et al., 2004). The WHI Study of Cognitive Aging (WHISCA), an ancillary study to the WHI testing more specific cognitive functions, in women 65 and over free of probable dementia, reported that CEE+MPA therapy had a negative effect on verbal memory and a trend for positive effects on figural memory (Resnick et al., 2006). Most recently, the WHIMS-MRI study found that CEE use with or without MPA was associated with small but measurable atrophy in the frontal cortex and hippocampus, brain regions important for cognition (Resnick et al., 2009). Thus, there is currently little consensus in clinical studies regarding the cognitive impact of estrogen-containing therapy. New investigations clarifying the complex effects of ovarian hormone loss and hormone therapies given to women during aging are warranted.

Crucial to advancement of the field is identifying the various administration parameters and components of hormone therapies that impact outcomes on cognition. Detailed hypothesis-driven and methodical assessments using basic science and system approaches are optimal for converging the many findings that seem contradictory. With emerging data and results from these types of studies, it is becoming clear that the cognitive effects of hormone therapy may not be contradictory at all. Findings may, in fact, be dependent on numerous variables not yet taken into account. One way to further our understanding of the impact of gonadal hormone loss and therapeutic interventions on cognition is by using animal models. Rodent models have been invaluable in providing insight into the cognitive effects of hormone therapies administered after hormone loss, while enabling experimental control not possible in human research. Most preclinical studies have utilized 17β-estradiol to test cognitive effects of hormone therapy in Ovx animals. For example, numerous studies have reported beneficial effects of 17β-estradiol on spatial learning and memory in young (Bimonte and Denenberg, 1999; Daniel et al., 1997; Daniel et al., 1999; Dohanich et al., 1994; Galea et al., 2001; Holmes et al., 2002; Luine et al., 1998; Luine et al., 2003; Marriott and Korol, 2003; McLaughlin et al., 2008; Packard and Teather, 1997b; Sandstrom and Williams, 2001) and in middle-aged or older female rats (Bimonte-Nelson et al., 2006; Foster et al., 2003; Gibbs, 2000b; Markham et al., 2002; Markowska and Savonenko, 2002; Savonenko and Markowska, 2003; Talboom et al., 2008; Ziegler and Gallagher, 2005). Effects of 17β-estradiol treatment in young and middle-aged rodents are also observed on the non-spatial visual object recognition task whereby animals are tested on whether they “recognize” a novel object (operationally defined by increased exploration of the novel object; Fernandez et al., 2008; Lewis et al., 2008; Luine et al., 2003).

Recently, our laboratory examined the effects of both tonic and cyclic CEE. In these rodent studies, the doses of CEE administered were relevant to what women take as hormone therapy, with the clinically-used dose only adjusted for body weight. We demonstrated that CEE enhanced spatial working memory and delayed memory retention, and protected against cholinergic challenge on spatial tasks, in Ovx middle-aged rats (Acosta et al., 2009b; Engler-Chiurazzi et al., 2011). Further, a single high dose CEE injection enhanced non-spatial working memory object recognition (Walf and Frye, 2008). However, low CEE doses have been shown to impair spatial working and reference memory performance (Barha and Galea, 2012; Engler-Chiurazzi et al., 2011), an effect we hypothesized to be due to higher circulating levels of estrone relative to 17β-estradiol, resulting after specific doses of CEE administration (Engler-Chiurazzi et al., 2011). Indeed, animals receiving low dose CEE showed increased serum estrone levels, while no increases were found in 17β-estradiol levels, relative to control animals (Enger-Chiurazzi et al., 2011; but see, Barha & Galea, 2012). Moreover, increases in circulating estrone levels were associated with greater

working memory errors in rats (Barha and Galea, 2012) and lower cognitive scores in women (Yaffe et al., 1998).

Therefore, our next goal was to methodically evaluate the impact of estrone on learning and memory in middle-aged rats. In contrast to the beneficial effects of CEE in Ovx rats, estrone treatment impaired spatial working memory and memory retention, and did not alter number of choline acetyltransferase (ChAT, the synthesizing enzyme of acetylcholine)-positive basal forebrain neurons, as 17β-estradiol does (Engler-Chiurazzi et al., 2011). Hence, evidence thus far indicates that estrone, the primary active metabolite after CEE administration in rats and women, is detrimental for cognition. To extend evaluations to other CEE components, we tested the cognitive effects of $\Delta^{8,9}$-dehydroestrone and equilin, two CEE components identified to be neuroprotective *in vitro* (Zhao and Brinton, 2006). We found that chronic $\Delta^{8,9}$-dehydroestrone treatment enhanced memory, whereas equilin had no effect, in Ovx rats (Talboom et al., 2008). Thus, other CEE components may have functional benefits on cognition, providing new treatment opportunities.

Responsiveness to estrogens may depend on many variables other than type of estrogen, including age. Young and middle-aged Ovx rats showed beneficial effects of 17β-estradiol treatment on the spatial reference memory Morris water maze task, and higher circulating 17β-estradiol levels correlated with better performance (Talboom et al., 2008). In contrast, aged Ovx rats were not responsive to the same 17β-estradiol regimen that enhanced spatial reference memory in young and middle-aged Ovx rats (Talboom et al., 2008), concurring with age-related interactions with 17β-estradiol replacement for spatial memory shown by others (Foster et al., 2003). However, some studies have shown that aged female rodents can exhibit cognitive enhancements after 17β-estradiol treatment. For example, 17β-estradiol injections enhanced spatial reference memory in 27–28 month old ovary-intact mice (Frick et al., 2002). The difference in results may relate to the type of 17β-estradiol administration as a cyclic versus tonic regimen. In this regard, for cognition, cyclic 17β-estradiol treatment enhanced responsiveness to tonic 17β-estradiol treatment in older Ovx rats (Markowska and Savonenko, 2002).

In addition to age, estrogenic effects on cognition may be influenced by many other factors including, but not limited to, timing of hormone administration relative to hormone loss, dose, mode of treatment, and whether progestogens are administered concomitantly. Some of the translational questions driving much of the newer preclinical research studying estrogens' impact on brain health and cognition during aging have been directly spawned from the WHIMS findings. Women participating in the WHIMS were between 65–79 years old, and had experienced ovarian hormone deprivation for a substantial amount of time prior to receiving CEE treatment (Shumaker et al., 1998). These findings beg the question of whether there is a window of opportunity for which hormone therapy can be effective. Indeed, recent preclinical studies found evidence of this. 17β-estradiol given immediately after Ovx enhanced spatial memory performance in middle-aged rats, but had no benefit when given 5 months after Ovx (Daniel et al., 2006). Additionally, 17β-estradiol treatment given immediately after Ovx increased cholineacetyltransferase (ChAT) levels in the hippocampus, an increase not seen when initiated 5 months after Ovx; the opposite pattern was seen in prefrontal cortex, wherein 17β-estradiol treatment given 5 months after Ovx, but not immediately after Ovx, increased prefrontal cortex ChAT levels (Bohacek et al., 2008). Further, 17β-estradiol given immediately or 3 months after Ovx, but not 10 months after Ovx, enhanced delayed-match-to-position performance (Gibbs, 2000b). There may also be a critical window for the well-established findings that 17β-estradiol regulates dendritic spines in the hippocampus (Woolley, 2000); we found that a 10 week delay after Ovx attenuated the effectiveness of 17β-estradiol-induced increases in CA1 apical spine density, as compared to treatment given immediately (McLaughlin et al., 2008). Further, increased cell

proliferation was observed in the dentate gyrus when 17β-estradiol was administered 1 week, but not 4 weeks, after Ovx (Tanapat et al., 2005). Thus, clinical and preclinical findings concur that the beneficial effects of estrogens may be dependent on early initiation relative to ovarian hormone loss (Khoo et al., 2010; Sherwin, 2005). However, the specific temporal parameters of these effects have not been discerned, and it remains unclear whether these findings can be extended to estrogens other than 17β-estradiol.

Important to the discussion of parameters contributing to the complexity involved in the cognitive impact of hormone therapy, is the consideration of menopause history (surgical or transitional). Although our laboratory recently found that CEE was beneficial for cognition (Acosta et al., 2009b; Acosta et al., 2010), we observed that these benefits were limited to rats that had undergone surgical menopause (Acosta et al., 2010). In surgically menopausal (Ovx) rats, CEE enhanced reference and working memory (Acosta et al., 2010). In contrast however, VCD-induced transitionally menopausal rats showed the opposite effect after CEE administration, with a CEE-induced increase in errors on these measures (Acosta et al., 2010). Further, CEE-treated Ovx rats showed better memory retention across an 8-hr delay relative to vehicle-treated Ovx rats, while CEE exerted no retention benefit in VCD transitionally menopausal rats (Acosta et al., 2010). Thus, CEE was beneficial after surgical menopause, but detrimental after transitional menopause (Acosta et al., 2010). Accordingly, human studies evaluating surgically menopausal women after hormone treatment show cognitive benefits of hormone therapy (Phillips and Sherwin, 1992; Sherwin, 1988), consistent with our CEE findings in Ovx rats (Acosta et al., 2009b; Acosta et al., 2010; Engler-Chiurazzi et al., 2011). Reports of positive effects of hormone therapy in studies including only oophorectomized women, and the current findings of differential cognitive effects of CEE depending on menopause history in the rodent model, collectively suggest that menopause history is a plausible factor that contributes to cognitive efficacy of hormone therapy.

Progestogens

Progestogens include steroids with a pregnane skeleton, including naturally-occurring progesterone as well as progestins (synthetic progesterones). Inherent to any discussion on the impact of hormone therapy on cognition, and the complexities involved in outcome, is that of combination therapy, which includes estrogen plus a progestogen concomitantly. Investigating combination therapy is crucial since women with a uterus taking estrogens must include a progestogen in their regimen to offset the increased risk of endometrial hyperplasia associated with unopposed estrogen treatment (Smith et al., 1975). Progestins may have a negative impact on cognition in women. For example, findings demonstrated that menopausal women taking CEE alone did not significantly differ from those taking placebo for dementia diagnoses in the WHIMS (Shumaker et al., 2004); in contrast, twice as many women receiving CEE plus the synthetic progestin MPA were diagnosed with dementia as compared to the placebo group in the WHIMS (Shumaker et al., 2003).

Rodent models have been instrumental in deciphering some of the complexities associated with combination therapy. In a rodent study of combination treatment, we showed that natural progesterone abolished 17β-estradiol-induced benefits on the spatial reference memory Morris water maze in middle-aged rats (Bimonte-Nelson et al., 2006). Additionally, while natural progesterone or 17β-estradiol alone did not influence performance on the Morris water maze (Chesler and Juraska, 2000), progesterone plus 17β-estradiol injections did impair performance (Chesler and Juraska, 2000; Lowry et al., 2010). These effects were not seen on the non-spatial Morris water maze, suggesting combination treatment has specific effects within the spatial domain (Chesler and Juraska, 2000). These effects may, however, be specific to reference memory, as long-term progesterone treatment enhanced

17β-estradiol's effects on the working memory delayed-match-to-position spatial t-maze (Gibbs, 2000b) (but see Chisholm and Juraska, 2012).

In both clinical and preclinical studies, progesterone administration has been associated with cognitive detriment. In pregnant women, there is the reported "maternal amnesia" phenomenon, hypothesized to result from high circulating progesterone levels during late pregnancy (Brett and Baxendale, 2001). Progesterone-induced memory detriments are also seen in healthy women; indeed, healthy women given a high oral progesterone dose showed cognitive impairment (Freeman et al., 1992). High circulating progesterone levels are evident following estropause in the rat (Lu et al., 1979). Many aged female rats enter a pseudopregnant estropause state, whereby progesterone values become significantly elevated but 17β-estradiol levels remain relatively unchanged (Huang et al., 1978; Wise and Ratner, 1980). This pseudopregnant state has been associated with impaired spatial memory (Warren and Juraska, 2000). Similarly, on the spatial Morris water maze, young cycling rats performed best during the estrus phase, when estrogen and progesterone levels are at their lowest, and worst during the proestrus phase, when estrogen and progesterone levels are at their highest (Warren and Juraska, 1997) (but see Berry et al., 1997; Stackman et al., 1997). Further, in contrast to the detrimental effects of Ovx in young animals, in aged female rats Ovx improves cognition (Bimonte-Nelson et al., 2003; Bimonte-Nelson et al., 2004b), an effect likely due to the removal of elevated progesterone levels seen with estropause. We have also shown that progesterone administration impairs spatial working and reference memory, and reverses the beneficial effects of Ovx seen in aged rats (Bimonte-Nelson et al., 2004b; Braden et al., 2010).

Since the synthetic progestin, MPA, is the progestin component in the commonly perscribed hormone therapy, Prempro®, it was a goal of our laboratory to examine the impact of MPA on a cognitive battery in a controlled rodent experiment. We found that MPA impaired memory retention after a delay on the water radial arm maze, and exacerbated overnight forgetting on the spatial reference memory Morris water maze task (Braden et al., 2010). MPA treatment also impaired spatial working memory, and detriments were particularly pronounced as the working memory load increased (Braden et al., 2010). Of note, MPA is also the sole hormone in the contraceptive Depo Provera®. While no clinical study has directly evaluated the impact of MPA on cognitive health in younger women using this contraceptive, one case study reported amnesic effects corresponding with Depo Provera® use in young women (Gabriel and Fahim, 2005). To further investigate our findings of MPA-induced cognitive impairments during aging, we conducted a study evaluating the long-term effects of MPA. Results showed that MPA administration in either young adulthood, middle-age, or at both times, impaired working memory when measured at the middle-aged time point (Braden et al., 2011). The deleterious effects of MPA were greater when animals received treatment during both young adulthood and middle-age, as impairments were observed on 2 orthogonal measures of working memory and, in particular, on trials with higher working memory demand (Braden et al., 2011). Further, combination MPA plus 17β-estradiol treatment was detrimental on the spatial reference memory Morris water maze task relative to other hormone-treated groups, including progesterone plus 17β-estradiol treatment (Chisholm and Juraska, 2012). The detrimental effects of MPA in combination with 17β-estradiol may be task and cue-use dependent, as chronic administration of MPA plus 17β-estradiol was beneficial on an alternation t-maze task, a task which can be solved using either a spatial or a non-spatial strategy (Chisholm and Juraska, 2012).

Collectively, evidence spanning clinical and basic science indicates progestogens negatively impact neuronal health, which could result in detrimental effects on brain functions such as learning and memory. Progesterone abolishes the beneficial effects of 17β-estradiol

(Bimonte-Nelson et al., 2006; Harburger et al., 2007) (but see Gibbs, 2000b) and attenuates 17β-estradiol's neurotrophic effects *in vivo* (Bimonte-Nelson et al., 2004a) and in vitro (Aguirre and Baudry, 2009). Progesterone has been shown to have neuroprotective properties, while MPA does not (Nilsen and Brinton, 2002). Relative to progesterone, MPA causes greater attenuation of 17β-estradiol-induced neurotrophic actions (Nilsen and Brinton, 2002). Thus, while a progestin is necessary as part of hormone therapy in women that have a uterus (Smith et al., 1975; Ziel and Finkle, 1975), accumulating evidence indicates that the addition of a progestin does not result in a positive impact on brain health and function during aging. Progestins are an important and necessary component of hormone therapy for many women and should not be undervalued. A systems and personalized approach, valuing and accounting for multiple aspects of women's health, is key to optimizing hormone therapy.

Androgens

Androgens are typically thought of as a "male" hormone; a masculinizing hormone which initiates permanent organizational effects on the male brain during a specific critical period in early development, and an activating hormone for male sex behaviors in adulthood. Why study androgens in females as a potential modulator of learning and memory? From our perspective, studying the impact of androgens on cognition in the female rodent model is important for several reasons. First, androgens bind to and activate the androgen receptor, which are expressed in the female brain. In particular, brain areas found to be important for cognition, such as the hippocampus and cerebral cortex, have been shown to express high concentrations of androgen receptors in female rodents (Simerly et al., 1990). Second, activation of these androgen receptors could ultimately impact cognition, as it results in changes in neuronal function via altering gene transcription (McPhaul and Young, 2001). Third, levels of androgen receptors in cognitive brain regions have been found to be modulated by Ovx and androgen administration, showing that androgen receptor levels are dependent upon circulating levels of androgens (Lu et al., 1998). It is therefore clear that androgens play an important role in normal brain functioning in female rodents. How androgens impact cognition in female rodents is still being deciphered, as research in this area is consistently emerging. This portion of the review will focus on the androgens that have been most studied, which are testosterone, dihydrotestosterone (DHT), and androstenedione.

Relations between endogenous testosterone levels and cognition have been noted in younger and older individuals. In general, the strongest associations have been seen in the older population in retrospective and randomized treatment studies. For example, testosterone was related to cognitive performance in young men and women, and spatial ability was related to seasonal changes in accordance with related alterations in testosterone levels (Kimura and Hampson, 1994; Neave et al., 1999; Silverman et al., 1999). Some evidence suggests an inverted U-shaped function for testosterone levels and spatial ability, with moderate levels optimal. An excellent example of this U-shaped function, which also exemplifies the importance of a broad perspective when analyzing the cognitive effects of hormones, is shown via the innovative insight of Dr. Doreen Kimura. For example, in one study, when males and females were both included in analyses, the perspective of an inverted U-shaped function was realized; this was not clearly evident when the sexes were analyzed separately. Specifically, higher relative levels of salivary testosterone were associated with better spatial ability performance in women, and lower relative levels of salivary testosterone were related to better spatial ability performance in men (Gouchie and Kimura, 1991).

Testosterone's mnemonic effects could be due to either DHT, or to conversion into estrogen; testosterone can be converted to either DHT, which binds to androgen receptors via 5α

reductase, or to estrogen via the aromatase enzyme (Becker, 1995). Several studies have been conducted assessing the impact of various types of androgens on cognition in the female rodent model. Bernice and Rader (2009) assessed the impact of androgen supplementation on cognition in the aged (20 to 22 month old) female mouse model by administering either testosterone, testosterone's metabolite DHT, or vehicle, and testing them on the Morris water maze, novel object recognition, and passive avoidance. Testosterone, but not DHT, improved performance on the Morris water maze compared to vehicle suggesting that testosterone's conversion to estrogens may relate to the impact of testosterone treatment for spatial reference memory (Benice and Raber, 2009). Enhancements may be specific to spatial navigation, since testosterone did not impact any other measure (Benice and Raber, 2009). In addition, DHT, but not testosterone, impacted passive avoidance scores, and neither DHT nor testosterone affected novel object recognition scores (Benice and Raber, 2009). Androgen-induced enhancements may be of a broader nature in younger animals, as administration of either DHT or testosterone enhanced performance on the Y maze, passive avoidance, and novel object recognition in 3 month old Ovx rats (Frye and Lacey, 2001). In this study, hormones were given post-training, thereby obviating issues of motivational or other non-cognitive factors that could impact interpretation of effects.

We have recently found evidence that the androgen androstenedione negatively impacts cognition in the female rat. This discovery was initially made via a correlational analysis between endogenous androstenedione levels and maze error scores, and then confirmed with experimental manipulation whereby androstenedione was exogenously administered (Acosta et al., 2009a; Acosta et al., 2010; Camp et al., 2012). Initially, we demonstrated that transitionally menopausal (VCD treated) middle-aged female rats exhibited superior cognitive scores across multiple domains, as compared to rats that had undergone surgical menopause. However, this effect was only apparent when the post-VCD follicle-deplete ovary was removed via Ovx. One of the more surprising findings from this study was that higher serum levels of androstenedione, which is released from the follicle-deplete menopausal ovary, correlated with poorer memory scores in VCD rats (Acosta et al., 2009a). In a follow-up study evaluating cognitive effects of CEE hormone therapy in transitionally and surgically menopausal rats, we again found a correlation between higher androstenedione levels and impaired performance in transitionally menopausal rats (Acosta et al., 2010). This correlation was evident for reference memory and two orthogonal working memory measures (Acosta et al., 2010). Importantly, these correlations were shown in ovary intact animals that had VCD treatment, which renders an androgen-rich environment from the postmenopausal ovary (Acosta et al., 2009a; Acosta et al., 2010). If androstenedione is in fact related to poorer memory, impairments should be evident after androstenedione administration to a "blank" ovarian hormone template. We tested this hypothesis in a study in which middle-aged (14 month old) Ovx rats were treated with one of two doses of androstenedione, or vehicle, and tested on a cognitive battery. Androstenedione administration that resulted in blood levels at the higher end of the physiological range in the female rat impaired spatial reference memory on the Morris water maze, impaired performance on the water radial arm maze when the working memory load was at its greatest, and impaired memory retention on a win-stay delay match to sample task, as compared to vehicle treatment (Camp et al., 2012). Thus, a correlation in the rat model showing that higher endogenous androstenedione levels were related to poorer memory performance led to methodical investigation and manipulation in the rat model; results showed that this androgen, released from the follicle-deplete ovary in both women and rats, markedly impairs memory.

Gonadotropins

Although it is well established that the gonadotropins follicle stimulating hormone (FSH) and lutenizing hormone (LH) are involved in regulating reproductive functions via negative and positive feedback loops, increasing evidence is indicating that gonadotropins, directly or indirectly, impact cognitive function as well, including within the spatial domain. Although the links between FSH and cognition do not appear to be realized (e.g., Acosta et al., 2009a; Luetters et al., 2007), there is strong evidence that LH is related to cognition, with the greatest support coming from the neurodegenerative disease literature (Webber et al., 2007). Supporting plausibility of LH effects on the brain and spatial cognition, it is of note that LH can cross the blood-brain-barrier (Lukacs et al., 1995). In addition, the highest density of LH receptors in the brain are found in the hippocampus (Lei et al., 1993; Zhang et al., 1999), a brain region intimately involved in spatial learning and memory, and affected by aging and AD.

We recently evaluated VCD-induced follicular depletion and Ovx effects on cognition in the middle-aged rat, and found a clear inverted U-shaped function for serum LH and number of spatial memory errors, with the highest and lowest LH levels associated with the best performance (Acosta et al., 2009a). A comparable effect was not seen with FSH (Acosta et al., 2009a). This relationship between LH and performance became apparent in scatterplots including all treatment groups, so that the range of values across groups could be noted (conceptually similar to Kimura's procedure described above; Gouchie and Kimura, 1991). This range of values was broad, because, as expected, Ovx increased LH levels due to a lack of ovarian hormone negative feedback after ovarian hormone loss, while sham control animals showed LH values in a lower relative range. When LH levels ranged from approximately 0-to-2 ng/ml, higher LH levels correlated with worse maze performance thereby revealing a positive relationship with errors. However, when LH levels ranged from approximately 2-to-10 ng/ml, higher LH levels correlated with better maze performance thereby revealing a negative relationship with errors (Acosta et al., 2009a). We noted a striking inverted U-shaped function when the groups were combined into the same scatterplot. This pattern was seen for multiple measures, including both spatial working memory and spatial reference memory. While there are limitations in this study in interpreting this relationship because LH levels were confounded by group membership, this quadratic relationship is nonetheless remarkable. Understanding this relationship between LH and memory can have clinical significance, especially given increasing evidence that LH levels are linked to pathologies associated with neurodegenerative disorders, as well as cognition (Webber et al., 2007). There are other studies reporting that higher LH levels are related to better cognitive performance, similar to the effects seen in our study in the Ovx animals. For example, tonic LH-releasing hormone treatment to elevate LH concentrations to Ovx levels, enhanced performance on visual-discrimination in young rats (Nauton et al., 1992), and enhanced non-spatial working memory in aged rats (Alliot et al., 1993). Relations between higher LH and better memory in these studies are likely related to LH levels being increased to that of Ovx animals. In contrast, corresponding with the Acosta et al. (2009a) findings in ovary-intact animals that higher LH levels correlated with poorer cognitive performance, in aged ovary-intact female mice, experimentally-induced LH attenuation decreased amyloid-β concentrations and enhanced cognition, while LH increases promoted biochemical brain changes consistent with AD; however, none of these studies correlated circulating LH levels with memory scores in individual subjects (Bowen et al., 2004; Casadesus et al., 2006; Casadesus et al., 2007). Other supporting evidence shows that men and women with AD had higher circulating LH levels than controls (Bowen et al., 2004; Short et al., 2001).

The growing literature evaluating the relationship between LH levels and cognitive performance suggests that it may subserve an inverted U-shaped function, with lower and higher levels resulting in optimal learning and memory, and intermediate levels resulting in poorest learning and memory. This is an important area that will require further study, with results possibly revealing important mediators of cognitive function. Effects could explain, in part, how hormone modulation impacts learning and memory.

Female Steroids and Cognition: Landmark and Most Recent Putative Mechanisms of Ovarian Hormone Action

Cholinergic and γ-Aminobutyric acid (GABA)ergic Systems

Abundant evidence suggests that the cholinergic and GABAergic systems are intimately related to the effects of female steroids on cognition. Pharmacological experiments using both peripheral and intracranial infusions show that the cholinergic system may mediate estrogen-induced effects. Much of the landmark work evaluating relations between estrogens and the cholinergic system has been done via the creative and methodical approach of combining hormones and pharmaceutical agents in the laboratory of visionary Dr. Robert Gibbs. In middle-aged Ovx rats, galanthamine, a cholinesterase inhibitor, combined with 17β-estradiol enhanced acquisition of a delayed matching to position (DMP) T-maze task relative to vehicle treatment, while the effects of 17β-estradiol or galanthamine alone did not differ from vehicle (Gibbs et al., 2011a). Donepezil, another cholinesterase inhibitor, combined with 17β-estradiol enhanced acquisition of the DMP task in animals with cholinergic lesions (<50% loss of cholinergic neurons), whereas 17β-estradiol and donepezil alone were ineffective (Gibbs et al., 2011b). 17β-estradiol has also been shown to alter cholinergic markers in the brain. In young adult Ovx rats given 17β-estradiol, maze acquisition correlated with increased ChAT activity in two targets of basal forebrain cholinergic innervation, the hippocampus and frontal cortex (Gibbs, 2002), and 17β-estradiol increased high affinity choline uptake in these regions (O'Malley et al., 1987; Singh et al., 1994). 17β-estradiol increased ChAT in the horizontal limb (Luine and McEwen, 1983; Luine, 1985; Singer et al., 1998) and in projection sites to hippocampus and cortex (Feng et al., 2004; Luine, 1985; Singh et al., 1994), and restored basal forebrain ChAT mRNA expression to levels of ovary-intact animals (Gibbs et al., 1994; McMillan et al., 1996). Lesioning the basal forebrain prevented 17β-estradiol-enhanced learning, indicating the basal forebrain is a key area through which 17β-estradiol cognitive enhancements occur (Gibbs, 2002; Gibbs, 2007). Other estrogens may also alter cholinergic markers as we recently showed that CEE enhanced the number of ChAT immunoreactive neurons in the vertical diagonal band of the basal forebrain. Estrogens may also alter cholinergic neurochemistry, as 17β-estradiol potentiated acetylcholine (ACh) release in the hippocampus during maze learning; this is especially noteworthy since the hippocampus is a primary projection site of the basal forebrain (Marriott and Korol, 2003).

Interestingly, increased release of ACh in the hippocampus may lead to muscarinic receptor M2 activation, which in turn, can suppresses the release of GABA (Birzniece et al., 2006; Daniel and Dohanich, 2001; Daniel et al., 2005). Hence, estrogen-mediated increases in ACh signaling through muscarinic activation may release hippocampal inhibition, and in turn allow for alterations in synaptic plasticity that may ultimately lead to enhanced cognition (Rudick and Woolley, 2001). However, ACh can also stimulate nicotinic receptors and activate GABA interneurons in CA1 (Alkondon et al., 1999) and several other hippocampal lamina (Alkondon and Albuquerque, 2001). Specifically, the α4β2 nicotinic receptor produces the strongest postsynaptic inhibitory current onto CA1 pyramidal neurons as compared to other nicotinic receptors (Alkondon and Albuquerque, 2001). Recently, our laboratory found that the estrogenic CEE component, $\Delta^{8,9}$-dehydroestrone, enhanced

memory and decreased hippocampal and entorhinal cortex α4β2 nicotinic receptor expression in Ovx rats, effects which correlated with better memory (Talboom et al., 2010). Hence, an estrogen-mediated reduction in hippocampal and entorhinal cortex α4β2 nicotinic receptor expression may lead to a suppression of GABA-mediated inhibition and subsequent cognitive enhancement. Progesterone has also been shown to enhance high affinity choline uptake in several cognitive brain regions, and it can potentiate 17β-estradiol-mediated increases in ChAT mRNA levels in the basal forebrain of Ovx rats (Gibbs, 1996; Gibbs, 2000a). Progesterone and progestins impact the GABAergic system, which may relate to their effects on cognition (Belelli and Herd, 2003; Braden et al., 2010; Paul and Purdy, 1992; Pazol et al., 2009; Wallis and Luttge, 1980). For example, we found that MPA impaired learning and memory, and altered hippocampal and entorhinal cortex glutamic acid decarboxylase (GAD; the synthesizing enzyme for GABA) concentrations in Ovx rats (Braden et al., 2010). Further, we demonstrated that MPA exposure during either young adulthood, middle-age, or both, produced cognitive detriments, and higher serum levels of MPA were associated with lower levels of GAD in the dorsal hippocampus (Braden et al., 2011). Understanding the possible long-term effects of MPA administration on cognition, and whether there is a subsequent long-term impact on the GABAergic system, is especially relevant as we embark on a new generation of menopausal women who were much more likely to have been prescribed contraceptives when younger, and then hormone therapy when older, as compared to generations before (Diczfalusy 1991).

The mechanism of MPA effects on cognition likely differs from the mechanism of progesterone effects on cognition. There is evidence that MPA's ring-A reduced metabolites (e.g., dihydroMPA and tetrahydroMPA) do not directly bind to the GABAA receptor (McAuley et al. 1993), as do natural progesterone's ring-A reduced metabolites (Paul and Purdy 1992). However, MPA might alter progesterone's metabolic conversions (Penning et al. 1985), which could be related to MPA-induced enhanced synaptic and extrasynaptic GABAA receptor-mediated inhibition (Belelli and Herd 2003) and changes in GAD (Braden et al. 2010). In fact, the same decrease in GAD levels in the dorsal hippocampus after administration of the GABAA agonist diazepam (Raol et al. 2005) indicates that MPA-induced decreases in GAD are a consequence of increased GABAA receptor activation.

Adult Neurogenesis

Adult neurogenesis is the process whereby new-born neurons are produced from progenitor cells populations in the adult central nervous system (Ming and Song, 2011). Whether neurogenesis has a functional impact on cognition has yet to be conclusively determined. However, the literature thus far indicates that female steroids do, in fact, have an effect on many experimental measures and parameters of neurogenesis. Some very recent studies have evaluated the potential effects that estrogens have on cognitive function. For example, 17β-estradiol, but not estrone, increased activation of new neurons in the dentate gyrus of young adult Ovx rats in response to the retrieval of spatial memory (McClure et al., 2012). However, the estrogenic-induced differences in this activation of new neurons do not seem to translate into regulation of cognitive behavior, as there were no differences in spatial memory between the treatment groups. Similarly, tonic low dose CEE treatment increased the number of new neurons in the dentate gyrus (Barha and Galea, 2012); however, these rats showed impaired spatial working and reference memory, again indicating that increases in neurogenesis do not necessarily parallel cognitive outcome. These divergent results between an effect on brain versus an effect on cognition stress the importance of testing functional outcome of brain changes, as brain changes do not always translate to cognitive changes.

Relative to the number of studies testing the effects of estrogens on neurogenesis, the impact of progesterone on neurogenesis is less studied. Results thus far show that progesterone

modulated the effects of 17β-estradiol on cell proliferation *in vivo* (see Pawluski et al., 2009), and the progesterone metabolite, allopregnanolone, enhanced cell proliferation *in vitro* (Wang et al., 2005). Hence, comprehensive evaluations testing the ability of progesterone alone to concurrently induce markers of neurogenesis and alter cognition using *in vivo* strategies are warranted. It is noteworthy that while female steroid effects on neurogenesis and its relation to cognitive function is a relatively new area of investigation, such interdisciplinary studies are increasing and may unveil exciting new mechanisms of steroid effects on cognition.

Signaling Cascades

The non-classic effects of ovarian steroids influence numerous signal transduction pathways, or signaling cascades, ultimately leading to modulation of protein kinases (reviewed in Falkenstein et al., 2000). Protein kinases phosphorylate many targets, and the phosphorylation event is usually the last step in a signal transduction cascade that results in a milieu of changes including functional alteration in proteins and modulation of gene transcription (Manning et al., 2002). Some of the kinases influenced by ovarian steroids, and implicated in cognition, are: mitogen-activated protein kinase (MAPK), extracellular-signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), and the mammalian target of rapamycin (mTOR). MAPK phosphorylates ERK; MAPK and ERK are the final targets of several other kinases including PI3K and Akt (i.e., PKB), and these signaling pathways modulate cognitive processes (e.g., Chen et al., 2005; Fan et al., 2010). For example, ERK activation (i.e., ERK phosphorylation) in the hippocampus is necessary for long-term memory (Kelly et al., 2003). Research has demonstrated that 17β-estradiol enhances memory via dorsal hippocampal ERK activation in Ovx mice (Fernandez et al., 2008). Indeed, dorsal hippocampal infusions of the MAPK inhibitor (U0126) blocked the memory enhancing effects of intracerebroventricular (i.c.) infusion of 17β-estradiol in Ovx mice (Fernandez et al., 2008; Zhao et al., 2010). In addition to 17β-estradiol, Orr and colleagues (2009) recently found that dorsal hippocampal infusions of progesterone increased ERK activation and the mTOR substrate S6K in the dorsal hippocampus of Ovx mice; ERK and mTOR activation were necessary for progesterone to facilitate memory. mTOR is a kinase that has effects on cell growth and proliferation via the regulation of protein synthesis (Hay and Sonenberg, 2004). mTOR is activated by ERK (Kelleher et al., 2004; Mendoza et al., 2011; Tsokas et al., 2005), and phosphorylation of 4E-BP1 and S6 in brain is regulated by the ERK pathway, which is known to play a role in synaptic plasticity (Kelleher et al., 2004). Collectively, ERK and mTOR appear to work together to influence synaptic plasticity (Hay and Sonenberg, 2004). 17β-estradiol has been shown to stimulate MAPK and PI3K via its actions at the G-protein coupled receptor 30 (GPR30) and the subsequent transactivation of epidermal growth factor receptors (Prossnitz et al., 2008). Collectively, these studies suggest that some of the cognitive effects of 17β-estradiol are mediated by GPR30 via signaling through the MAPK and ERK pathways. Furthermore, progesterone appears to enhance object memory via ERK and mTOR, while the mechanism of this effect is still under investigation.

Epigenetics

Interest in mechanisms through which the activational effects of ovarian hormone are realized has led to multi-scale molecular and genetic investigations. Broadly defined, the epigenome is a collection of heritable modifications (e.g., histone modification and DNA methylation) that alters gene transcription via mechanisms other than modification of the underlying genetic sequence (see Russo et al., 1996). Several studies have demonstrated that histone modification and DNA methylation regulate formation of hippocampal-dependent memories (e.g., Levenson et al., 2004; Miller et al., 2008), and that 17β-estradiol can mediate epigenetic change (Zhao et al., 2010; Zhao et al., 2012). Specifically, 17β-estradiol,

via MAPK/ERK signaling, increases histone acetylation (i.e., histone H3) in the dorsal hippocampus, and this histone modification is necessary for 17β-estradiol's memory enhancement in Ovx mice (Zhao et al., 2010; Zhao et al., 2012). However, how estrogen-induced modifications in the epigenome generalize to progesterone-induced and androgen-induced modifications is a question for future research. A recent study has shown that, similar to 17β-estradiol, progesterone activates ERK signaling in the dorsal hippocampus and enhances memory in Ovx mice (Orr et al., 2012), and may therefore similarly modify the epigenome.

Hormone Receptors and the Cognitive Effects of Hormones

The cognitive effects of steroid hormones discussed thus far are in part, mediated by distinct expression of receptors in the brain. Since its discovery in 1966, estrogen receptor-alpha (ERα) was the first, and thought to be the only, member of the nuclear receptor superfamily that exhibites specificity for 17β-estradiol (Toft and Gorski, 1966). It was not until 30 years later that the second ER subtype, ERα, was discovered (Kuiper et al., 1996) The two ERs share a significant degree of sequence homology; however, they also have important differences in their ligand-binding domain and unique distribution patterns in the brain, suggesting divergent roles of these receptors on biological function (Enmark et al., 1997; Matthews and Gustafsson, 2003; Tremblay et al., 1997). Of note, both ERs are found in brain regions thought to regulate cognitive function, including cerebral cortex and hippocampus (Gonzalez et al., 2007; Mitra et al., 2003; Osterlund et al., 2000; Pau et al., 1998; Register et al., 1998; Shughrue et al., 1997).

A few seminal studies have recently brought to light the importance of assessing changes in expression levels of the ERs as a function of age, as it may reflect transitions in 17β-estradiol responsiveness of the brain that ultimately lead to cognitive deficits. As aging ensues, 17β-estradiol responsiveness seems to decline as ERα expression levels decrease in human hippocampus (Ishunina et al., 2007; Tohgi et al., 1995). Similarly, ERα (Adams et al., 2002), but not ERα (Waters et al., 2011), decreases in the hippocampus of aged, compared to young Ovx rats. Some neurological diseases that affect memory, such as Alzheimer's disease, are also associated with decreased ERα and increased ERα expression in the hippocampus (Ishunina et al., 2007; Perlman et al., 2005; Savaskan et al., 2001). Furthermore, ERα polymorphisms are associated with increased incidence of Alzheimer's Disease among women (Corbo et al., 2006; Ji and Dani, 2000; Olsen et al., 2006; Yaffe et al., 2002; Yaffe et al., 2009). Collectively, these findings highlight the clinical significance of characterizing the age-related changes in ERs; in particular, decreased ERα/ ERα ratio during aging seems to be associated with cognitive deficits.

These decreases in the ERα/ ERα ratio may be age-dependently reversed by 17β-estradiol. 17β-estradiol treatment increases ERα, but not ERα, in the hippocampus of aged Ovx rats (Adams et al., 2002; Waters et al., 2011), suggesting that ERα retains 17β-estradiol responsiveness while ERα does not. In contrast, 17β-estradiol increases ERα without affecting ERα expression in the hippocampus of middle-aged ovariectomized rats (Bohacek and Daniel, 2009). This 17β-estradiol -induced ERα expression is long lasting, as it is also found in aged Ovx rats that received transient 17β-estradiol treatment discontinued 7 months prior at middle-age (Rodgers et al., 2010). Even more provocative is the finding that this prior 17β-estradiol treatment is also associated with improved memory, suggesting two intriguing tenets. The first is that 17β-estradiol has a long-term effect on ERα expression and cognitive function. Second, these long-term effects do not require 17β-estradiol to be on board at the time of cognitive testing. Significant clinical implication can be drawn by these studies, as these reports illustrate that age-related decreases in ERα/ ERα ratio are associated with cognitive dysfunction, both of which can potentially be enhanced

permanently by transient exposure to 17β-estradiol following loss of ovarian function, if initiated in earlier in life.

Delineating the individual roles of the ERs on cognition is a considerable challenge; in this regard, ER knockout (ERKO) mice are an invaluable tool. Studies using this model implicate divergent functions of ERα and ERα on cognition, depending on types of learning. For example, ERα is important for emotional learning, as performance in inhibitory avoidance task is impaired in ERαKO, but not ERαKO mice (Fugger et al., 2000). By contrast, disruption of ERα, but not ERα, impairs spatial learning on the Morris water maze, suggesting that ERα is required for spatial learning (Fugger et al., 2000; Rissman et al., 2002).

An important caveat must be considered, however, when interpreting these findings. Because ER activity is disrupted throughout development of these ERKO mice, it is difficult to distinguish between organizational and activational effects. Thus, moving forward, it becomes increasingly critical to combine other available tools with the ERKO model to circumvent this confound. Two important studies have capitalized on recent advancements in molecular and pharmacological techniques. First, Foster et al (2008) used a viral vector-mediated gene transfer to deliver the ERα gene in the ERαKO mice and found that restoration of ERα in the hippocampus improves spatial learning in Ovx animals. This finding is remarkable, given that this enhanced cognitive function is evident in the absence of 17β-estradiol treatment. This study also implies that learning deficits observed in ERαKO mice are not only due to organizational effects, but also likely to be mediated by hippocampal ERα activity in adulthood. Second, Liu et al (2008) combined the use of the selective estrogen receptor modulators (SERMs) with the ERKO model to show that 17β-estradiol or a selective ERα, but not ERα, agonist improves spatial memory in wildtype and ERαKO, but not ERαKO mice. This result gives further credence to the concept that ERα activation during adulthood is pro-cognitive in the spatial domain.

Mounting evidence from studies using SERMs corroborate the idea put forth by the ERKO model that the two ER subtypes regulate distinct learning types. Acute treatment with an ERα, but not ERα, agonist enhances performance in the spatial water maze and inhibitory avoidance (Rhodes and Frye, 2006), while ERα, not ERα, agonist enhances performance in object placement and object recognition (Frye et al., 2007). However, using similar parameters, Jacome et al (2010) reported opposite findings, implicating ERα in enhanced object placement and object recognition performance. In this case, the difference in the strain of rats used in the two studies (Long Evans versus Sprague Dawley, respectively) may have contributed to the discrepancies, as other conditions were similar. In general, species, age, and duration of treatment may also be important factors, as chronic treatment of either ERα or ERα agonists enhances cognition in young rats (Hammond et al., 2009), impair cognition in middle-aged rats (Neese et al., 2010), and has no cognitive effects in adult monkeys (Lacreuse et al., 2009). These studies underscore the complexity of factors involved in using SERMs and warrant further investigation of potential parameters that impact cognitive outcome.

Prospects of using combined tools to elucidate the distinct functions of ERα and ERα are promising. In recent years, technological advances have flourished in a variety of disciplines, including genetic (i.e., conditional transgenic mice), pharmacological (SERMs), and molecular (gene transfer and antisense oligonucleotide) avenues for region- and time-specific manipulation of the ERs. Thus, we are at a pivotal point where it is now possible to resolve some of the key obstacles that have stymied the field. By embracing these seemingly confounding factors and exploiting all available tools in a multi-disciplined manner, we can advance our knowledge of the roles of these receptors on cognitive function.

General Conclusions

Gonadal hormones have activational effects on cognition. Interest in elucidating the factors that mediate these effects has intensified over the last decade. Notably, this peaked interest is within the realm of both the depth and breadth of the impact that ovarian hormones might exert on cognition. Of these effects, the significance of age-related cognitive decline, and how it may be exacerbated by concurrent gonadal hormone loss, has been an increasingly prominent area of focus in female rodents and in women. Efforts have recently been made to restore balance of the hormonal milieu in an attempt to ameliorate age-related cognitive deficits. The clinical and basic science literature has presented many elegant, methodically controlled, clearly interpretable experiments to better understand the parameters that govern the profound consequences of hormone loss and hormone treatment on cognition and brain health. Animal models have served as a valuable tool in characterizing the parameters that might lead to clinical intervention, and will be key to future discoveries. Researchers have identified the intricate relationships between these factors by understanding their individual contributions on cognition. This type of systematic approach has guided much of the discoveries in the field, including the differential cognitive effects of estrogens, progestogens, and androgens. Indeed, the timing, route, dose and duration of administration are also important factors to consider. Research is now moving to understanding the effects of these variables in concert, as well as interactions between different types of hormones when administered concomitantly. This knowledge is key to translating preclinical data to the clinic, wherein women typically have exposure to endogenous ovarian hormones, and also take combination hormone therapies concurrently. An overview of the existing literature on the impact of hormone therapy on cognition might seem controversial, but when taking these variables into account, we can appreciate the multitude of considerations involved in optimizing treatment for menopause. We are now in an exciting time when technological advances in the field of neuroscience are meeting the demands and enthusiasm of scientists who wish to better understand hormone effects on the brain and cognition. Many interdisciplinary scientists now perform animal studies with a clinically-driven experimental design, which is key to discoveries of a translational nature. In this domain, the holy grail is to use these discoveries to expand the window of opportunity to ultimately enhance cognition in aging women.

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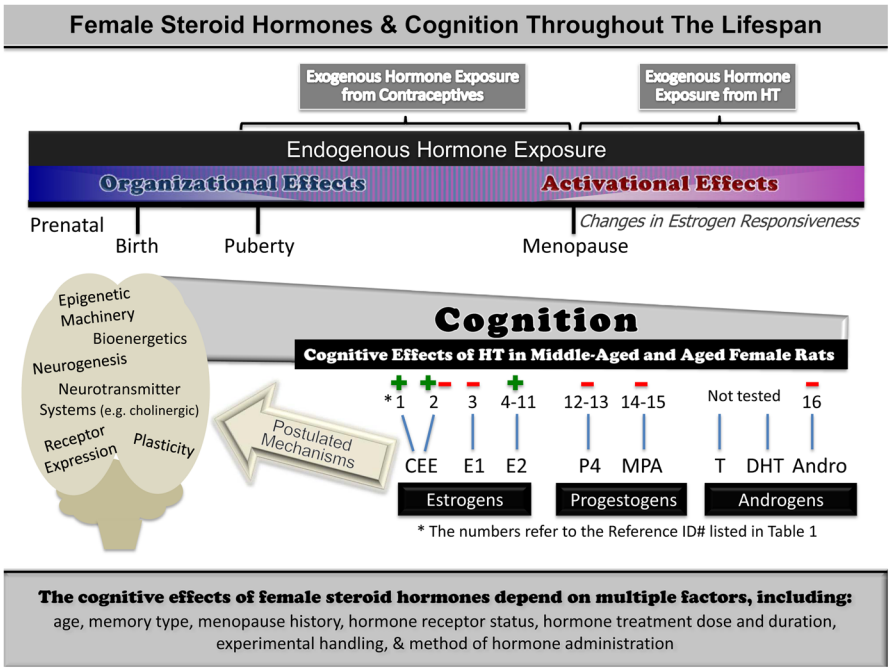

Figure 1.

Female steroid hormones can impact the brain and cognition throughout the lifespan. In women, female steroid hormone exposure encompasses both endogenous and exogenous exposures in a lifetime. Endogenous hormone exposure occurs during the prenatal environment, birth, puberty, and menopause, and exogenous hormone exposure occurs from contraceptives during reproductively active years and/or hormone therapy (HT) during menopause. Organizational and activational effects on the brain interact and ultimately impact cognitive outcome. Female steroid-induced effects on cognitive outcome depend on many factors. Putative neurobiological mechanisms underlying hormone-induced alterations in cognition include those listed in the brain schematic in the figure. Regarding research investigating the cognitive effects of various types of HT in middle-aged and aged rats, the plus sign (+) denotes positive effects on cognition and the minus (-) sign denotes detrimental effects on cognition. The numbers under the plus and minus signs refer to the corresponding publication/Reference ID# listed in Table 1.

Table 1

Effects of female steroid administration on spatial memory in middle-aged and aged female rats. Only hormones given independently are reported here.

Hormone	Reference ID#	Dose	Regimen	Behavior Examined	Effect on cognition	Reference
CEE	1	10μg injection	Cyclic	MWM, DMS	+	Acosta et al., 2009
		20μg injection	Cyclic	MWM, DMS		
		30μg injection	Cyclic	MWM, DMS	+	
	2	12μg pumps	Tonic	DMS, MWM	−	Engler-Chiurazzi et al., 2011
		24μg pumps	Tonic	DMS	+	
		36μg pumps	Tonic	DMS, WRAM	+	
E1	3	8.0μg /day pumps	Tonic	DMS	−	Engler-Chiurazzi et al., 2012
E2	4	0.25mg/60 day release pellet	Tonic	MWM	+	Talboom et al., 2008
	5	10% estradiol benzoate capsule Low- 0.5 cm	Tonic	MWM	+	Foster et al., 2003
		10% estradiol benzoate capsule High- 1 cm	Tonic	MWM	+	
	6	25% E2 implant	Tonic	MWM	+	Markham et al., 2002
		16.67μg E2/kg in .5cc injections	Acute	MWM	+	
	7*	25% E2 implant in a 5 mm silastic capsule	Tonic	DMP	+	Gibbs et al., 2000
	8	.25mg, 60 day release pellet	Tonic	MWM	+	Bimonte-Nelson et al., 2006
		.50mg, 60 day release pellet	Tonic	MWM	+ Only on Day 1 Trial 2	
		10μg injection	Cyclic	MWM	+	
	9*	10μg injection + 3mm E2 pellet	Cyclic +Tonic	DNMP, MWM	+	Markowska et al., 2002
	10*	3mm E2 pellet	Tonic	T-maze active avoidance	+	Savonenko et al., 2003
	11	47μg/kg/day in drinking water	Tonic (constant, every day)	MWM	+	Lowry et al., 2010
		47μg/kg/day in drinking water	Cyclic (3 out of every 4 days)	MWM	- (Relative to tonic E2, not vehicle)	
P4	12	(3) P4 pellets of 200mg, 90 day release	Tonic	WRAM	-	Bimonte-Nelson et al., 2004
	13	21mg pumps	Tonic	WRAM	−	Braden et al., 2010
MPA	14	21mg pumps	Tonic	WRAM, MWM	−	Braden et al., 2010
	15	3.5mg injection	Cyclic	WRAM, MWM	−	Braden et al., 2011
Andro	16	8mg/kg	Tonic	WRAM, DMS, MWM	−	Camp et al., 2012

Morris water maze (MWM), Water radial arm maze (WRAM), Delayed matched-to-sample plus maze (DMS), Delayed non-match to position (DNMP).

(+) denotes a positive effect on cognition

(-) denotes a negative effect on cognition

* indicates that a turn strategy can be used for successful performance; animals are not "encouraged" to use space

17β-estradiol (E2)

Progesterone (P4)

Medroxyprogesterone acetate (MPA)

Androstenedione (Andro)

Table 2

Effects of combination estrogens + progestogens administration on spatial memory in middle-aged and aged female rats.

Hormone	Dose	Regimen	Behavior Examined	Effect on cognition	Reference
E2 + P4	10μg injection E2 + 500μg injection P4	Cyclic E2 + Cyclic P4	*DMP	+	Gibbs et al., 2000
	0.25mg E2 pellet (60 day release) + Two 200mg P4 pellets (90 day release)	Tonic E2 + Tonic P4	MWM	− (relative to tonic E2 alone, not vehicle)	Bimonte-Nelson et al., 2006
	10 μg injection E2+ 2 pellets of 200mg P4, (90 day release)	Cyclic E2+ Tonic P4	MWM	− (relative to cyclic E2 alone, not vehicle)	
	25% E2+ 75% and 100% P4 implant	Tonic E2+ Tonic P4	MWM	+	Markham et al., 2002
	47μg/kg/day E2 in drinking water + 40mm P4 implant	Tonic E2+ Tonic P4	MWM	+ (relative to tonic E2 + MPA, not vehicle)	Lowry et al., 2010
E2+ MPA	47μg/kg/day E2 in drinking water + 1.5mg 90 day release MPA pellet	Tonic	MWM	− (relative to cyclic E2, tonic E2, & tonic E2+P4, not vehicle)	Lowry et al., 2010
	47 μg/kg/day E2 in drinking water + 1.5mg 90 day release MPA pellet	Tonic	*T-maze alternation, delayed alternation	+ Relative to vehicle, cyclic E2, & tonic E2	Chisholm et al., 2012

Morris water maze (MWM), Water radial arm maze (WRAM), Delayed matched-to-sample plus maze (DMS), Delayed non-match to posotion (DNMP).

(+) denotes a positive effect on cognition (−)

denotes a negative effect on cognition

17β-estradiol (E2)

Progesterone (P4)

Medroxyprogesterone acetate (MPA)

*indicates that a turn strategy can be used for successful performance; animals are not “encouraged” to use space