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Estrogens and Cognition: Friends or Foes?:

An evaluation of the opposing effects of estrogens on learning and memory

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Abstract

Estrogens are becoming well known for their robust enhancement on cognition particularly for learning and memory that relies upon functioning of the hippocampus and related neural systems. What is also emerging is that estrogen modulation of cognition is not uniform, at times enhancing yet at other times impairing learning. This review explores the bidirectional effects of estrogens on learning from a multiple memory systems view, focusing on the hippocampus and striatum, whereby modulation by estrogens sorts according to task attributes and neural systems engaged during cognition. We highlight our findings that show the ability to solve hippocampus-sensitive tasks typically improves under relatively high estrogen status while the ability to solve striatum-sensitive tasks degrades with estrogen exposures. Though constrained by dose and timing of exposure, these opposing enhancements and impairments of cognition can be observed following treatments with different estrogenic compounds including the hormone estradiol, the isoflavone genistein found in soybeans, and agonists that are selective for specific estrogen receptors, suggesting that activation of a single receptor type is sufficient to produce the observed shifts in learning strategies. Using this multi-dimensional framework will allow us to extend our thinking of the relationship between estrogens and cognition to other brain regions and cognitive functions.

Introduction

Estrogens belong to a class of steroid hormones most commonly recognized for their roles in. reproductive physiology and behavior. However, as evidenced by the topic of this special issue, estrogens also have powerful effects on cognition, acting to modulate many aspects of brain structure and function. Estrogens' roles in the brain are especially meaningful for women's health, as many women experience marked changes in cognition and affect following natural or surgical menopause (Morrison et al., 2006).

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The potential “non-reproductive” actions of estrogens on learning and memory gained particular interest among basic scientists following findings that the hippocampus, a brain structure critical for certain types of cognition, undergoes substantial changes in neuron morphology and neurotransmission in response to 17β-estradiol, the principal circulating estrogen in women prior to menopause (Gould et al., 1990; Woolley et al., 1990). Estradiol was also found to induce structural and functional changes in other neural systems, including the striatum, amygdala, and cortex, aligning well with earlier reports of estradiol modulation of the hypothalamus (Carrer and Aoki, 1982; Dohanich et al., 2009).

Behavioral studies in laboratory animals confirmed that changes in hormone levels lead to altered performance on memory tasks that engage these different brain areas (McEwen and Alves, 1999; Dohanich et al., 2009). Importantly, estradiol does not uniformly alter cognition, as it can enhance, impair, or have no effect on learning and memory processes depending on the cognitive demands of a given task (Gold and Korol, 2010; Korol, 2004). Further studies showed that mnemonic outcomes following treatment with estrogens are sensitive to many other variables such as dose, timing, age, the type of estrogen used, and the duration of hormone deprivation prior to treatment (Dohanich et al., 2009). Adding another layer of complexity, estrogens can be locally synthesized in the brain (Hojo et al., 2004; Remage-Healey et al., 2011) and may act like neuromodulators or neurotransmitters to up-or down-regulate information flow through the brain. Finally, estrogens are also known to exert their effects in the brain through novel signaling mechanisms, acting through membrane-associated cascades that alter neuronal signaling themselves and that may also influence the transcriptional activities of classical nuclear hormone receptors (Mani et al., 2012; Vasudevan and Pfaff, 2008) or transactivate neurotransmitter receptor systems (Meitzen and Mermelstiein, 2011).

Shifting viewpoints on estrogenic regulation of learning and memory

Until relatively recently, estrogen replacement with and without progesterone was a popular hormone therapy to protect against the symptoms of hormone loss, including changes in cognitive function, as women transition through menopause. However the health benefits of estrogens were challenged by the findings from the Women’s Health Initiative (WHI) reports, and the subsequent fallout from and the media surrounding the reports, suggesting that conjugated equine estrogens and synthetic progestins found in the commonly prescribed hormone replacement treatment Premarin® and Prempro® can increase risk for various cancers, stroke, and potentially Alzheimer’s disease (Espeland et al., 2004; Rapp et al., 2003; Rossouw et al., 2002; Shumaker et al., 2003). These findings were used to support the view that ovarian steroids may be detrimental to health and to brain health in particular. However, the generalizability of the WHI findings have since been put into question because of participant selection based on age, time since menopause, and severity of menopausal symptoms, selection of hormone treatments that are not made specifically from the endogenous hormones estradiol and progesterone, and the validity of the cognitive battery used to test memory that is instead a screen for dementia (Sherwin, 2009). In essence, the results failed to address the important question of whether estrogens given at or around the time of reproductive senescence protect against decline in learning, memory, and brain health.

Estrogens regained their status for neural protection and beneficial actions on cognition and related brain functions through direct tests of these design flaws. Substantial progress has been made using a variety of experimental models to demonstrate that there is a window of opportunity around the perimenopausal period for estrogens to protect the brain against declines in cognitive function and related neurodegenerative diseases (Daniel, 2012; Gibbs, 2000; Resnick and Henderson, 2002). When administered to middle-aged female rodents close to the time of hormone deprivation, estrogens improve memory for several different cognitive tasks (Bimonte-Nelson et al., 2006; Daniel et al., 2006; Fernandez and Frick, 2004; Markham et al., 2002; Neese et al., 2014; Rodgers et al., 2010; Talboom et al., 2008). In contrast, estrogen-induced memory enhancements are not seen following prolonged periods of hormone deprivation (Daniel et al., 2006; Gibbs, 2000), a loss of responsiveness that extends to measures of neuronal plasticity and transmission (Daniel, 2012). This decreased sensitivity appears to become more robust with age, as elderly rats appear to either lose cognitive responses to treatment (Gresack et al., 2007; Savonenko and Markowska, 2003; Talboom et al., 2008) or require higher doses of estrogens (Foster et al., 2003; Frick et al., 2002) and increased task difficulty (Korol et al., 2007) to detect estrogen-related memory improvements. Notwithstanding these enhancements, not all estrogens are equally effective even when given around the time of hormone deprivation.

Classic estrogens are C18 steroid hormones present endogenously as 17β-estradiol, estrone, and estriol, plus their sulfate and glucuronide conjugates. Estradiol is the most potent naturally occurring estrogen, followed by estrone and estriol, and is also the main circulating estrogen in humans of reproductive age (Kuhl, 2005; Rannevik et al., 1995). While levels of all estrogens decline precipitously at menopause, estrone becomes the predominant species following reproductive senescence (Rannevik et al., 1995). Interestingly, until now, the most widely-used postmenopausal estrogen replacement therapy did not involve administration of estradiol, but was instead a complex cocktail of estrogenic compounds purified from the urine of pregnant horses that is taken orally and results in increased levels of estrone and reduced 17β-metabolites (Bhavnani, 1998; Bhavnani, 2003).

Studies examining the use of these conjugated equine estrogens in postmenopausal women, including the Women’s Health Initiative, mostly report null, mixed, or negative cognitive effects of estrogens whereas the majority of studies utilizing estradiol have found cognitive benefits (Sherwin and Henry, 2008). In rodent studies, conjugated equine estrogens both impair (Barha and Galea, 2013) and enhance (Acosta et al., 2009b) spatial memory, outcomes that appear to be dose-dependent and correlated to relative serum levels of estradiol and estrone (Engler-Chiurazzi et al., 2011). In contrast to the nuances of conjugated equine estrogens, a wide body of work demonstrates that estradiol generally improves hippocampus-sensitive cognition in rodents (see Dohanich et al., 2009).

Indeed, estrogen treatment may not be the long sought after silver bullet for cognition, but not because the hormones are detrimental to the overall health of the post-reproductive female. Rather, elevated levels of estrogens not only enhance cognition but also impair cognition even in healthy young adult females depending upon the task attributes, which memory systems are engaged, and the physiological state of the organism (for review see Dohanich et al., 2009). These often overlooked but robust impairing effects suggest that

estrogens, and perhaps more generally other steroids, have opposing actions on cognition, shifting abilities across different types of learning strategies and memory processes.

Estrogens regulate learning and memory in a dissociable manner based on attributes of the behavioral task and neural systems engaged. For example, increased levels of estradiol, either endogenously or through exogenous administration, enhance performance on spatially-driven, working memory, or explicit tasks that rely on the hippocampus, such as the radial arm maze (Holmes et all, 2002; Fader et al., 1999; Luine et al., 1998; Daniel et al., 1997), swim task (Kiss et al., 2012; Bimonte and Denenberg, 1999; Packard and Teather, 1997), delayed matching-to-position (Gibbs, 2000), place task (Zurkovsky et al., 2007; Zurkovsky et al., 2006; Davis et al., 2005; Korol and Kolo, 2002), and object placement (Frye et al., 2007; Luine et al., 2003). Improvements in hippocampus-sensitive learning and memory are not immutable, however, as magnitude and direction of effects are sensitive to many factors such as age of the subjects, task difficulty, stress level, enrichment, estradiol dose, and period of hormone depletion (for review see Dohanich et al., 2009).

Although estradiol largely promotes the use of cognitive strategies that engage the hippocampus, elevations in hormone levels impair the use of processes that engage the dorsal striatum. Learning that requires stimulus-response strategies or egocentric navigation rules such as cued win-shift on a radial arm maze (Galea et al., 2001), response learning (Zurkovsky et al., 2011; Zurkovsky et al., 2007; Davis et al., 2005; Korol and Kolo 2002), and cued swim task (Daniel and Lee, 2004; Pleil et al., 2011) becomes impaired with estradiol exposure. Furthermore, estrogens are detrimental to the performance of operant tasks such as delayed alternation (Neese et al., 2010a; 2010b; Neese et al., 2012; Wang et al., 2009).

The opposing effects of estrogens on different types of cognition resonate well with the theory of multiple memory systems purporting that different brain structures act as parallel processors for a given memory task, each optimized to handle particular types of information and relationships (White and McDonald, 2002; White et al., 2013). While many brain areas are likely to be engaged during cognitive activity, there may be specific regions that are selectively required for effective task solution; the physiological status of the respective neural systems predicts the ability to solve tasks with specific cognitive demands. For example, findings from studies that disrupt learning and memory with functional or structural lesions (Packard et al., 1989; Packard and McGaugh, 1996; White and McDonald, 2002; Chang and Gold, 2003a, 2004; Featherstone and McDonald, 2004; Hallock et al., 2013) and that correlate cognitive performance with functional (Bohbot et al., 2004; Iaria et al., 2003), neurochemical (Chang and Gold, 2003b; Gold et al., 2013), and molecular signatures (Columbo et al., 2003; Colombo, 2004) reveal the importance of hippocampal function in allocentric or place learning and striatal function in egocentric or response learning. Tasks with specific cognitive attributes such as these can engage the canonical memory systems, i.e. hippocampus or striatum, depending on which neural structure provides optimal processing of the task features.

Estrogenic shifts in cognition: differential activation of multiple memory systems

Estradiol does not modulate learning and memory capacity in a singular manner, enhancing all or some types of cognition. Much of our work on estrogens and cognition dissociates the effects of estrogens on hippocampus- and striatum-sensitive learning strategies to create a conceptual framework in which estrogens modulate cognition by shifting the pattern of engagement of multiple memory systems that optimally process different kinds of information. The magnitude and possibly direction of effects of estrogens on cognition vary by age, reproductive status, and even reproductive experience (Barha et al., 2015; Gatewood et al., 2005; Workman et al., 2013). Moreover, we recently characterized age-related shifts from place to response learning strategies in males (Korol et al., 2014), suggesting that the interaction of age and estrogen status on multiple memory systems is that much more complex. Thus, the majority of studies described herein were conducted using virgin young adult female rats to test first how estrogens modulate learning and memory across memory systems before extending questions to contexts of aging, hormone timing, parity, and menopause etiology (Acosta et al., 2013; Daniel, 2012; Frick, 2009; Galea et al., 2014). It is important to note, however, estradiol-induced enhancements in place learning originally observed in young adults are also seen in middle aged (Neese et al., 2014) and elderly (Korol et al., 2007) multiparous rats, suggesting that our behavioral tasks and treatments are useful in assessing cognitive function across the lifespan.

To test the effects of estrogens on learning across multiple memory systems, we have used place and response learning tasks. These maze-based tasks are ideal for targeting hippocampus-or striatum-sensitive cognitive processes as their demands are well matched in all areas except the strategy needed to obtain a food reward. The place task requires rats to learn the spatial location of the reward using extra-maze cues by always going towards the same place in the testing room, while the response task requires the rat to adopt a consistent turning strategy to reach the goal (Tolman et al., 1946). These tasks use the same apparatus, appetitive reinforcement, and pre-training handling regimen and thus have similar levels of stress and cognitive difficulty (Korol and Kolo, 2002). The balanced nature of the place and response tasks is very important, as stress and aversive or appetitive conditions can differentially affect the outcomes of estrogen memory modulation (Dohanich et al., 2009). As estrogens have non-mnemonic effects on motor function, motivation, and food drive (McEwen and Alves, 1999), the comparable features of the tasks used here obviate the confounds introduced by these variables. In sum, the place and response tasks serve as good models for examining the selective cognitive actions of estrogens.

Using these place and response learning tasks, we have generated several sets of results (Korol and Kolo, 2002; Pisani et al., 2012b; Zurkovsky et al., 2006; 2007) demonstrating that estrogens enhance place learning by increasing accuracy across training trials and by decreasing the trials it takes to reach a predetermined criterion. Mirroring these improvements, the same doses of estrogens impair response learning by decreasing accuracy across acquisition periods and by increasing the number of trials to reach criterion (Figure 1). Because estrogens shift the ability to solve these tasks in opposite directions and because

non-cognitive behaviors such as choice time and exploration speed are relatively unaffected by treatment, we propose that estrogens not only alter how much we learn but also, and more importantly for our conceptual and experimental approaches, the manner by which we learn.

These estrogen-induced cognitive shifts are highlighted by the use of behavioral tasks that can be solved in multiple ways, e.g. dual-solution tasks. When young adult female rats were trained to find food in a T-maze where place and response strategies provided equally effective solutions, significantly more rats with high estradiol levels (proestrus) selected place strategies compared to response strategies while rats with low estradiol (estrus) showed the converse, i.e. choosing response strategies over place strategies. The different strategies were evident when examined across the estrous cycle (Korol et al., 2004) or when examined in ovariectomized rats treated with two days of 10 μg of estradiol benzoate (Figure 2), which results in serum estradiol levels similar to those found in proestrus (Korol and Kolo, 2002). An important finding in the dual-solution task was that rates of learning measured by trials to meet a criterion of ninety percent accuracy were the same for rats with high and low estradiol levels, showing that hormone status shifted the strategy used but not necessarily learning ability in general or the strength of memory formation. The consensus from multiple reports is that rats with relatively high estradiol levels are biased towards hippocampus-sensitive place strategies and away from striatum-sensitive response or cued strategies and hormone-deprived rats demonstrate the opposite: they select response strategies over place strategies (Daniel and Lee, 2004; Korol et al., 2004; Quinlan et al., 2008).

What has grown out of these initial experiments is that our place and response learning tasks may serve as behavioral assays for the function of or plasticity in hippocampus and striatum. If so, the direction of estrogen effects on cognition will generalize to other tasks that sort according to the memory system predominating during the task, such as hippocampus or striatum. Delayed alternation in operant conditioning tasks is believed to rely on cortico-striatal processing and is impaired by estrogens including estradiol and genistein in young adult, middle-aged, and elderly rats (Neese et al., 2010a; 2010b; Neese et al., 2012; Wang et al., 2009; Neese et al. 2014). For example, chronic treatments of estradiol initiated at the time of ovariectomy in 12-month-old female rats significantly impair working memory in a spatial alternation task (Figure 3) believed to rely on intact prefrontal cortex function. Performance decrements due to estradiol are particularly robust as memory load increases, i.e. at delays greater than 0 seconds but shorter than 18 seconds. Thus, estrogens interfere with information processing that relies on the function of the striatum, cortical-striatal connections, and related circuits.

We recently tested the opposing actions of estrogens in two novel recognition tasks that are differentially sensitive to hippocampus and striatum manipulations, tested by disrupting the function of each structure with lesions and chemical inactivation.. In both recognition tasks, rats are allowed to explore two objects placed near opposite ends of an arena over three study sessions (S1-S3) followed after a specific delay by a subsequent test trial. In the location recognition task, the two familiar objects are moved closer together for the test trial. In the object recognition task, both familiar objects are replaced by novel objects and

positioned in the same spatial locations (Figure 4A). The rats' memory for the original object patterns is expressed as time spent exploring the novel object arrangement relative to time spent exploring the familiar object arrangement in the last study session (S3). Hippocampal manipulations such as lidocaine inactivation disrupt recognition of location change but not of object change (Figure 4B; Goodrich-Hunsaker et al., 2008). Conversely, striatal inactivation impairs object recognition but not location recognition.

The tasks share the important quality of site specificity with our maze tasks yet they differ with regard to the apparatus used (arena vs maze), specifics of training paradigm (four 5-min sessions vs scores of 30-sec trials), and motivators (novelty vs food reward), to name a few. However, similar to findings in our maze-based tasks, elevated levels of estradiol, endogenously across the cycle or exogenously through systemic injections (45 μg/kg estradiol benzoate 48 and 24 h before testing to ovariectomized rats; Figure 4C), improved recognition in the hippocampus-sensitive location recognition task but blocked recognition in the striatum-sensitive object recognition task. Conversely, hormone deprivation produced good performance on the striatum-sensitive object recognition task but not the hippocampus-sensitive task (Figure 4C). These findings reveal a novel task-by-structure double dissociation that is sensitive to the opposing effects of estrogens, strengthening the idea that estrogens enhance hippocampal function at the expense of striatal function and vice versa: estrogen depletion can enhance striatal function at the expense of hippocampal function. Taken together, the sum of the results suggests that estrogens are not generally good or bad for brain and cognition, but instead are both, shifting the memory system engaged toward the hippocampus and away from striatum.

Estrogenic regulation of the balance of memory systems: independent or interactive?

As mentioned above, dissociations between the brain region manipulated and task performance reveal multiple memory systems that can operate independently as a single processor, giving rise to the notion of canonical memory systems and tasks. However, the tenet of independent memory systems is complicated by findings that memory systems can also interact in a cooperative or competitive manner whereby activity of one system respectively potentiates or decreases the contribution of a parallel neural system (White et al., 2013).

The hippocampus and striatum are two structures shown to interact competitively. Lesions or chemical inactivation of one system improves learning and memory in tasks that tap the intact structure (Chang and Gold, 2003a; White and McDonald, 2002). Furthermore, the corollary is also true: potentiation of one system may interfere with function of the noncanonical system, impairing cognitive performance that depends on that system. What follows, then, is the possibility that the facilitation of place learning and impairment of response learning by estrogens reflect the singular action of estrogens on either the hippocampus or the striatum that, through competition, leads to the opposing actions. For example, estrogens may improve hippocampal function, thereby impairing striatal function because of competitive inhibition of hippocampus on striatum. Conversely, estrogens may impair striatal function, thereby improving hippocampal function by releasing competitive

inhibition of the striatum on hippocampus. Alternatively, estrogens may act on each structure independently, improving place learning through modulation of hippocampus and impairing response learning through modulation of the striatum, without modulating the interactions between memory systems.

Evidence from direct brain infusions of estradiol supports the latter possibility that estrogens modulate learning and memory through independent actions on hippocampal and striatal memory systems. Young adult ovariectomized rats received bilateral hippocampal infusions of estradiol 48 and 24 hours prior to training and three weeks following ovary removal, matching the systemic treatments given in previous work (Korol and Kolo 2002; Zurkovsky et al., 2006). The rats showed significant improvements in place learning with no apparent effects on response learning. Similar infusions into the striatum produced impairments in response learning with no measurable effects on place learning (Zurkovsky et al., 2007). Furthermore, blockade of classical estrogen receptors (ERs) in the hippocampus with hippocampal implants of 10% ICI 182,780, prevented place learning enhancements seen with two days of systemic estradiol treatment (Zurkovsky et al., 2006). Likewise, striatal implants of ICI 182,780 reversed the response learning impairments seen with systemic estradiol (Kent et al., 2005). Together the results suggest that estradiol in the canonical memory system is both necessary and sufficient to produce place learning enhancements and response learning impairments and seem to do so through estrogen receptor-mediated events at each structure.

Despite the clear dissociation in effects of central infusions of estradiol, inactivation experiments present a conundrum regarding how estrogens shift the balance of memory systems. When the hippocampus is inactivated with the $GABA_A$ agonist muscimol, rats at proestrus with endogenously high levels of estradiol shift from place to response strategy use in a dual solution task that allows both strategies during training (Figure 5). Importantly, estrous cycle stage interacts with muscimol dose such that increasing doses of muscimol are needed to produce increased shifts towards response learning as endogenous levels rise across the estrous cycle. Thus, the effective dose for response learning impairments is high at proestrus and intermediate at diestrus.

The results align well with theories suggesting that estradiol decreases inhibitory tone in the hippocampus through modulation of GABA signaling, perhaps through ERα activation (Huang and Woolley, 2012), and thus higher concentrations of the GABA agonist muscimol are needed to effectively block functional output (McElroy and Korol, 2005). However, the results also suggest that endogenous elevations in ovarian hormones shift memory systems through *competitive* interactions, presenting an alternative interpretation from that drawn by the findings from central infusions described above. If estradiol works independently to enhance hippocampus and to suppress striatum, under high hormone states of proestrus and in the presence of hippocampal muscimol, place and response strategies would both be inhibited and a random selection of place and response learning strategies, i.e. no observed strategy bias, and slower overall learning reflected in higher trials to reach criterion would be expected. Instead, we observed that under high hormone states without the function of the hippocampus rats reach criterion in the same number of trials and can effectively use response strategies, suggesting that the response learning impairment with high hormones is

due to increased activation of the hippocampus. One possibility for the conflicting findings is that in the latter case rats were gonadally intact, while in the former, rats were ovariectomzed and replaced with estradiol alone; hormones other than estradiol, such as progesterone, may alter competitive interactions between hippocampus and striatum. Direct tests of this possibility have not yet been made, however we find that progesterone treatment in estradiol-primed rats shifts strategies towards striatum-sensitive response strategies (Figure 2).

Regardless of how the balance across brain regions is shifted, what comes into view through this multiple memory systems lens is that the opposing actions of estrogens on cognition sort by the brain systems engaged during task performance and that, by logical extension, estrogens can both up- and down-regulate the neural plasticity in brain areas that are respectively involved in cognition. The neurobiological mechanisms responsible for bidirectional regulation of cognition undoubtedly depend on many features of the canonical memory system related to estrogenic sensitivity, including receptor subtypes, distributions, and downstream signaling mechanisms.

The role of different estrogen receptor subtypes in learning strategy shifts

Estradiol acts through multiple types of estrogen receptors (ER) in the brain. Throughout the brain, ER subtypes ERα and ERβ are detected as classical nuclear receptors but also can be localized to the plasma membrane (Milner et al., 2005; Milner et al., 2001; Shughrue et al., 1997; McEwen et al., 2012; Meitzen and Mermelstein, 2011; Mhyre and Dorsa, 2006). The G-protein coupled estrogen receptor (GPER), formerly identified as an orphan receptor called GPR30, is a novel seven-transmembrane domain G protein-coupled receptor that binds estradiol with high affinity but is structurally and genetically unrelated to ERα and ERβ (Prossnitz and Barton, 2009). GPER can be located in the plasma membrane and densely expressed in other membrane-bound cellular structures, particularly the endoplasmic reticulum (Brailoiu et al., 2007; Matsuda et al., 2008; Prossnitz and Barton, 2009). ERα, ERβ, and GPER are all expressed in the hippocampus and striatum, but with distinct nuclear and extra-nuclear distributions and densities, activation through which will lead to different modes of signaling and downstream effects on neural function.

In the hippocampus, classical ERα and ERβ and GPER are detected in relatively high abundance in both nuclear and extranuclear membrane sites in neurons and glia (Brailoiu et al., 2007; Milner et al., 2005; Milner et al., 2001; Shughrue et al., 1997), allowing for both genomic-initiated transcriptional events and nongenomic- or membrane-initiated signaling pathways. Like estradiol, the highly-specific GPER agonist G1 (Bologa et al., 2006) activates ERK in neurons, increases calcium currents through L-type voltage gated calcium channels (Sun et al., 2010), and increases excitatory post-synaptic currents in hippocampal slices (Lebesgue et al., 2009). In the striatum, while levels of nuclear ERs are strikingly low (Shughrue, 1997), moderate to high levels of ERα, ERβ, and GPER are found at extranuclear sites (Almey et al., 2012; Grove-Strawser et al., 2010; Kuppers and Beyer, 1999; Schultz et al., 2009). Therefore, it is likely that the primary mode of signaling in the striatum is through membrane-associated ERs or transactivation of other receptors.

Because the mnemonic effects of estrogens are mediated through local actions in the hippocampus or striatum (Zurkovsky et al., 2006; 2007; Kent et al., 2005), the differential expression of ER subtypes across these structures may lead to different outcomes on learning when a specific receptor is targeted. Investigating the contributions of distinct ER subtypes to shifts in learning and memory is valuable because certain natural compounds and pharmaceuticals, such as phytoestrogens and selective estrogen receptor modulators (e.g. tamoxifen) bind to estrogen receptors with varying selectivity, and their cognitive effects are largely unknown. Acute treatments of the phytoestrogen genistein mimic the bidirectional effects of estradiol on place and response learning (Pisani et al. 2012b). Genistein demonstrates twenty-fold selectivity for ERβ over ERα (Kuiper et al., 1998), pointing to a possible role of ERβ in both hippocampus-sensitive and striatum-sensitive cognition.

Previous studies implicate the actions of ERβ as critical for the memory enhancing effects of estrogens on radial arm maze (Liu et al., 2008), object recognition (Jacome et al., 2010; Frick et al., 2010) and social transmission of food preference (Clipperton et al., 2008), but others point to signaling through ERα, especially when hormone treatments were given over short periods (Frye et al., 2007; Phan et al., 2011), or to activation of both receptors (Hammond et al., 2009; Qu et al., 2013). A small group of reports shows that activation of GPER can also enhance memory for tasks that engage the hippocampus (Ervin et al., 2013; Gabor et al., 2011; Hammond et al., 2009 Hawley et al., 2014).

Information regarding the roles of ERα, ERβ, or GPER in hippocampus- or prefrontal cortex-sensitive cognition is accumulating while relatively less is known about the effects of these receptor subtypes on striatum-sensitive learning. The distribution of ERα in extranuclear sites of cholinergic neurons in the striatum and the ability of striatal cholinergic neurons to regulate GABAergic signaling (Almey et al., 2012, Schultz et al. 2009) suggests that activation of ERα may mediate striatum-sensitive response learning impairments. Hormone loss with ovariectomy increases AMPA receptor density in the striatum (Cyr et al., 2001) that is attenuated by estradiol and ERα agonists but not ERβ agonists (Le Saux et al., 2006). The decrease in AMPA binding may reduce excitatory cortical glutamate input (Davis et al., 2005), decrease striatal synaptic plasticity, and obstruct striatum-sensitive information processing. Sensitive detection methods reveal expression of ERβ predominantly in dopamine afferents to the striatum even though ERα density is substantially higher in the striatum *per se* (Almey et al., 2012; Mitra et al., 2003; Creutz and Kritzer, 2002; Shughrue and Merchenthaler, 2001; Kuppers and Beyer, 1999). ERβ agonists may therefore produce impairments in response learning with expected dose-response functions shifted to the right compared to those for ERα agonists.

We recently conducted a large-scaled study in young adult female rats using a range of doses of ER-selective agonists to characterize the possible contributions of different ERs in the learning strategy shifts frequently observed with estradiol (Pisani et al. 2012a). Rats ovariectomized for three weeks were treated systemically with compounds selective for ERα (propyl pyrazole triol—PPT) or ERβ (diarylpropionitrile—DPN; or Br-ERb-041, a brominated analog of the non-steroidal compound also known as WAY-200070; Malamas et al., 2004) for two days before training on either place learning or response learning mazes.

Each compound was tested at four different doses in separate groups of rats, ranging from 3.3 ug/kg to the highest dose of 1000 ug/kg.

These experiments were designed to maintain an appreciation for dose-response functions and to follow the guidelines proposed for the creation of mechanistically-based dose-response modeling (Andersen et al., 1999), including the use of multiple doses and the consideration of receptor binding profiles, pharmacokinetics, pharmacodynamics, and behavioral outcomes in dose selection. In featuring dose-sensitivity, we adopted a fairly unique approach for the estrogens and memory field, a perspective that may be useful for assessments of other estrogen-sensitive behaviors and for clinical applications.

We found that two days of systemic treatment with the ERα agonist PPT and ERβ agonists Br-ERb-041 or DPN led to place learning enhancements and response learning impairments but with dose-response functions that were specific to each agonist and task. Place learning enhancements emerged at a single optimal dose for the highly selective agonists PPT (333 ug/kg; range = 33–1000 ug/kg) and for Br-ERb-041 (100 ug/kg; range = 10–333 ug/kg), creating an inverted dose-response function. For the less-selective and lower-affinity DPN, place learning enhancements were observed across a broader range of doses DPN (100–1000 ug/kg; range = 33–1000 ug/kg). Response learning impairments were also sensitive to dose and compound, with the most selective effects observed for Br-ERb-041 at the same moderately low dose (100 ug/kg) that enhanced place learning. PPT and DPN both impaired response learning at the two highest doses of 333 and 1000 ug/kg. Thus, we failed to see a rightward shift in dose needed to detect ERβ-mediated impairments predicted from ER distributions across the striatum.

In separate experiments targeting the membrane-related estrogen receptor GPER (Pisani et al. 2013), the GPER agonist G1 failed to modulate place learning when administered 48 and 24 h before behavioral training but impaired response learning at the highest dose of 100 ug/kg. Interestingly, when an additional dose of G1 at 10 ug/kg was given 30 minutes prior to training in rats primed for two days with the same dose, G1 produced a robust enhancement in place learning. Collectively, these nuanced effects highlight the importance of considering dose and timing and also point to the convergence of slow, durable estrogen effects with more rapid signaling actions (Gold and Korol, 2010; Vasudevan and Pfaff, 2008).

When investigating the mnemonic effects of a compound, frequently only one dose is examined; the selected dose is sometimes chosen based on pharmacological or other properties but appears to often be picked arbitrarily. Importantly, conclusions may be drawn that a compound has no effect or unidirectional effects when in actuality its response is biphasic, simply because an insufficient number of doses were used. It is becoming clear that the mnemonic effects of estrogens vary by dose, even for established patterns of learning modulation, such as improving hippocampus-sensitive learning and impairing striatum-sensitive learning. Behavioral dose-effect functions are not monotonic, but rather demonstrate an inverted pattern in which cognitive changes are observed at an optimal dose of estrogens, while lower and higher doses have no effect or opposite effects. Estrogens generally enhance the performance of hippocampus-sensitive tasks at low to moderate levels

but lose efficacy or impair performance at higher concentrations (Inagaki et al., 2010; Barha et al., 2010; McLaughlin et al., 2008; Holmes et al., 2002; Packard and Teather, 1997; Pisani et al. 2012b). Non-linear dose responses to estrogenic compounds are widely reported and occur across an array of physiological systems (Calabrese, 2001).

In addition to dose, the timing of estradiol effects may also reveal important information about the mechanisms by which hormones modulate cognition. In this regard, it is notable that the rapid actions of estrogens through membrane-initiated events appear to play a critical role in mediating the cognitive effects of estradiol. Estrogens impair response learning and enhance place learning within 2 hours of central administration (Korol et al., 2010; Zurkovsky et al., 2011) and improve object placement, object recognition, contextual fear conditioning, and radial arm maze performance with only 40 mins of exposure (Phan et al., 2012; Barha et al., 2010; Sinopoli et al., 2006). These treatment schedules are short enough to largely exclude genomic-level actions of estrogen receptors and thus point to rapid mechanisms of neuromodulation. Additionally, antagonizing GPER in cycling rats leads to impairments on the delayed matching-to-position task, indicating that membrane receptors play a key role in estrogen effects on spatial learning and memory (Hammond et al., 2012). Furthermore, rapid signaling mechanisms may be critical for estrogen-induced shifts in learning, as memory enhancements for hippocampus-sensitive tasks are abolished when the PKA (Lewis et al., 2008) or MAPK (Fan et al., 2010; Walf and Frye, 2008; Fernandez et al., 2008) pathways are blocked.

Concluding remarks

Our multiple memory systems approach can be used to clarify some of the conflicting reports of improved, impaired, or unchanged cognitive performance. Capitalizing on tasks that maximize the participation of different brain areas, the results described here, and summarized in Table 1, highlight the intricate relationship between estrogens and cognition; they are not solely “tried-and-true friends” or “fretful foes”, but clearly both. Moreover, the effects of estrogens on learning and memory can no longer be described simply as enhancements or impairments in function based on independent memory systems. Instead, these bidirectional effects are subject to modulation themselves by the ER systems that are activated, the dose and timing of exposures, the specific attributes of the tasks at hand, the potential for interactions across memory systems, and by the features of the individual such as age, reproductive status, and general health. Understanding the neural mechanisms determining when and what types of cognitive functions benefit from estrogen exposure may have important implications for understanding the changes in brain health that accompany menopause.

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Highlights

- Estrogens are known to improve some types of learning and memory
- A growing body of evidence suggests that estrogens including estradiol can robustly impair cognition
- Bidirectional effects of estrogens on cognition sort by task attributes and memory system
- Activation of classical and membrane-associated estrogen receptors produce both enhancements and impairments in cognition

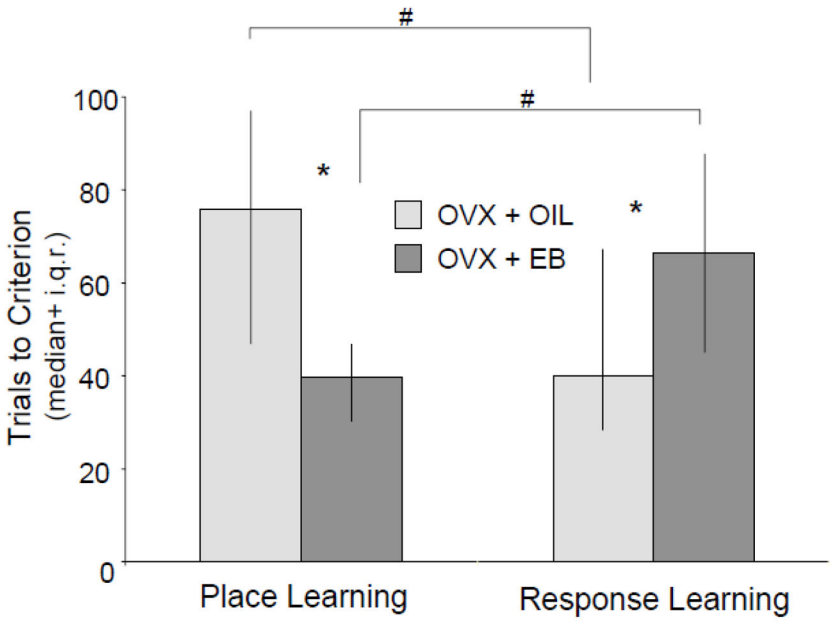

Figure 1.

Young adult rats were ovariectomized for 21 days before training on a place learning or on a response learning task in a plus-shaped maze. Estradiol-benzoate (EB; 10 μg in 0.1 ml sesame oil) was injected (s.c.) once daily for two days before training. Rats treated with estradiol take significantly fewer trials to reach criterion on place learning but significantly more trials on response learning. Rats with low hormone levels show the opposite effects of slow acquisition for the place learning task and fast acquisition for response learning. * = $p < 0.05$ between treatments within task; # = $p < 0.05$ within treatments across tasks using Mann-Whitney analyses. Adapted from Korol and Kolo, 2002.

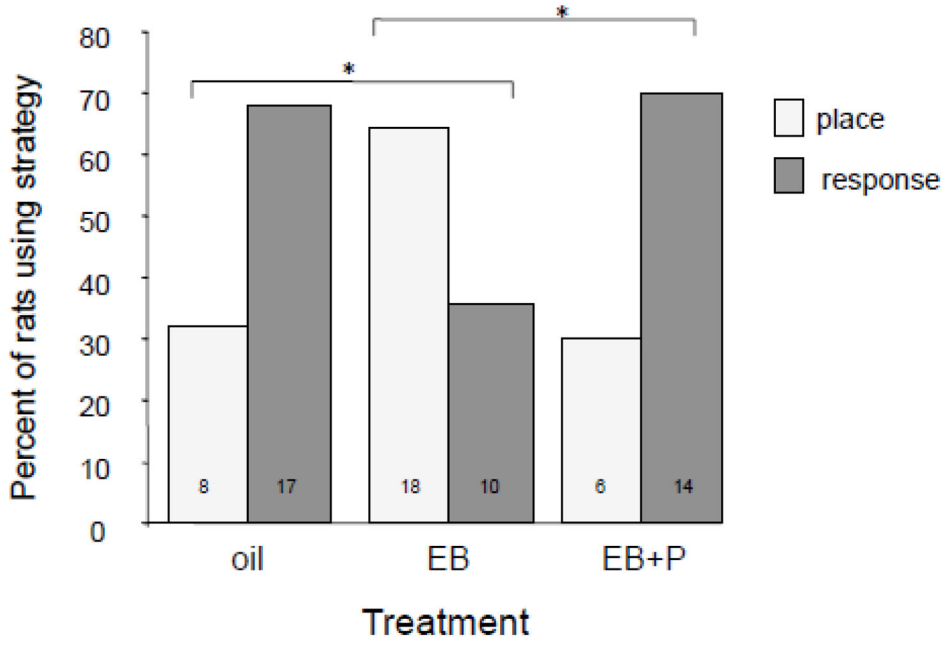

Figure 2.

Rats were ovariectomized then trained and tested for strategy on the dual solution task 21 days later. 48 and 24 hours prior to training rats were treated for two days with oil vehicle (s.c.), or estradiol benzoate (EB; 10 μg g/kg, s.c.). A separate group of rats received EB plus progesterone (500 ug/kg) 4 hours prior to training. The data show that EB for two days produces a place bias in learning strategy that is reversed with progesterone treatment. * = significant ($p < 0.05$) shifts in learning strategy between oil and EB and between EB and EB +P treatments,

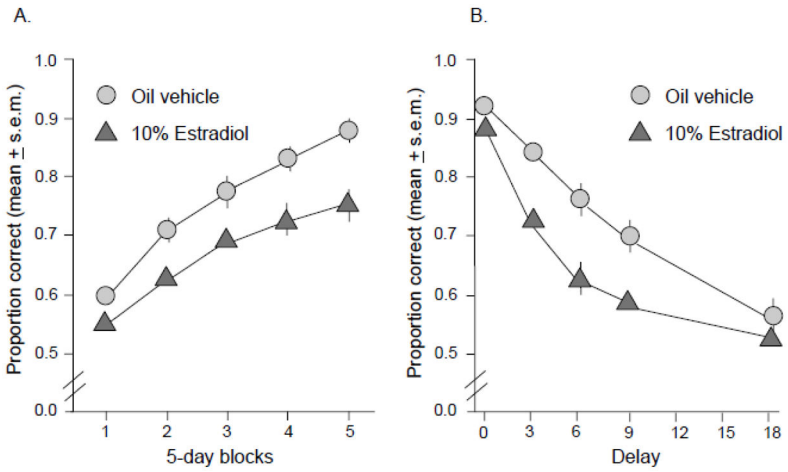

Figure 3.

Effects of chronic estradiol treatment on spatial alternation in an operant conditioning task in middle aged ovariectomized female rats. (A) Proportion correct on the DSA task across 5-day blocks of testing for the vehicle control and estradiol-treated groups. [a]Estradiol treated<vehicle treated, ($p < 0.05$). (B) Proportion correct on the DSA across 5 delays for the vehicle control and estradiol treated groups. [a]Estradiol treated<vehicle treated, ($p<0.05$).

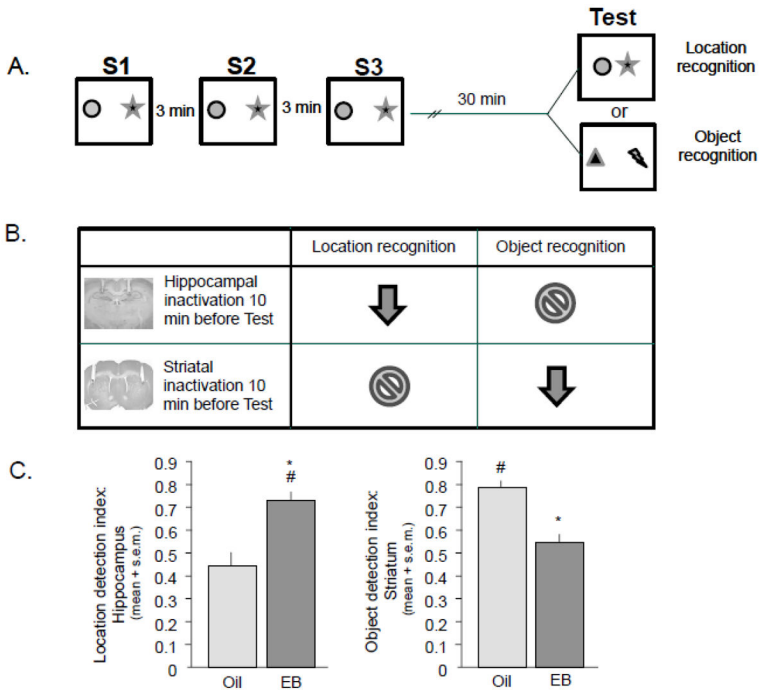

Figure 4.

Procedure and results for location and object recognition tasks. A. Schematic of the general procedure for the recognition tasks. Rats explore arena for three 5-min study sessions (S1, S2, S3) after which they are tested 30 min later on a location recognition Test where same objects are moved closer together or an object recognition task where both objects are replaced with novel ones. B. Lidocaine infused into the hippocampus 20 min after S3 and 10 min prior to Test impairs location recognition but not object recognition, whereas infusions into the striatum impair object recognition but not location recognition. These findings reveal a brain structure X task double dissociation. C. Systemic treatments of estradiol-benzoate (EB) to young adult ovariectomized female rats enhance hippocampus-sensitive location recognition (left panel) and impair striatum sensitive object recognition (right panel) measured with a location detection index derived with the formula: T/S3+T.; * = $p < 0.05$ between treatments within task; # = $p < 0.05$ within treatments between tasks.

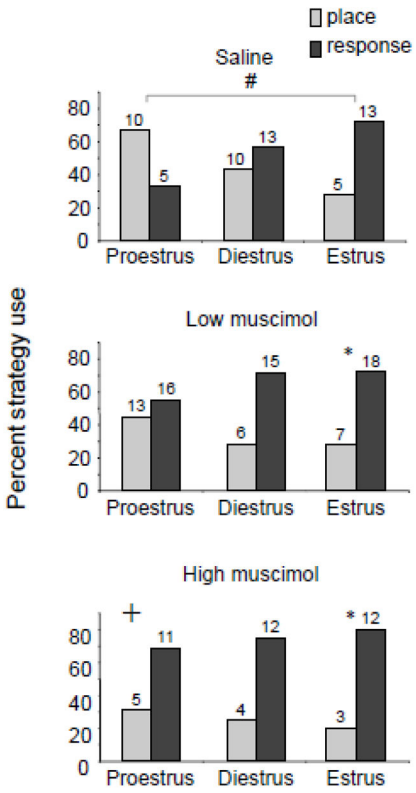

Figure 5.

Strategy selection and the effects of muscimol treatment and estrous cycle stage. (Top) Strategy biases across the estrous cycle in saline treated rats. Note that significant differences between groups appeared with proestrous rats using a place strategy and estrous rats using a response strategy. Diestrous rats demonstrated no strategy bias. (Middle, bottom) Low (middle) and high (bottom) muscimol treatment shifted strategy use toward response. *$p < 0.05$ within estrous cycle group; #$p < 0.05$ between estrous cycle groups within muscimol treatment; +$p < 0.05$ relative to saline controls within estrous cycle group. Adapted from McElroy and Korol, 2005.

Table 1

Summary of results from our lab demonstrating the opposing actions of estrogens on learning and memory across a variety of tasks. Studies were conducted in ovariectomized, young adult virgin Sprague-Dawley female rats and treatments administered 48 and 24 h before behavioral training unless otherwise specified.

Behavioral task	Direction of learning modulation	Treatment or cycle stage	Dose, timing, other notes
Place task	↑	EB; systemic injection	10 μg to young adult [a,b,c] and elderly rats[c], 4.5 μg/kg to young adult[d] and middle-aged[e] LE rats; enhancement blocked by intrahippocampal ICI 182,780[b]
	↑	ES; intracranial infusion	0.5 μM infusion into dorsal hippocampus; infusion into dorsolateral striatum had no effect on place learning[f]
	↑	ES; intracranial infusion	A single 0.5 μM infusion into dorsal hippocampus enhanced place learning when given 2 h, but not 15 min, before training[g]
	↑	Genistein; oral pellets	Multiple daily oral dosings to LE rats beginning 48 h before training[d]
	↑	PPT; systemic injection	333 μg/kg to LE rats; higher (1000 μg/kg) and lower (33, 100 μg/kg) doses not effective[h]
	↑	DPN; systemic injection	100, 333, and 1000 μg/kg to LE rats[h]
	↑	Br-Erb-041; systemic injection	100 μg/kg to LE rats; higher (333 μg/kg) and lower (10, 33 μg/kg) doses not effective[h]
	↑	G1; systemic injection	10 μg/kg to LE rats; only effective when given 30 min before training after 48 and 24 h of G1 priming[i]
Metric change in object location	↑	Proestrus	LE rats in proestrus showed better recognition of a change in metric pattern than rats in estrus[j]
	↑	EB; systemic injection	45 μg/kg to LE rats[j]
Rewarded spontaenous alternation	↑	Proestrus, diestrus	Rats in proestrus and diestrus showed increased spatial alternation behavior compared to rats in estrus[k]
Response task	↓	EB; systemic injection	10 μg to SD rats[a,l], 4.5 μg/kg and 45 μg/kg to LE rats[d]; impairment blocked by intrastriatal ICI 182,780[l]
	↓	ES; intracranial infusion	0.5 μM infusion into dorsolateral striatum; infusion into dorsal hippocampus had no effect on response learning[f]
	↓	ES; intracranial infusion	A single 0.5 μM infusion into dorsolateral striatum imapired response learning when given 2 h, but not 15 min, before training[m]
	↓	Genistein; oral pellets	Multiple daily oral dosings to LE rats beginning 48 h before training[d]
	↓	PPT; systemic injection	333 and 1000 μg/kg to LE rats[h]
	↓	DPN; systemic injection	333 and 1000 μg/kg to LE rats[h]
	↓	Br-Erb-041; systemic injection	100 μg/kg to LE rats; higher (333 μg/kg) and lower (10, 33 μg/kg) doses not effective[h]

Behavioral task	Direction of learning modulation	Treatment or cycle stage	Dose, timing, other notes
	↓	G1; systemic injection	100 μg/kg to LE rats 48 and 24 h before training; no acute dose required[i]
Double object recognition	↓	EB; systemic injection	45 μg/kg to LE rats[j]
Operant delayed spatial alternation	↓	17-β estradiol; silastic capsule	Chronic estradiol replacement impaired DSA performance in young adult[n,o], middle-aged[o,p], and elderly[o] LE rats
	↓	Genistein; oral pellets	Chronic daily oral dosings impaired DSA performance in middle-aged LE rats[q]
	↓	DPN; systemic injection	Chronic daily injections of 20 μg/kg; higher (80, 200 μg/kg) doses not effective[p]
	↓	PPT; systemic injection	Chronic daily injections of 200 μg/kg subtly impaired DSA performance late in testing under long delays[p]
Dual solution strategy	Place	Proestrus; EB, systemic injection	Proestrous rats showed preference for place over response strategies with no change in learning speed[k,r]
	Response	Estrus; Oil; systemic injection	Estrous rats showed preference for response strategies with no change in learning speed[k,r]

Abbreviations: EB: 17β-estradiol benzoate; ES: 17β-estradiol 3-sulfate; SD: Sprague-Dawley; LE: Long-Evans; OVX: ovariectomized; DSA: delayed spatial alternation.

[a] Korol and Kolo, 2002;

[b] Zurkovsky et al., 2006;

[c] Korol et al., 2007. Experiments were conducted using Fischer 344 x Brown Norway rats.

[d] Pisani et al., 2012b;

[e] Neese et al., 2014;

[f] Zurkovsky et al., 2007; ES was infused directly into the dorsal hippocampus or dorsolateral striatum 48, 24, and 2 h before behavioral testing.

[g] Korol et al., 2010;

[h] Pisani et al., 2012a;

[i] Pisani et al., 2013;

[j] Tunur et al., 2012;

[k] Korol et al., 2004;

[l] Kent et al., 2005;

[m] Zurkovsky et al., 2011;

[n] Wang et al., 2008;

[o] Wang et al., 2009;

[p] Neese et al., 2010a;

[q] Neese et al., 2012;

[r] McElroy and Korol, 2005.