Physiology & Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Physiology & Behavior

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

# Using a memory systems lens to view the effects of estrogens on cognition: Implications for human health

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ARTICLE INFO

*Keywords:*
Hippocampus
Striatum
Memory systems
Estrogen signaling
Metabolism

ABSTRACT

Understanding the organizing and activating effects of gonadal steroids on adult physiology can guide insight into sex differences in and hormonal influences on health and disease, ranging from diabetes and other metabolic disorders, emotion and stress regulation, substance abuse, pain perception, immune function and inflammation, to cognitive function and dysfunction accompanying neurological disorders. Because the brain is highly sensitive to many forms of estrogens, it is not surprising that many adult behaviors, including cognitive function, are modulated by estrogens. Estrogens are known for their facilitating effects on learning and memory, but it is becoming increasingly clear that they also can impair learning and memory of some classes of tasks and may do so through direct actions on specific neural systems. This review takes a multiple memory systems approach to understanding how estrogens can at the same time enhance hippocampus-sensitive place learning and impair striatum-sensitive response learning by exploring the role estrogen receptor signaling may play in the opposing cognitive effects of estrogens. Accumulating evidence suggests that neither receptor subtype nor the timing of treatment, i.e. rapid vs slow, explain the bidirectional effects of estrogens on different types of learning. New findings pointing to neural metabolism and the provision of energy substrates by astrocytes as a candidate mechanism for cognitive enhancement and impairment are discussed.

## 1. Introduction

The clinical importance of elucidating the contributions of estrogens and other reproductive hormones to neurological and behavioral functions is far reaching and encompasses issues ranging from studying sex as a biological variable in health and disease to deciphering the impact of environmental endocrine disruptors on neural health. Understanding the developmental and adult consequences of estrogen exposures can advance understanding of independent and interacting contributions of genes, hormones, and environment to individual differences in brain function and dysfunction that may relate to sex differences or similarities. Moreover, understanding the extent of estrogen effects on basic neurobiological functions, such as neural transmission, has the potential to inform mechanisms of neurological disorders, particularly those that have endocrine underpinnings and promote health practices for all sexes [1]. For example, knowledge about estrogen regulation of neural transmission, tissue excitability, and seizure development has translational value for understanding and treating catamenial epilepsy and other seizure disorders in males and females. Understanding hormonal regulation of affective behaviors, including effects on mood states and neurochemistry will undoubtedly promote diagnosis and treatment of post-partum depression. Endocrine consequences of non-neural health problems, such as reproductive senescence and polycystic ovarian syndrome, and their treatments that typically mimic or disrupt estrogen signaling, may inadvertently modulate brain function. Finally, we currently are experiencing excessively high exposures to environmental estrogens and other endocrine disrupting chemicals [2] that may mimic or block endogenous hormone function in both males and females across different stages of the lifespan, creating equally unintended neural and behavioral health outcomes. Understanding the etiology and mechanisms of these outcomes will allow for development of effective treatments and preventions.

Estrogens are no longer solely considered to be female sex hormones given their broad reaching effects on a variety of non-reproductive behaviors in both males and females [3]. Similarly, the pervasive nature of estrogens is evident in their regulation of form and function across a wide array of tissues and cellular processes. The brain is one estrogenic target that has received considerable attention over the last several decades given how robustly estrogens can organize and activate behaviors in males and females [4] comprising not only mating and parenting [5–7] but also those related to feeding and energy balance [8],

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https://doi.org/10.1016/j.physbeh.2017.11.022
Received 8 August 2017; Received in revised form 17 November 2017; Accepted 20 November 2017

navigation [3,9], emotion, aggression, and stress regulation [5,10–13], and cognition [9,14–17]. Thus, estrogens are thought to act quite robustly across the brain but may do so in very different ways depending upon the sex of the organism [17–20], dose and timing of hormone exposure [6,7,16,21], and brain region of interest [16].

Perhaps one of the more compelling arguments for pursuing the effects of hormones on brain and cognition comes from the gender bias in Alzheimer's disease (AD). AD is the most prevalent form of dementia and the only top-ten lethal condition in the United States without effective treatments or known etiologies. The incidence and prevalence of AD are higher in women who are two to three times as likely as men to be living with AD even after accounting for longevity, suggesting a sex difference in the risk and etiology of the disease [22]. When combined with the evidence that age is the biggest risk factor for sporadic AD [22], the sex difference in demographics highlights the possibility that menopause and the accompanying decline in circulating ovarian hormones contribute to higher risk in women. Despite the hotly debated results from the Women's Health Initiative [23,24], converging lines of clinical and preclinical evidence strongly confirm that naturally occurring estrogens given around the time of natural or surgical menopause confer neural protection against dementia and that women who take hormone replacement therapies are at lower risk for AD [25–27].

Estrogens facilitate learning and memory in tasks believed to rely on brain regions such as the hippocampus and entorhinal cortex that are ravaged by degeneration associated with AD [28]. However, as will be discussed in detail below, estrogens not only enhance hippocampus-sensitive forms of learning and memory but also impair learning and memory in non-hippocampal tasks that depend on the integrity of other neural systems such as the caudate/putamen (striatum) and frontal cortex [16]. Thus, loss of ovarian hormones during menopause may indeed *enhance* cognitive function and may relate to changes in structure and function of the striatum. Interestingly, not all brain areas are damaged by AD and some regions, such as the caudate nucleus, may actually be enlarged. A recent report using magnetic resonance imaging demonstrated that compared to non-demented people with mild cognitive impairment those with AD had increases in caudate volume accompanying the decline in hippocampal volume [29]. Detailed analysis of contributing variables suggested that the demographic factors of gender and age, but not an AD diagnosis, may have driven the effects, as caudate enlargement was positively associated with older age and being female, and most certainly being post-menopausal. Thus, elucidating the dynamic interplay between hormone status and function of different neural systems will undoubtedly advance our understanding of healthy aging along with AD and other neural disorders.

The work described herein is based on the philosophy that there are brain states or contexts that can enhance or impair the ability to process information needed to solve specific tasks. Hormones can create these brain states responsible for improvements or impairments in cognition depending upon the specific attributes of the task at hand [30]. This review will highlight findings showing that estrogens bidirectionally modulate learning and memory in young adult female rats depending on the type of problem to be solved and the memory system engaged during learning; the focus here will be on the hippocampus and striatum. Recognizing early in the evolution of this work that female subjects were explicitly omitted from behavioral neuroscience studies, and perhaps even more so from those focused on neural mechanisms of learning and memory, our research program was borne out of a need to study hormonal modulation of learning in the female in its own right, as its own paradigm. This task of focusing on estrogen modulation of cognition is not so much a protest against the unwarranted male bias in neuroscience [31] as it is an attempt to equalize the foundation of knowledge based on females before moving towards the important goal of assessing the impact of sex on brain and cognitive health, an imperative now recognized by researchers, funders, and editors [32–34]. Nearly all of the work discussed here was conducted with females alone; however, in some cases we have data from male rats that can be used as points of comparisons even though the experiments themselves were not explicitly designed as direct tests of sex influences and did not examine estrogen effects in males. Notwithstanding these limitations, these exploratory approaches might provide a foundation upon which we can build studies to assess sex as a biological variable for the selectivity of estrogen modulation of learning [34,35].

## 2. A focus on estrogens and learning strategy using a memory systems lens

Just as males and females express qualitatively different reproductive behaviors as a result of both organizational and activational effects of hormones, there are sex and gender differences in cognitive functions such as declarative memory detected by recall of information from narratives [36], in sensory-motor dexterity [37,38], and in spatial information processing [9,37–40]. To solve a navigation problem based on using visual cues, males tend to rely on room geometry while females have a propensity to use landmark cues, suggesting that sex differences reflect the quality of information used and not necessarily the amount of information that is stored [9]. In humans, abilities that are sensitive to biological sex tend to fluctuate across the menstrual cycle [37,39], such that male-preferred abilities are high during low hormone stages and low during high hormone stages while female-preferred strategies are high during high hormone stages and low during low hormone stages [41]. It follows that ovarian hormone status, which fluctuates across the reproductive cycle, may maximize or minimize sex differences, in some cases creating and in other cases eliminating differences depending on the type of task being assessed. For example, with high hormone status, young adult female rats do well on spatial navigation tasks but poorly on place preference learning or delayed alternation conditioning tasks [42–44], suggesting that testing during high hormone phases might produce apparent sex differences in conditioning but not in spatial navigation. Thus, better resolution of sex differences in cognition might be obtained if regular fluctuations in hormones across the estrous cycle are considered.

Because of the numerous findings that estrogens increase hippocampal plasticity [45], considered by many to underlie memory, a positive relationship between estrogens and cognition has been readily presumed and supported by many results that estrogens enhance memory. However, a finer analysis of decades of work is that estrogens produce robust yet mixed effects on learning and memory – at times enhancing, at times impairing, and at other times having no measurable effects on cognition. The direction of effect seems to vary with task, treatment, and subject factors including sex, age, and reproductive status [17,28,46,47], the type of estrogen, its dose, and regimen [16,48], and task attributes such as type of memory probed, stressful elements, or phase of learning [14,16,30,42,49,50]. Given these varied effects, it is possible that estrogens up- or down-regulate cognition by modulating function of select neural systems that mediate learning and memory during the training experience.

The diverse effects of estrogens on learning and memory fit well with a multiple memory system framework developed by many [51–59] positing that individuals can and do use different brain regions to solve tasks with different cognitive attributes. Theoretically, any brain region can be considered a memory system if it plays a key role in cognition; however, not all brain regions show selective engagement under different task conditions and thus cannot be dissociated based on task attributes. The hippocampus and striatum are two brain regions that have features making them particularly good prototypes for tests of hormonal modulation of multiple memory systems. First, both are large structures that are histologically separate and therefore relatively easy to manipulate and to assay. Second, the involvement of hippocampus and striatum in different types of learning and memory is readily dissociable through cognitive tasks that tap one system over the other. Shown largely in rats, with parallel findings using virtual tasks and imaging in humans [60], hippocampus-sensitive tasks include spatial