



Sex, estradiol, and spatial memory in a food-caching corvid



Michelle A. Rensel^{a,*}, Jesse M.S. Ellis^a, Brigit Harvey^a, Barney A. Schlinger^{a,b,c}

^a Department of Integrative Biology and Physiology, The University of California, Los Angeles, 610 Charles E Young Drive East, Los Angeles, CA 90095, USA

^b Laboratory of Neuroendocrinology, Brain Research Institute, The University of California, Los Angeles, 610 Charles E Young Drive East, Los Angeles, CA 90095, USA

^c Department of Ecology and Evolutionary Biology, The University of California, Los Angeles, 610 Charles E Young Drive East, Los Angeles, CA 90095, USA

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ABSTRACT

Estrogens significantly impact spatial memory function in mammalian species. Songbirds express the estrogen synthetic enzyme aromatase at relatively high levels in the hippocampus and there is evidence from zebra finches that estrogens facilitate performance on spatial learning and/or memory tasks. It is unknown, however, whether estrogens influence hippocampal function in songbirds that naturally exhibit memory-intensive behaviors, such as cache recovery observed in many corvid species. To address this question, we examined the impact of estradiol on spatial memory in non-breeding Western scrub-jays, a species that routinely participates in food caching and retrieval in nature and in captivity. We also asked if there were sex differences in performance or responses to estradiol. Utilizing a combination of an aromatase inhibitor, fadrozole, with estradiol implants, we found that while overall cache recovery rates were unaffected by estradiol, several other indices of spatial memory, including searching efficiency and efficiency to retrieve the first item, were impaired in the presence of estradiol. In addition, males and females differed in some performance measures, although these differences appeared to be a consequence of the nature of the task as neither sex consistently out-performed the other. Overall, our data suggest that a sustained estradiol elevation in a food-caching bird impairs some, but not all, aspects of spatial memory on an innate behavioral task, at times in a sex-specific manner.

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Introduction

In addition to their well-established role in the organization and activation of reproductive behaviors, sex steroid hormones also play a key role in modulating cognitive function. For example, estradiol and testosterone treatment have been shown to improve spatial memory in laboratory rodents (Daniel et al., 1997; Locklear and Kritzer, 2014; reviewed in Luine, 2014). Presumably, these effects are achieved through enhancement of neuronal connectivity and activity via estradiol's promotion of dendritic spine formation (Mukai et al., 2010; Romeo et al., 2004; Woolley, 1998) and long-term potentiation in the hippocampus (HP) (Córdoba Montoya and Carrer, 1997). However, estradiol's impact on spatial memory function is not always positive; instead, its influence depends on a variety of factors, including dose, duration, type of memory (i.e., working vs. reference memory), sex, and species differences in responsiveness (Galea et al., 2002; Lipatova et al., 2014; Luine, 2014; Woolley, 1998). In addition, hormonal mediation of spatial memory in non-model organisms, including those that do *not* undergo regular estrous cycles, such as birds, has only recently been explored (Bailey et al., 2013; Hodgson et al., 2008; Oberlander et al., 2004; Rensel et al., 2013).

Whereas circulating estradiol in females likely plays a role in spatial memory, local production of estradiol in the HP may mediate spatial memory in the absence of ovarian input in females or in males with little circulating estradiol. Although gonadectomy is used in many studies to examine the effects of sex steroid depletion on memory, this technique does not eliminate extra-gonadal sources of testosterone and estradiol such as those synthesized in the adrenals and brain, or other potential precursors in the full estrogen synthetic pathway (Schlinger et al., 2008).

In oscine songbirds, the enzyme aromatase is abundant in the HP in both males and females (Saldanha et al., 1998, 1999, 2000, 2004; Shen et al., 1995), and the brain expresses the upstream enzymes necessary for de novo estradiol synthesis (London et al., 2006). In addition, when compared to breeding birds, aromatase activity persists or even increases in the HP of some non-breeding birds, in contrast with aromatase expression and activity in the hypothalamus which is generally elevated only during breeding, when circulating testosterone is elevated (Balthazart et al., 1990; Soma et al., 1999, 2003). Similarly, treatment of intact and castrated male and female zebra finches with testosterone has no effect on aromatase activity in the HP, although activity in the pre-optic area (POA) increases in response to testosterone (Vockel et al., 1990). These observations suggest that the preservation of local estradiol synthesis in the HP is important for behavior and/or physiology during non-breeding periods when extra-gonadal sources of androgens and estrogens may be important.

* Corresponding author.

E-mail address: mrensel@ucla.edu (M.A. Rensel).

In the current study, we examined the nature of the relationship between estradiol and spatial memory in the Western scrub-jay (*Aphelocoma californica*; hereafter referred to as scrub-jay), a member of the corvid family (including jays, magpies, crows, and ravens) that routinely uses spatial memory to relocate food caches in nature. Scrub-jays not only possess impressive spatial learning and memory capabilities, but also display evidence of episodic memory (*what, where, and when*) with respect to food caches (Clayton and Dickinson, 1998). In addition, the HP of the scrub-jay (relative to body mass) is one of the largest of corvids studied to date (Pravosudov and de Kort, 2006). The avian HP, which is situated on the dorsal surface of the brain, is homologous to the mammalian HP (Mayer et al., 2013). In addition, lesions to the songbird HP produce deficits in spatial learning and memory that are restored by HP transplants (Patel et al., 1997; Watanabe and Bischof, 2004). Based on their natural history and strong spatial capabilities, this species represents an excellent system in which to examine the interplay between estradiol, food caching, and spatial memory.

Scrub-jays create caches in which to hide food year-long; however, favored fresh foods such as insects and larvae are less abundant in the winter, leading jays to utilize previously stored, less-perishable food items to survive. Accordingly, caching behavior increases during the fall acorn mast, enabling individuals to store acorns for later retrieval in times of need (De Gange et al., 1989). It is plausible that HP production of estradiol facilitates this behavior when jays are in non-breeding condition, as a) previous research has demonstrated non-breeding behavioral dependence on local neuroestrogen production (e.g., aggression in song sparrows, *Melospiza melodia*; Soma et al., 2000) and b) we have biochemical and immunocytochemical evidence for aromatase in the non-breeding scrub-jay HP (Fig. 1). Additionally, there is evidence for both estrogen receptor (ER) expression and non-genomic effects of estradiol in the songbird HP (Gahr et al., 1993; Heimovics et al., 2012; Hodgson et al., 2008; Metzendorf et al., 1999). We therefore hypothesized that estradiol production, presumably acting within the HP, facilitates memory for cache locations in non-breeding scrub-jays.

To test the hypothesis that estradiol facilitates spatial memory in scrub-jays, we manipulated whole body, systemic estradiol levels in wild-caught, adult male and female scrub-jays and assessed spatial memory using a well-characterized cache and recovery testing paradigm (e.g., Clayton et al., 2006). We reduced endogenous estradiol

through the use of an aromatase inhibitor, fadrozole (FAD). This ensured that sources of circulating estradiol (predicted to be inactive due to the non-breeding state) as well as brain estradiol were blocked (as in Cherrier et al., 2005; Hodosy et al., 2009; Moradpour et al., 2006; Rensel et al., 2013). In some of these individuals, estradiol levels were replaced or increased with a subcutaneous estradiol implant.

In addition to investigating the role of estradiol, we explicitly tested for sex differences in spatial learning and memory. Sex differences in spatial memory have been reported in studies of rodents (e.g., Jonasson, 2005; Sutcliffe et al., 2007), with males tending to perform with greater efficiency as compared to females. However, these differences may not arise from a decrement in memory in females, but rather from a sex difference in strategy employed to complete the task (Tropp and Markus, 2001; Williams and Meck, 1991). Interestingly, to our knowledge no previous assessment of spatial memory in scrub-jays has considered sex-specific effects. In light of our hypothesis that estradiol regulates spatial memory, we were particularly interested in investigating how sex interacted with our experimental treatment to affect cache recovery.

Materials and methods

Western scrub-jays were captured using peanut-baited Potter traps in multiple locations in Southern California and brought into captivity during the summer months (July–August). Appropriate state and federal collecting permits were obtained prior to capture. We caught a total of 18 individuals (independent young and adults) in 2013 ($n = 6$ females and 12 males). In addition, one individual was captured as a nestling and hand-raised in captivity during the summer of 2012 (a female); this individual participated in preliminary caching and retrieval tests prior to the current experiment. We confirmed that in the current experiment, behavioral measures obtained from this hand-raised individual were within the range of variation observed among the other individuals. Captive jays were housed in groups of 1–4 in rooftop aviaries and provided with ad libitum water and food (Roudybush Daily Maintenance Diet) supplemented with fresh fruits, vegetables, worms, and peanuts. The number of individuals housed per aviary varied because some individuals were less aggressive when caged with fewer conspecifics, whereas others were amenable to housing in larger groups. However, regardless of housing numbers,

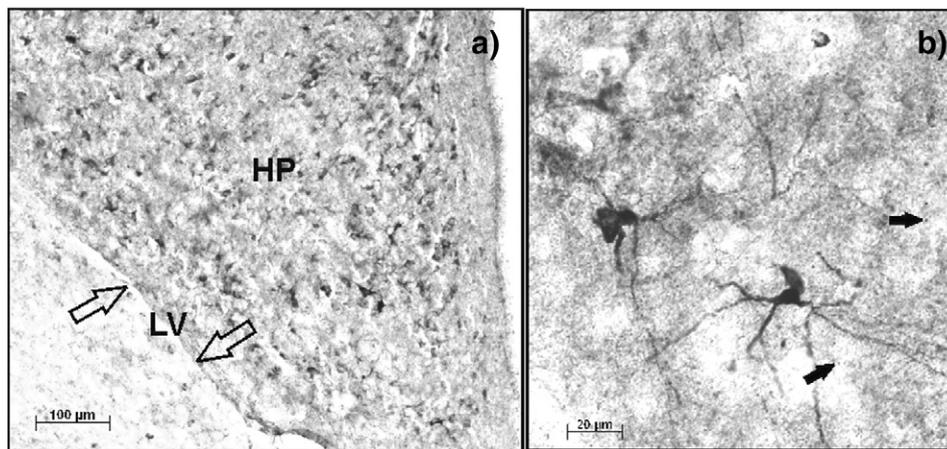


Fig. 1. Low (a) and high (b) power photomicrographs showing localization of aromatase staining in the adult scrub-jay HP. a) An abundance of stained soma and fibers are found in the HP, while relatively low levels of staining are found in the adjacent telencephalon. Open arrows point to the lateral ventricle (LV). b) At high power, the degree of somal and fiber staining in the HP is easily observed, as well as staining of punctate structures (dark arrows). Immunohistochemistry was performed as follows: after perfusion with 4% paraformaldehyde, the brains were sectioned at 40 μm and stored in an antifreeze at $-20\text{ }^{\circ}\text{C}$. Immunohistochemistry was performed following established protocols (Ellis and Ritters, 2013; Heimovics and Ritters, 2005) with the following changes: because the brains were fixed with formaldehyde, no sodium borohydride was used and associated washes were eliminated. Anti-aromatase primary antibody (Saldanha et al., 2000) was used at 1:5000 in 0.1 M phosphate buffered saline (PBS). Secondary was biotinylated goat anti-rabbit (1:1000; Vector Labs). After incubating in AB solution, sections were washed twice for 5 min each in PBS, then washed three times in 0.175 M sodium acetate (Hoffman et al., 2001). After treatment with diaminobenzidine (DAB), sections were washed in 0.175 sodium acetate $2\times$ for 5 min before a final 5 min wash in PBS.

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