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Abstract

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ESTROGEN MODULATES LEARNING IN FEMALE RATS BY ACTING DIRECTLY AT DISTINCT MEMORY SYSTEMS<sup>1</sup>L. Zurkovsky,<sup>2</sup> S.L. Brown,<sup>3</sup> S. Boyd,<sup>3</sup> J.A. Fell,<sup>3</sup> and D.L. Korol<sup>2,3\*</sup><sup>2</sup> Neuroscience Program, University of Illinois, Champaign, IL 61820<sup>3</sup> Department of Psychology, University of Illinois, Champaign, IL 61820\* Correspondence and Reprints: Donna L. Korol, Ph.D., Department of Psychology, University of Illinois, 603 E. Daniel St., Champaign, IL 61820, Tx: (217) 333-3659, Fax: (217) 244-5876, e-mail: [dkorol@uiuc.edu](mailto:dkorol@uiuc.edu)

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## Abstract

Physiologically high levels of circulating estradiol enhance the use of place learning and impair the use of response learning to find food on a land maze. These two types of learning are impaired by lesions of distinct neuronal structures, i.e. the hippocampus and striatum, respectively. Moreover, it has been shown in male rats that compromising hippocampal function can promote the use of response learning, while compromising striatal function can promote place learning. These findings suggest an ongoing competition between the hippocampus and striatum during cognition, such that intact functioning of one structure somehow obstructs the relative participation of the other. The goal of this study was to determine if estrogen's opposing effects on place and response learning in female rats are due to direct actions, either independent or interacting, at the hippocampus and striatum. We infused 0.5 •M 17 $\beta$ -estradiol 3-sulfate sodium or vehicle bilaterally into the dorsal hippocampus or dorsolateral striatum of ovariectomized young adult female rats, 48, 24 and 2 hours before training. Rats were

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tested on one of three appetitive tasks in a Y-maze: place learning, response learning, or response learning with reduced visual cues (cue-poor condition). Intrahippocampal estradiol infusions enhanced place learning, reversing a cannula-induced impairment, whereas intrastriatal infusions had no effects on place learning. Estradiol infusions into neither structure significantly affected response learning when extramaze cues were visible. However, in the response task, cue-poor condition, intrastriatal but not intrahippocampal infusions impaired learning. These data demonstrate that estrogen modulates place and response learning at the hippocampus and striatum respectively, most likely through independent actions at these two structures.

Keywords: hippocampus, striatum, hormones, cognition, strategy

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Estrogen has repeatedly been shown to influence learning and memory in navigational tasks, at times improving and at other times impairing performance (for review see [Dohanich, 2002](#)). Several ideas have been proposed to account for the mixed effects of estrogen on cognition, including the possibility that the efficacy of estrogen treatment varies with motivating factors of the task ([Wilson et al., 1999](#)), stress state of the animals ([Wood and Shors, 1998](#)), type of memory ([Fader et al., 1999](#); [Galea et al. 2001](#)), and duration and type of hormone treatment, ([Luine et al., 1998](#); [Thomas et al., 2002](#); [Gibbs, 2000](#)).

Accumulating evidence from our and other laboratories suggests that the varied effects may also result from estrogen biasing the relative contributions of memory systems during cognition, thereby shifting the learning strategy an animal uses to solve a task, perhaps producing impairments in some learning contexts and enhancements in others (for review see [Korol, 2004](#)). For example, in a dual solution appetitive T-maze task that can be solved either by place (“go there”) or response (“turn this way”) strategies, female rats at proestrus, a point in the estrous cycle when estrogen and progesterone are elevated, use a place strategy ([Korol et al., 2004](#)). This type of learning is considered hippocampus-sensitive because it is consistently modulated by manipulations to this structure ([Chang and Gold, 2003](#); [Packard and McGaugh, 1996](#)). Conversely, when hormones are lowest, rats at estrus prefer to use a response strategy, considered a dorsal striatum-sensitive task. Together, the data suggest that fluctuations in reproductive hormones across the cycle bias learning strategy through the activation of different memory systems ([Korol et al., 2004](#)).

The dissociation of the effects of hormones on learning strategy is supported by findings from numerous studies examining the effect of ovariectomy plus hormone administration on learning and memory (for review see [Korol, 2004](#)). Estrogen treatments administered to ovariectomized rats enhance performance on hippocampus-sensitive

tasks, such as retention in the spatial version of the swim task (Packard and Teather, 1997a), acquisition and working memory in radial maze and swim tasks (Bimonte and Deneberg, 1999; Daniel et al., 1997; Daniel and Dohanich, 2001; Luine et al., 1998; Sandstrom and Williams, 2001), and delayed alternation in the T-maze (Fader et al., 1998). Hormone-deprived rats show enhanced performance on hippocampus-insensitive behaviors, particularly those dependent on an intact dorsal striatum such as cued (Daniel and Lee, 2004), win-stay (Galea et al., 2001) and response (Korol and Kolo, 2002) learning. Furthermore, when trained on a hippocampus- or striatum-sensitive task with the same basic training protocol except for the specific cognitive demands, i.e. place vs response learning, respectively, rats that receive estradiol treatment exhibited enhanced performance on the place task and impaired performance on the response task (Korol and Kolo, 2002). Importantly, rats deprived of estradiol demonstrated the opposite pattern of effects: enhanced performance on response and impaired performance on place learning.

The idea that different neuronal structures mediate different attributes of learning is supported by findings from both human and non-human animal studies using various paradigms that alter or measure the function or participation of specific neuronal structures. Consensus from these studies, mostly conducted with male rats, is that learning to navigate a maze with the extramaze cues is impaired by manipulations that decrease the functional integrity of either the dorsal hippocampus or its main afferent/efferent tract, the fornix, but is not impaired by disruption of the dorsal striatum (Becker et al. 1980; Packard and McGaugh, 1992; Packard and Teather, 1997b). Furthermore, performance in tasks requiring egocentric responses or stimulus-response pairings is impaired by lesions to the dorsal striatum but not the hippocampus (McDonald and White, 1993; Devan and White, 1999; Kesner et al., 1993). Interestingly, temporary inactivation of the striatum with lidocaine impaired response learning only when access to the extramaze visual cues was diminished with low lighting or a curtain (Chang and Gold, 2004). These and other examples of double and triple dissociations (White and McDonald, 2002) support the idea that different memory systems disproportionately contribute to learning depending on the nature of the task and the training environment.

The precise nature of the interactions between memory systems is relatively unknown and currently under extensive investigation. In some instances the function of the hippocampus and dorsal striatum appear independent and dissociable such that manipulations of one structure fail to influence performance on the non-canonical task (Cook and Kesner, 1988; Packard and White, 1991; Packard and McGaugh, 1992; Kesner et al., 1993; Packard and Teather, 1997b; Kobayashi and Iwasaki, 2000). However, a growing literature suggests that the function of the hippocampus and striatum may interact (Mizumori et al., 2004; White, 2004). For example, lesions to the hippocampus or the fimbria/fornix can enhance acquisition of cued, response, or win-stay tasks, suggesting that an

intact hippocampus obstructs learning in these contexts (Packard et al., 1989; McDonald and White, 1993; Matthews and Best, 1995; Chang and Gold, 2003). Furthermore, subpopulations of hippocampal and dorsal striatal neurons may both be active during learning and performance of place and response tasks (Mizumori et al., 2004). These and other findings support the idea that both structures play important roles in mediating place and response learning and that at times the dorsal striatum may compete with the hippocampus and at other times collaborate for control of cognition.

Given our previous results that estrogen enhances place learning and impairs response learning, it is possible that estrogen acts at distinct neural sites, specifically hippocampus and striatum, to modulate learning strategy. What is less clear is whether estrogen acts at both structures or solely through one structure to modulate both learning attributes, i.e. to enhance place and to impair response learning.

If estrogen acts at each memory system independently, we would expect to find simple dissociations: intrahippocampal application of estrogen will only enhance place learning, and intrastriatal infusions will only impair response learning. If estrogen alters the competitive balance between hippocampus and striatum to produce its effects, then estrogen into the hippocampus of an ovariectomized animal would dually enhance place and impair response learning. Alternatively, but not mutually exclusively, intrastriatal infusions of estrogen may also impair response and enhance place learning.

We tested these predictions by infusing bilaterally estradiol or vehicle into either the dorsal hippocampus or dorsolateral striatum of ovariectomized young adult rats. Separate groups of rats were then tested on place and response learning tasks. Our findings support the hypothesis that estrogen acts directly at the hippocampus to enhance place learning and at the striatum to impair response learning.

## Experimental Procedures

### Subjects

Three-month-old Sprague-Dawley virgin, female rats were obtained from Harlan (Oregon, WI barrier) in squads of 10–12 rats. Rats were housed individually in plastic cages with free access to food and water until food restriction was initiated. Lights were maintained on a 12:12 light:dark cycle. Rats were given at least one week to habituate to the vivarium before any procedures were initiated.

All rats underwent bilateral ovariectomy 21 days prior to behavioral training. They were allowed seven days to recover before guide cannulae were implanted bilaterally into the neural site of interest (see below). One week

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prior to maze training, rats were food restricted to 85% of the free feeding weight plus 5 g to account for normal growth. Rats received a bilateral infusion of treatment or vehicle 48, 24, and 2 hrs prior to training. Immediately after training was complete, rats were sacrificed for collection of brains for histology.

All procedures were approved by the University of Illinois Institutional Animal Care and Use Committee and are in compliance with the Guide for the Care and Use of Laboratory Animals (National Institute of Health, 1986).

## Experimental Groups

Three maze tasks were used: place training with visual cues, response training with visual cues, and response training with diminished visual cues. Rats with hippocampal implants (HC) and striatal implants (DS) were randomly assigned to one of the three behavioral tasks and one of two drug treatments, vehicle control (artificial cerebral spinal fluid, aCSF) or 17- $\beta$  estradiol-3-sulfate (E2-S). Thus, there were three tasks (place, response, and response, cue-poor), two neural sites (HC, DS) and two treatments (aCSF, E2-S), creating twelve main treatment groups. Three controls were also included: 1) Unimplanted control (UC) rats without cannulae to control for effects of tissue damage due to cannula implantation, 2) rats with cannulae aimed at the cortex just dorsal to the hippocampus or the striatum to control for the spread of hormone beyond the site of interest, and 3) rats with unilateral DS infusions trained on rotational behavior to test the efficacy of the E2-S. UC rats were unimplanted, ovariectomized rats receiving no hormonal treatment but trained on each task. Cortical controls included two groups of rats receiving E2-S: One with cannulae aimed at the cortex overlying the hippocampus and trained on the place task and the other with cannulae in the cortex overlying the striatum and trained on the response, cue-poor task. Controls for hormone efficacy had striatal cannulae and were tested for rotational behavior following unilateral E2-S and aCSF exposure. This latter control group was not food restricted or trained on maze learning tasks but was otherwise treated like maze-tested groups.

## Ovariectomy

Rats were anesthetized (i.p.) with ketamine (74 mg/kg) and xylazine (5 mg/kg) and given pre- and post-operative injections of the analgesic Rimadyl (5 mg/kg, s.c.). Bilateral removal of the ovaries was done through a dorsolateral approach under aseptic conditions (see [Korol and Kolo, 2002](#)). All ovariectomies were complete as evidenced by smears (see below) and inspection upon sacrifice.

## Cannula Implantation

Approximately one week after ovariectomy, rats were anesthetized with ketamine (74 mg/kg, i.p.) and xylazine (5

mg/kg; i.p.) and received 30,000 units of penicillin (i.m.; Dura-Pen; Henry Schein, Inc., Indianapolis, IN) prior to stereotaxic surgery. Sterile, stainless steel guide cannulae (22 gauge, 6mm; Plastics One, Inc., Roanoke, VA) aimed either at the dorsal hippocampus (AP -3.8, ML 2.5, 1.9 mm ventral to dura) or the dorsal striatum (AP +0.2, ML 3.6, 2.8 mm ventral to dura), were implanted bilaterally in all rats (Figure 1A, B). Coordinates were chosen based on reports demonstrating effects of hippocampal and striatal inactivation on place and response learning (Packard and McGaugh, 1996; Chang and Gold, 2003; 2004) and were adapted from the atlas of Paxinos and Watson (1986). Cannulae for cortical control groups were implanted just dorsal to the hippocampus (0.8 mm ventral to dura; Figure 1A) or to the dorsal striatum (1.0 mm ventral to dura; Figure 1B). Four stainless steel jeweler's screws were placed into the skull for anchors and the assemblage was cemented in place with dental acrylic. To keep cannulae open, 28 gauge stylets (Plastics One, Inc., Roanoke, VA) cut to the length of the guide cannulae were inserted at the time of surgery and were removed only during the central infusions. Rats received pre- and post-operative injections of Rimadyl (5 mg/kg, s.c.) for analgesia.

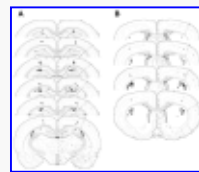


Figure 1

Infusion sites aimed at the A) dorsal hippocampus or overlying cortex and B) dorsolateral striatum or overlying cortex. Circle shading represents the task used during training, black = place, gray = response, white = response, cue-poor.

## Central Hormone Injections

All maze-tested rats with cannulae received bilateral 0.5  $\mu$ L infusions of hormone or vehicle 48, 24 and 2 hours prior to training. The time points for central injections were chosen to mimic exposure to estrogen when injected peripherally at 48 and 24 hours before training, an acute replacement schedule shown previously to modulate learning (Korol and Kolo, 2002). Because serum hormone levels remain elevated 24 hours after a second estradiol injection (Woolley and McEwen, 1993) and because the time course of clearance following central E2-S infusions is relatively unknown, the third injection 2 hours prior to training was added to ensure the presence of estrogen in the brain at the time of training.

The hormone treatment groups received 0.5  $\mu$ M  $17\beta$ -estradiol 3-sulfate sodium (E2-S; Sigma-Aldrich, Inc., St. Louis, MO) a dose previously found to be effective in altering measures of cardiovascular function (Saleh et al., 2000) while control groups received aCSF vehicle (in mM: 128 NaCl, 2.5 KCl, 1.3 CaCl<sub>2</sub>, 2.1 MgCl<sub>2</sub>, 0.9 NaH<sub>2</sub>PO<sub>4</sub>, 2.0 Na<sub>2</sub>HPO<sub>4</sub>, 1.0 dextrose, adjusted to pH 7.4). The sulfated form of estradiol was chosen for its water

solubility, thereby enabling infusions in aCSF vehicle. The hormone or vehicle was infused through a 28g injection needle (Plastics One Inc., Roanoke, VA) fit to extend 1 mm beyond the guide cannula. Infusions were made for 1 min with a CMA/100 microinjection pump (CMA Microdialysis AB, North Chelmsford, MA) set at rate of 0.5  $\mu$ L/min. Needles were left in place for 1 min after infusion to allow the solution to diffuse from the cannula tips. The same procedures were used for unilateral infusions prior to tests of rotational behavior.

## Training Procedures

**Maze tasks.** Three weeks after ovariectomy, separate groups of rats were trained on one of three tasks: place learning, response learning and response learning with diminished visual cues (response, cue-poor). Squads of 10–12 rats were trained, with assignments distributed across different treatments and tasks. Each task required food-restricted rats to find food on the same three-arm radial maze. For standard place and response learning, training was done in the same room with the same cues. For the response, cue-poor condition, the maze was encircled with a curtain to minimize access to extra-maze visual cues.

**Training apparatus and environment.** The maze was Y-shaped with three symmetrical arms each extending 18 cm in length, 5 cm in width, with 3 cm-high walls made of clear Plexiglas®. It was placed on a stand 25 cm above the floor. At the end of each arm was a food boat where the reward (1/2 Frosted Cheerio®) was placed. The training room contained various two- and three-dimensional extra-maze cues, for example a black curtain, black and white-stripped box, hanging tennis balls, various placards, etc. Two halogen lights aimed towards the ceiling provided ambient lighting.

**General training protocol.** All training was confined to one day and took place during the light phase, 3–9 hours before lights off. To habituate rats to the training environment, animals were placed in a clean holding cage and left in the training room for 15 minutes prior to the initiation of testing. Each trial began by placing the animal into a start arm and allowing it to enter one arm to find the food reward. If the rat entered the correct arm, it was allowed to remain in the goal arm for 10 seconds to eat the food reward or until it turned to exit. If the rat entered the incorrect arm, it was removed from the maze and placed in a clean holding cage either 10 seconds after arriving at the end of the arm or just after turning to exit. If no choice was made after three minutes, the trial was terminated. Between trials, rats remained in the holding cage for a 30-second intertrial interval. Rats were trained to a criterion of 9 correct choices in 10 trials.

**Place task.** Rats with either HC (n's: aCSF = 9, E2-S = 10) or DS (n's: aCSF = 7, E2-S = 9) infusions or that were unimplanted with no treatment (UC; n = 10) were trained to find a food reward at the end of a goal arm in the place task. Throughout training, the reward remained in a fixed location relative to the extra-maze room cues. The goal

location was assigned randomly and counterbalanced across rats within a treatment condition. The two remaining arms served as start positions and were also quasi-randomized and counterbalanced within blocks of 20 trials. To reduce the use of intra-maze cues, the maze was rotated randomly using preset stops at 120° intervals.

**Response task.** Rats with either HC (n's: aCSF = 8, E2-S = 9) or DS (n's: aCSF = 8; E2-S = 7) infusions or that were UC (n = 8) were trained in the response task. Rats were rewarded for making a specific turn, either right or left, at the choice point of the maze. The rewarded turn, right or left, was randomly counterbalanced across rats within a treatment condition. Across training trials, the start arm was assigned quasi-randomly and counterbalanced within blocks of 12 trials across all three arms of the maze. The goal arm was assigned to maintain the directional relationship between start and goal. Again, the maze was rotated during the intertrial interval to reduce the use of intra-maze cues.

**Response, cue-poor task.** Rats with HC (n's: aCSF = 8; E2-S = 8) or DS (n's: aCSF = 7; E2-S = 7) infusions or that were UC (n = 11) underwent identical treatment to those on the standard response task except that a beige curtain was placed around the perimeter of the room to obstruct access to visual room cues.

**Cortical Controls.** To reduce the numbers of rats used, cortical controls were included only for tasks and neural sites for which the effects of estrogen treatment were statistically significant. Rats with cannulae positioned in the cortex overlying the hippocampus or striatum were tested after E2-S treatment in the place task (n = 6) or the response task, cue-poor condition (n=4), respectively.

**Rotation behavior.** To test whether the selected dose of sulfated estradiol was active in the brain, contralateral rotation behavior was measured after unilateral infusions of the hormone or vehicle in the striatum (n = 8). Previous work found that unilateral intrastriatal application of 17 $\beta$ -estradiol alone enhanced rotations contralateral to the hemisphere of treatment (Roy et al., 1990). Here, rats were ovariectomized and had cannulae implanted bilaterally into the dorsal striatum. Microinjections were given with the same dosage (0.5 $\mu$ M in a volume of 5 $\mu$ L) and schedule (48, 24 and 2 hours before behavioral measurement) as described above. To control for natural rotation tendencies, all animals were tested under each treatment, E2-S and aCSF, with a one-week wash-out period between testing sessions. The order of treatment was randomly assigned and counterbalanced across rats. Injection hemisphere was randomly assigned and kept constant across both testing sessions. For testing, rats were placed in a clear, circular arena with banked walls for a 10-min testing period, during which quarter turns in each direction were recorded manually by the experimenter.

## Determination of Estrogen Status

Vaginal smears were collected daily for 5 days prior to training to determine that ovariectomies were complete and estrous cycles had ceased. A small sterile swab (calcium alginate tips, Fisher Scientific, Pittsburgh, PA), soaked in sterile saline, was gently inserted into the vagina. Vaginal cells were fixed to a clean slide with ethanol and later stained with hematoxylin and eosin. They were then staged using the methods of [Long and Evans \(1922\)](#).

### Assessment of cannula placements

Immediately after training, animals were euthanized with an overdose of pentobarbital and were perfused transcardially with phosphate-buffered saline followed by 10% formalin. Brains were stored in 10% formalin and cryoprotected in a 20% sucrose/formalin solution for at least 48 hours before being sectioned at 45  $\mu$ m in a cryostat. Rats were excluded if one or both cannulae were misplaced or if there was evidence of tissue damage that extended beyond the implantation site. Placements for all groups are shown in [Figure 1](#).

### Data Analysis

**Measures.** Rates of learning were assessed by the number of trials needed to reach the criterion of 9 correct out of 10 consecutive trials. Rotation behavior was determined as the proportion of contralateral rotations out of total rotations. Percent change in the proportion of contralateral rotations under aCSF compared to estradiol treatment was calculated for each rat.

**Statistical analysis.** To determine the site-specific effects of centrally injected E2-S on learning, separate comparisons were made within task and neural site between aCSF and E2-S. Because of the arbitrary ceiling of 100 trials, Mann-Whitney nonparametric tests were used to assess the effects of hormone treatment on trials to criterion. Based on results presented below, it is clear that cannula-induced damage to the hippocampus and striatum produce disparate effects on place and response learning; thus, it is critical to compare statistically groups receiving aCSF and E2-S treatments in the same neural site and trained on the same task.

Trials to criterion data from unimplanted controls were compared to HC- and DS-aCSF-treated rats within each task using Mann-Whitney tests. Comparisons across tasks in unimplanted, untreated control rats were conducted with Kruskal-Wallis tests and post-hoc paired comparisons.

Rats infused with E2-S into the cortex overlying the hippocampus or dorsal striatum were compared to rats receiving aCSF or E2-S into the structure of interest, using Mann-Whitney non-parametric tests.

For rotation behavior, paired t-tests were used to evaluate within subject differences in contralateral rotations following E2-S and aCSF infusions.

All statistical analyses were run with  $\alpha = 0.05$ .

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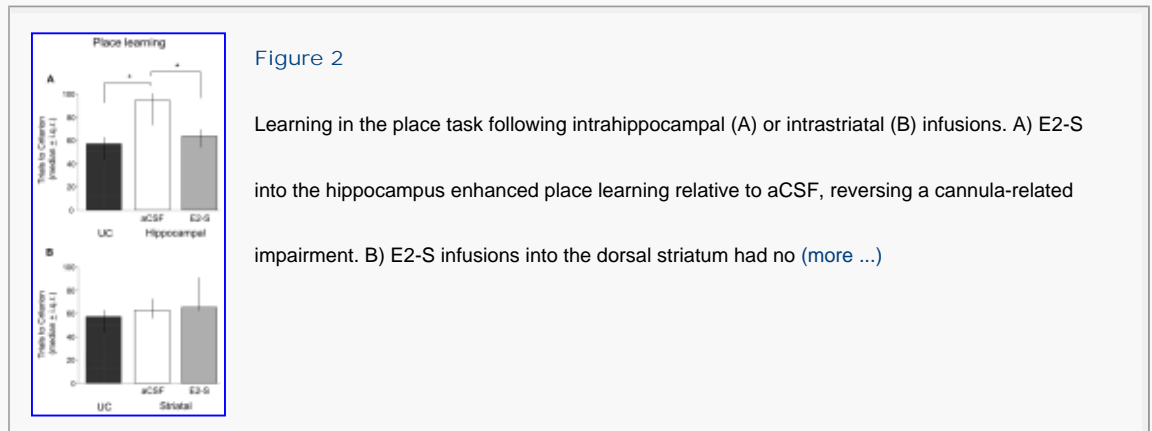
## Results

Rats included in the final analyses showed typical diestrous vaginal smears of ovariectomized rats for five days prior to training (data not shown), indicating a lack of estrous cycles.

### Maze Training: Place and Response Learning Tasks

Place learning was enhanced by intrahippocampal infusions of E2-S, reversing a cannula-induced impairment, but was not affected by intrastriatal infusions of E2-S. Conversely, response learning was impaired by intrastriatal but not intrahippocampal infusions of E2-S, with impairments reaching statistical significance only when visual cues were reduced.

**Place Learning.** Administration of E2-S to the hippocampus enhanced performance on the place task, seen by a significant decrease in trials to reach criterion for E2-S rats compared to aCSF controls (Figure 2A; median aCSF = 94 and E2-S = 63.5;  $U(9,10) = 12.5$ ,  $p < .01$ ). E2-S injected into the dorsal striatum had no significant effects on trials to criterion in the place learning task (Figure 2B; median aCSF = 63 and E2-S = 65;  $U(7,9) = 22.5$ ,  $p > .3$ ).



Site of cannula implant and infusion significantly affected learning in the place task. Rats with hippocampal cannulae treated with aCSF took significantly more trials to reach criterion than did UC, untreated ovariectomized rats (Figure 2A; median HC-aCSF = 94 and UC = 57;  $U(9,10) = 8$ ,  $p < .005$ ). Cannula implantation into the striatum had no significant effect on place learning as trials to criterion in rats treated with intrastriatal aCSF (median = 63) were similar to those in UC rats (median = 57; Figure 2B;  $U(7,10) = 24.5$ ,  $p > .3$ )

**Response learning: cue-rich environment.** E2-S injections into the hippocampus had no significant effects

on response learning (Figure 3A; median aCSF = 62 and E2-S = 48;  $U(8,9) = 36$ ,  $p > .9$ ). E2-S injections into the dorsal striatum also had no significant effects on response learning when visual cues were available (Figure 3B; median aCSF = 18 and E2-S = 33;  $U(8,7) = 17.5$ ,  $p > .2$ ).

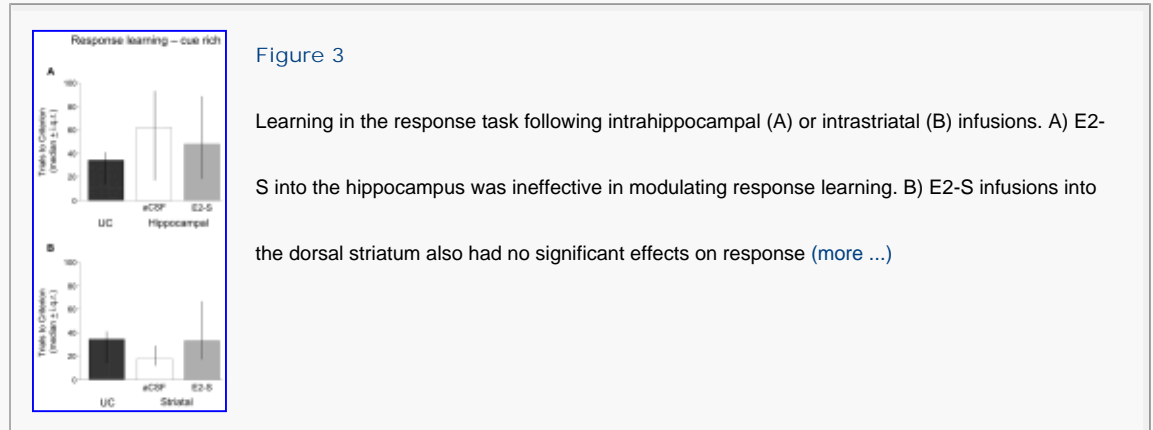


Figure 3

Learning in the response task following intrahippocampal (A) or intrastratial (B) infusions. A) E2-S into the hippocampus was ineffective in modulating response learning. B) E2-S infusions into the dorsal striatum also had no significant effects on response ([more ...](#))

Cannula implant status did not significantly affect learning in the response task when cues were available.

Compared to UC rats (median = 34), trials to reach criterion were not significantly different for rats with HC aCSF infusions (median = 62;  $U(8,8) = 17$ ,  $p > .1$ ) or for rats with DS aCSF infusions (median = 18;  $U(8,8) = 25$ ,  $p > .4$ ).

**Response learning: cue-poor (curtained) condition.** Performance on the response, cue-poor task was not significantly influenced by infusions of E2-S to the hippocampus (Figure 4A). Rats in aCSF and E2-S-treated groups demonstrated similar trials to criterion (median aCSF = 41.5 and E2-S = 45;  $U(8,8) = 26$ ,  $p > .5$ ). E2-S injections into the dorsal striatum impaired performance of response learning when visual cues were obstructed (Figure 4B). Rats treated with E2-S took significantly more trials to reach criterion than did rats with vehicle aCSF (median aCSF = 18 and E2-S = 40;  $U(7,7) = 5$ ,  $p < .02$ ).

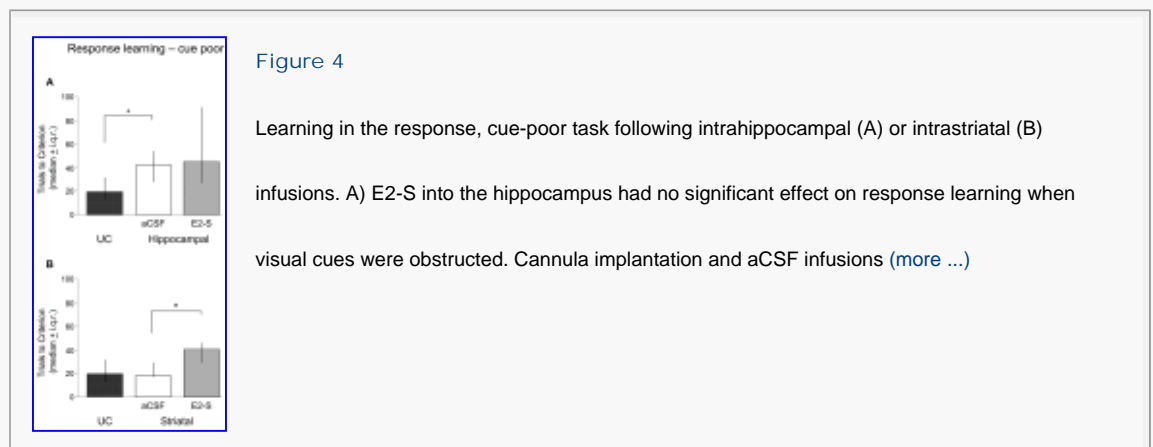


Figure 4

Learning in the response, cue-poor task following intrahippocampal (A) or intrastratial (B) infusions. A) E2-S into the hippocampus had no significant effect on response learning when visual cues were obstructed. Cannula implantation and aCSF infusions ([more ...](#))

Compared to unimplanted, untreated controls, cannula implantation and infusion into the hippocampus impaired learning in the response, cue-poor task while implantation into the striatum did not (Figure 4A, B). Specifically,

compared to UC rats (median = 19), trials to reach criterion were different for rats with HC aCSF treatments (median = 41.5;  $U(8,11) = 20$ ,  $p < .05$ ) but not for those with DS aCSF infusions (median = 18;  $U(7,11) = 38.5$ ;  $p > .9$ ).

**Cortical controls.** Cortical infusion of E2-S failed to produce significant effects on learning in either the place or the response, cue-poor task. Specifically, E2-S infused into the cortex overlying the hippocampus did not enhance place learning. No significant group differences in trials to criterion were found between rats with E2-S infusions into the cortex overlying the hippocampus (median = 77.5) and rats with aCSF directly into the hippocampus (median = 94;  $U(9,6) = 25$ ,  $p > .8$ ). Scores were significantly higher in rats with cortical infusions of E2-S than in rats with hippocampal treatments of E2-S (median = 63.5;  $U(6,10) = 11$ ,  $p < .04$ ; data not shown). Similarly, E2-S injections into the cortex overlying the striatum did not significantly impair performance on the response, cue-poor task. Trials to reach criterion for rats receiving E2-S into the cortex overlying the striatum (median = 13) were similar to those from rats with aCSF to the striatum (median = 18;  $U(7,4) = 9$ ;  $p > .3$ ) and were significantly lower than values from rats with E2-S to the striatum (median = 40;  $U(7,4) = 2$ ,  $p < .03$ ; data not shown).

**Effects of task in unimplanted controls.** There was a significant task-dependent effect on learning in UC rats, i.e. rats that were ovariectomized and without hormone treatment or cannula implantation ( $H(2,29) = 16.7$ ,  $p < .0005$ ). Specifically, UC rats trained on the place task took significantly longer to reach criterion (median = 57) than did rats trained on either the response task (median = 33;  $p < .02$ ) or the response, cue-poor task (median = 19;  $p < .0005$ ). Scores on the two response tasks were not significantly different from each other ( $p > .5$ ), though performance on the response task without visual cues available was better than performance on the response task with cues (see [Figures 2, 3, and 4](#)).

### Contralateral Rotation: Unilateral Estradiol-3-Sulfate Injections

Compared to vehicle administration, E2-S infusions significantly enhanced rotations contralateral to the treated hemisphere. Within-animal comparisons revealed a 29% ( $\pm 10\%$ ) increase (data not shown;  $t(7) = 2.8$ ,  $p < .05$ ) in contralateral rotations following unilateral estradiol application.

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## Discussion

Our findings suggest that estrogen acts at distinct neural sites to modulate performance on two maze tasks that differ in the cognitive strategy required for successful completion. Specifically, hormone injections into the hippocampus but not striatum of ovariectomized rats enhanced place learning, a task requiring the use of extramaze cues to find a food reward. The enhancement following intrahippocampal estrogen treatment reflected a reversal of impairment caused by cannula implantation. Conversely, intrastriatal estrogen impaired response learning when access to visual cues was diminished, a task in which rats are rewarded for making the correct body turn. Importantly, intrahippocampal injections were ineffective in modulating response learning with or without cues available. Together, these data suggest that estrogen enhances and impairs learning in a site-specific manner, effects that cannot be explained by actions at any single structure.

The faster learning on the response tasks observed in the unimplanted control rats mirrors our previous findings (Korol and Kolo, 2002) in which rats that were ovariectomized and hormone deprived for three weeks, i.e. the duration used presently, performed better on a response than on a place task. Performance on other tasks that also tap function of the dorsal striatum, e.g. cued versions of the swim and radial maze tasks, is enhanced in rats with relatively low estrogen status (Daniel and Lee, 2004; Galea et al. 2001).

### Site-specific dissociations in the modulation of memory systems

Functional dissociations between the hippocampus and striatum are well established, where lesions of each structure impair a specific type of task. Hippocampal or fornix lesions impair the use of extramaze cues to navigate through a maze, whereas striatal lesions impair the use of body-movement and intramaze cues (Packard and McGaugh, 1992; Kesner et al., 1993). These patterns in learning support the well-known belief that each structure is specialized for processing specific types of information or attributes (for review see White and McDonald, 2002). Our data support distinct roles for the hippocampus and striatum in learning, and suggest that estrogen acts within those established parameters by affecting place learning through actions at the hippocampus and response learning through actions at the striatum.

The finding that E2-S infusions into the hippocampus enhance place learning is supported by converging lines of work demonstrating robust effects of intrahippocampal estrogen on other cognitive behaviors and on direct measures of hippocampal function (for review see Dohanich, 2002). Intrahippocampal infusions of estradiol-cyclodextrin, a rapidly metabolized form of estrogen, enhance 24-hour memory in the spatial version of the swim task in male and ovariectomized female rats (Packard and Teather, 1997c). Further, chronic (Gibbs, 1999)

systemic estrogen treatments attenuate the cognitively impairing effects of cholinergic muscarinic antagonists delivered to the hippocampus on delayed matching to position tasks, supporting further estrogen's potential actions at the hippocampus and interactions with the cholinergic system. Consistent with a synergistic role of estrogen and acetylcholine, systemically administered doses of scopolamine that alone were subeffective on performance in the swim task, blocked the learning enhancement caused by intrahippocampal estrogen injections (Packard et al., 1996). Potentiated acetylcholine release in the hippocampus has been demonstrated following potassium stimulation (Gibbs et al. 1997) or maze learning (Marriott and Korol, 2003). The finding that estrogen facilitates forebrain cholinergic activity has been shown using many other approaches (Luine, 1985; Singh et al., 1994; Gibbs et al. 2004; Simpkins et al., 1997), and reflects one candidate mechanism through which estrogen modulates hippocampal inhibition (Rudick et al. 2003) and NMDA receptor properties (Daniel and Dohanich, 2001). Given these data showing extensive estrogen effects on hippocampal function, as well as findings linking estrogen to learning-associated synaptic plasticity, such as long-term potentiation (Cordoba Montoya and Carrer, 1997; Foy et al., 1999), long-term depression (Day and Good, 2005) dendritic spine formation (Gould et al., 1990; Woolley and McEwen, 1993) and phosphorylation of cAMP response element binding protein (Wade and Dorsa, 2003), it is not surprising that direct estrogen infusions enhance place learning, a cognitive function shown to be sensitive to hippocampal manipulations.

The current experiments test directly the effects of striatal estrogen on striatum sensitive learning. Others have shown that enhancements in learning following peripheral injections of estrogen are not associated with changes in striatal muscarinic receptor binding (Vaucher et al., 2002) or acetylcholinesterase activity (Das et al., 2002).

However, the tasks used in these studies, object recognition memory and single-trial passive avoidance, respectively, may fail to engage the striatum sufficiently, or the measure, cholinergic muscarinic receptor binding, may not reflect the neural mechanism related to the tasks. In addition to our previous work using systemic injections (Korol and Kolo, 2002), findings from others show that elevations in peripheral estrogen impair performance on tasks sensitive to striatal manipulations. Learning in a cued win-stay task was impaired by daily injections of estradiol 4 hrs prior to training (Galea et al. 2001). Furthermore, when trained on tasks that have multiple solutions, rats with high plasma estradiol prefer to use extramaze cues, similar to the presumptive strategy used during place learning (Korol et al., 2004), whereas rats with low plasma estradiol use striatum-sensitive body movements (Korol et al., 2004) or intramaze cues (Daniel and Lee, 2004). Consistent with the logic that low estrogen profiles may promote the use of non-hippocampal strategies, rats with low plasma estradiol are more attentive to intramaze cues than are those with high levels (Tropp and Markus, 2001).

The finding that rats receiving E2-S into the striatum were impaired on response learning only when the visual

cues were reduced is somewhat different from predictions based on our results with systemic injections, that striatal estrogen would impair learning in the cue-rich response task. The need to obstruct the room cues in order to observe impairments by intrastriatal estrogen suggests that when present, extra-maze cues may be used to solve the response task and that structures other than the striatum participate in solving the cue-rich response task. Thus, following *systemic* estrogen treatment, impairments in response learning with visual cues present (e.g. [Korol and Kolo, 2002](#)) may result from additive actions of estrogen at the striatum and at other structures. Supporting these possibilities, [Chang and Gold \(2004\)](#) found that lidocaine infusions into the striatum of young adult males disrupted response learning in a visually cue-poor but not cue-rich environment. There are other reports showing that impairing striatal function allows the use of hippocampus-sensitive strategies on dual solution tasks ([McDonald and White, 1994](#); [Packard and McGaugh, 1996](#); [Devan and White, 1999](#); [Okaichi, 2001](#)).

How estrogen acts at the striatum to produce learning impairments is still in question. Despite the paucity of nuclear alpha and beta estrogen receptors, ([Shughrue et al., 1997](#)) there is evidence that estrogen can both augment and dampen striatal neurotransmitter function. Compared to estrogen deprivation, estrogen treatment in ovariectomized rats enhances dopamine release ([Becker and Beer, 1986](#)) and appears to act directly at striatal neurons ([Becker, 1990](#)). Postsynaptically, estradiol increased the quantity ([Roy et al., 1990](#); [Bazzett and Becker, 1994](#)) and density ([Falardeau and Di Paolo, 1987](#)) of D<sub>2</sub> dopamine receptors. Given the robust actions of estrogen on dopamine function, it is likely that estrogen may impair response learning by acting on striatal dopamine function. An estrogen-induced effect on D<sub>2</sub> receptors has recently been connected to striatum-sensitive learning. Sensitivity to the impairing effects of D<sub>2</sub>, but not D<sub>1</sub>, receptor antagonists on accuracy in a task using response strategies was enhanced in ovariectomized rats chronically treated with estradiol compared to cholesterol vehicle ([Daniel et al., 2006](#)).

Paradoxically, numerous studies suggest that increasing striatal dopamine activity, a documented effect of estrogen, enhances performance on striatum-sensitive tasks, not impairs function as our data suggest. For example, D<sub>2</sub> dopamine receptor agonists injected into the striatum enhanced performance on a win-stay task ([Packard and White, 1991](#)), a task shown to be sensitive to striatal lesions ([McDonald and White, 1993](#)). Moreover, substantia nigra lesions that damage dopaminergic afferents to the striatum impaired learning the cued version of the swim task ([Miyoshi et al. 2002](#); [Da Cunha et al., 2003](#)), again a task that is thought to engage striatum-sensitive learning strategies ([Packard and McGaugh, 1992](#)). Differences in the dynamics of dopamine release and receptor kinetics may account for discrepancies between our findings and anticipated results based on studies using acute pharmacological treatments. Forty-eight hours of estrogen exposure may produce patterns of dopamine related

activity that are very different from those resulting from pre-training infusions of dopamine agonists and antagonists (Becker, 1999).

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Estrogen's effects on striatum to regulate learning may also extend beyond its actions on dopamine to other neurotransmitter systems. Estradiol treatment leads to increased ChAT activity in the striatum (Gibbs, 1996), which in turn may lead to increased cholinergic inhibition of striatal output (Bonsi et al., 2003; Zhou et al., 2002). Furthermore, estradiol has been shown to decrease NMDA and AMPA receptor binding in striatum (Cyr et al., 2000), supporting the possibility that estrogen may weaken neural plasticity in the striatum and impair response learning.

### Confinement of estrogen actions to the site of interest

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Estrogen infusions into the cortex overlying the hippocampus and striatum did not reproduce effects seen with direct infusions into the structures. In rats receiving E2-S into the cortex overlying the hippocampus, performance was significantly worse compared to rats with E2-S treatments into the hippocampus but was not different from that in rats receiving aCSF. Thus, estrogen in the cortex was not an effective modulator of place learning. Complementary findings were obtained with infusions into the cortex dorsal to the striatum. Taken together the results suggest that the enhancement of place learning and impairment of response learning did not result from the spread of hormone into the overlying cortex. This lends further support to the idea that E2-S has site-specific actions on different attributes of learning.

### Cannula-related impairments in learning

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The presence of intrahippocampal, but not intrastriatal, cannulae appeared to impair learning in the place task. Even small hippocampal lesions amounting to less than 20% of total hippocampal volume, can result in impaired acquisition and probe test performance on a spatial swim task (Moser, Moser and Andersen, 1993). The high sensitivity to disruption of the hippocampus is possibly due to the ordered projection pathways within the structure and the presence of longitudinal fibers running along the dorsal surface (Amaral and Witter, 1995). Therefore, a small amount of damage could block processing required by a larger portion of the hippocampus.

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As noted above, a substantial body of literature suggests that blocking striatal but not hippocampal function impairs egocentric learning (Kesner et al. 1993; Kobayashi and Iwasaki, 2000) and prevents the use of an egocentric strategy (Packard and McGaugh, 1996). Thus, it was surprising that response learning without cues was impaired by cannula implantation into the hippocampus but was impervious to striatal cannulae. Differences in

training procedures may contribute to this apparent discrepancy. Many of the reports supporting the idea of multiple, independent memory systems used training paradigms spanning multiple days, compared to the single-day massed training used in the present study. Recent findings demonstrate a transient rise in hippocampal acetylcholine during massed training in a cue-poor response task in conjunction with the expected increase during place learning (Pych et al., 2005). Thus, early in training the hippocampus was activated during both place and response learning tasks.

Further support for a role of the hippocampus during response learning comes from studies of unit activity in hippocampus and striatum during tests of place and response learning. Unit activity in hippocampal neurons correlates not only to location, but also to egocentric movements, heading direction, and behavioral trajectories (Mizumori et al., 2004). Neural representations in both structures include information important for both tasks, such that disrupting hippocampal integrity would interfere with certain components of response learning. The relative increased sensitivity of the hippocampus to lesions might translate into impaired learning in both tasks following hippocampal cannula implantation. Importantly, despite the effects of hippocampal damage on place and response tasks, relative to aCSF controls, estrogen treatments to the hippocampus were only effective in modulating learning for the place task, constraining the effects of estrogen to neural site and task.

### Estrogen enhances place and impairs response through independent mechanisms

Our results that, relative to vehicle controls, intrahippocampal estrogen enhanced place learning and intrastriatal estrogen impaired response learning suggest that estrogen acts in a site-specific manner without altering the competitive balance between the hippocampal and striatal memory systems. The independent action of estrogen at the hippocampus and striatum is somewhat different from what is reported in male rats following structural or functional lesions. When global manipulations of function are made with lidocaine inactivation or hippocampal lesions, interactions between hippocampus and striatum emerge. The findings that fornix lesions in male rats enhanced a cued win-stay task (Packard et al., 1989; McDonald and White, 1993) popularized the idea of competition between memory systems: intact functioning of the hippocampus may impede learning of a striatum-sensitive task by “winning” control over information access and behavioral responses during learning. Other work demonstrating that disrupting hippocampal functioning enhances response learning confirmed this finding (Schroeder et al., 2002; Chang and Gold, 2003).

More selective manipulations, such as intrahippocampal injections of acetylcholine antagonists (Kobayashi and Iwasaki, 2000) or dopamine agonists (Packard and White, 1991), do not produce the same results. Thus, it is



1980; Kolb et al., 1982), areas shown to respond to estrogen treatments (Ansonoff and Etgen, 2001; Cyr et al., 2000; Edwards et al., 1999; Womble et al., 2002). Examination of these and other structures need to be made in order to understand fully the modulatory effects of estrogen on different components of cognition.

## Abbreviations Used In Text

aCSF artificial cerebrospinal fluid

DS dorsolateral striatum

E2 17 $\beta$ -estradiol

E2-S 17  $\beta$ -estradiol 3-sulfate

UC unimplanted controls

HC dorsal hippocampus

i.p intraperitoneal

•L microliters

n number of animals in a group

s.c subcutaneous

## Footnotes

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