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Role of estrogen in balancing contributions from multiple memory systems

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Abstract

In addition to modulating memory per se, estrogen alters the learning strategy used to solve a task, thereby regulating the quality of information processed by the brain. This review discusses estrogen's actions on cognition within a memory systems framework, highlighting our work with a variety of paradigms showing that learning strategy is sensitive to estrogen even when learning rate is not. Specifically, high levels of gonadal steroids, in particular, elevations in estrogen, bias female rats toward using hippocampal-sensitive approaches while low levels of gonadal steroids promote the use of non-hippocampal sensitive strategies. In light of findings from a variety of approaches involving the hippocampus in allocentric and the striatum in egocentric response patterns, it is likely that estrogen alters the relative participation of these, and most undoubtedly other, neural systems during cognition. Changes in neuromodulators such as acetylcholine that regulate other processes such as inhibitory tone and excitability reflect one mechanism by which estrogen may orchestrate learning and memory.

Keywords: Reproductive hormones; Learning strategy; Modulation; Hippocampus; Striatum

1. Introduction

Several lines of evidence from many species and paradigms support the idea that estrogen modulates cognitive performance. The direction of effects relies on many variables including stress, type and duration of hormone regimen, and specific task demands. Emerging from the findings is the idea that estrogen not only modulates memory formation and maintenance processes in some contexts, but also biases the learning strategy used to solve a task, thereby changing *what* and *how* information is learned, and thus not only *how much* is learned, i.e., the strength of the memory. Work in our laboratory suggests that rats with high estrogen levels use place or allocentric strategies quite effectively, outperforming hormone-deprived rats on tasks that require the configuration and use of extra-maze cues for successful completion. Conversely, rats with low or negligible estrogen levels tend to use response or egocentric strategies on tasks in which the use of a directional turn, e.g., left or right, is required for acquisition. Because of estrogen's actions across a broad range of neural systems it is quite likely that estrogen exerts its actions on cognition by altering the relative participation of specific memory systems, acting much like a conductor, orchestrating the dynamics, timing and coordination of multiple cognitive strategies during learning (McGaugh, 2001). That there are such differences in learning style is certainly not a new thought. William James (1890, Chapter XI) eloquently stated, "Suffice it meanwhile that each of us literally *chooses*, by his ways of attending to things, what sort of a universe he shall appear to himself to inhabit." In this way, estrogen may in fact regulate the type of

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information to which an organism attends or processes by acting at anatomically and neurochemically distinct neural systems.

Discussion in this review will highlight findings from our laboratory suggesting that estrogen promotes the use of hippocampal-sensitive solutions, and that in the absence of estrogen, striatal-sensitive or other strategies prevail. Though the focus will be on the hippocampus and dorsal striatum, this is not intended to suggest that these two memory systems reflect the only brain sites involved in cognition or in these tasks, nor does it imply that estrogen acts solely at these two sites. Rather, many have reported that using simple maze tasks, these two strategies and the involvement of the hippocampus and dorsal striatum in these strategies can be dissociated, facilitating studies investigating the roles of hippocampus and dorsal striatum and the underlying neural mechanisms in estrogen's effects on cognition. Further, we have adapted and developed a variety of tasks that dissociate place and response solutions with evidence suggesting that these strategies map onto the hippocampus and dorsal striatum.

It is not surprising that ovarian steroids alter the function and morphology of brain areas considered primarily involved in reproduction, e.g., ventromedial nucleus of the hypothalamus (Frankfurt, Gould, Woolley, & McEwen, 1990). Areas not traditionally considered reproductive in nature are also sensitive to estrogen, responding quite dramatically to the presence and absence of ovarian steroids. In a series of studies, increases in circulating estrogen, from exogenous administration or natural fluctuations across the estrous cycle, led to significant increases in the density of dendritic spines in hippocampal CA1 pyramidal cells compared to those measured during states of low or negligible hormone levels (Gould, Woolley, Frankfurt, & McEwen, 1990; Woolley, Gould, Frankfurt, & McEwan, 1990). These and similar (Murphy & Segal, 1996) results suggest that estrogen modulates hippocampal connectivity and information processing, possibilities supported by demonstrations that estrogen enhances excitability and synaptic plasticity in hippocampus (Foy & Teyler, 1983; Korol et al., 1994; Teyler, Vardaris, Lewis, & Rawitch, 1980; Wong & Moss, 1992; Woolley, Weiland, McEwen, & Schwartzkroin, 1997) perhaps through regulation of NMDA receptor binding (Cyr et al., 2001; Daniel & Dohanich, 2001; Shors, Falduto, & Leuner, 2004; Woolley & McEwen, 1994; Woolley et al., 1997). While it remains unclear whether estrogen actually acts through these changes in hippocampal morphology and physiology to produce its effects on cognition, there is indirect evidence that ovarian steroid treatments that produce increases in dendritic spines (Sandstrom & Williams, 2001) and NMDA binding (Daniel & Dohanich, 2001) also enhance working memory.

2. Estrogen and cognition

Currently, there are many reports demonstrating robust effects of estrogen on cognition, however as mentioned above, the efficacy of action depends upon several variables (for review see Dohanich, 2002). Most importantly from the viewpoint of multiple memory systems, the type of task, phase of learning, and the type of memory tapped may all be critical variables in determining whether or not estrogen enhances cognition. Given the morphological, physiological, and chemical changes in hippocampus induced by ovarian steroids (McEwen, 2002), it is likely that behaviors that rely on intact hippocampal function will also be sensitive to elevations in estrogen. To assess the effects of ovarian steroids on a task shown to be sensitive to a variety of hippocampal manipulations, rats with different hormone regimens were tested on the place version of the swim task. Rats were either gonadally intact or ovariectomized and treated with oil vehicle or with a cyclic regimen of estradiol and progesterone to mimic a 5-day estrous cycle. Training, which took place within one day and consisted of 18 trials collapsed into six blocks, required rats to find a hidden platform in a water tank through the use of the extramaze cues. Rats with high circulating levels of estrogen either at peak concentrations following cyclic injections of estradiol and progesterone or during proestrus, i.e., the phase of the estrous cycle in which estradiol and progesterone are high, performed more poorly than did rats at nadirs in their hormone cycle or with no hormone treatment (Korol et al., 1994; Fig. 1A). This performance deficit by hormone treatment is supported by other reports demonstrating that swim task performance is impaired by elevations in estrogen plus progestins across the estrous cycle (Frye, 1995; Warren & Juraska, 1997).

Importantly, in our study, the impairment was evident in the first trial/first block of training, suggesting that estrogen and/or progesterone treatment influenced performance variables independent from mnemonic measures. Though performance was initially worse in the high hormone treatment group, the slopes of the learning curves reflecting changes in pathlength across trial block 1–6 were not significantly different across treatment groups, suggesting that acquisition was not influenced by hormone status.

One explanation for the initial performance deficit can be seen through a more detailed analysis of swim trajectories. Across training, animals in the high estrogen and progesterone group spent more time near the wall of the tank compared to other groups. The thigmotaxis displayed by the high hormone rats prevented effective searching for the submerged platform, potentially impairing performance. Once rats with high levels of estrogen began to search the tank, performance improved to the level of other groups. Even during the

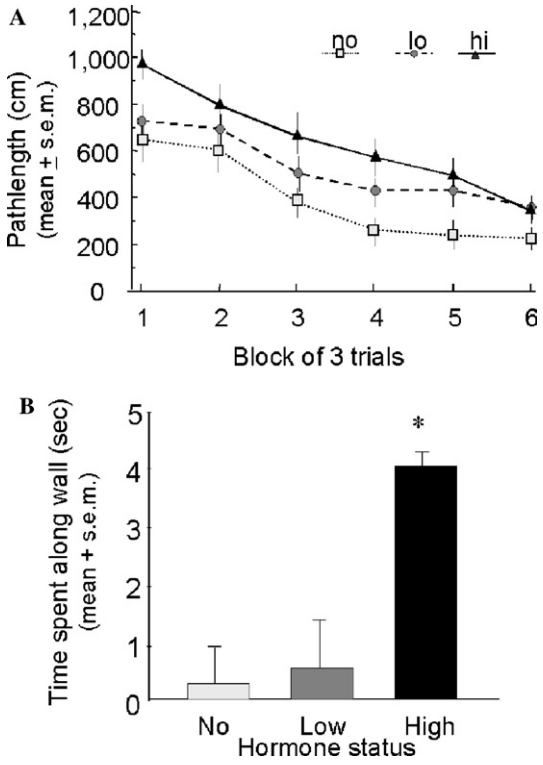

Fig. 1. Effects of estrogen status on performance in the spatial version of the swim task. No = ovariectomized rats without estrogen; Lo = sham-operated rats at estrus/metestrus and ovariectomized rats given cyclic treatment tested when hormone levels were low; Hi = sham-operated rats at proestrus and ovariectomized rats given cyclic treatment tested when hormone levels were high. (A) Data reflect distance traveled (pathlength) to reach the platform across six training blocks of three trials each. (B) The amount of time rats spent swimming along the tank edge during the first 15 s of the probe test.

probe trial, however, the amount of time spent along the wall during the first 15 s was significantly higher for rats with high profiles of estrogen ($F(2,24) = 4.9$, $p < .02$; Fig. 1B). Enhanced thigmotaxis may reflect a stimulus–response strategy stemming from an inability to initiate the appropriate behavioral responses to spatial information (Devan & White, 1999). Changes in the interactions between memory systems (Devan & White, 1999), in anxiety levels (Treit & Fundytus, 1988) or both (Packard & Cahill, 2001) may produce this response bias.

These and similar findings reported by others suggest that estrogen paired with progesterone impairs acquisition in the swim task particularly at times when stress levels may be elevated such as at early phases of training (Frye, 1995) or when water temperature is substantially low and glucocorticoids particularly high (Rubinow, Beverly, Arseneau, & Juraska, 2003). In fact, when tested *after* acquisition, estrogen enhances working memory in various versions of the swim task, especially at increased working memory loads (Bimonte & Denenberg, 1999; Sandstrom & Williams, 2001). Thus, ovarian steroids may impair cognition during periods of relatively high stress, such as early phases of the swim task, and enhance performance of specific tasks including those tapping working memory when stress levels are relatively reduced.

That high circulating levels of estrogen predispose rats to use ineffective approaches to solve the swim task raises the possibility that estrogen alters the strategy used during learning. Given a different set of rules in the swim task, for example using a circling strategy, estrogen might have *promoted* learning. Moreover, estrogen may interact with the stressful nature of the task thereby altering learning strategy, as has been shown in males (Kim, Lee, Han, & Packard, 2001), and leading to deficits. Pairing of ovarian hormones with stress has been shown to impair learning in other contexts (Markus & Zecevik, 1997; Wood & Shors, 1998). Nonetheless, if the type of strategy used to solve a task per se is modulated by estrogen, then rats with different hormone profiles might also be expected to use different learning styles to solve relatively non-stressful tasks.

3. Estrogen and learning strategy

To test the idea that estrogen and possibly other gonadal steroids, modulate learning strategy, we trained gonadally intact, cycling young adult females at different points along the estrous cycle in a task allowing free choice of the cognitive strategy used to solve the task. This dual-solution T-maze task is specifically designed to assess the use of place or allocentric and response or egocentric solutions while rats learn to find food on a simple maze (Restle, 1957; Tolman, Ritchie, & Kalish, 1947). Several different approaches, including lesions, functional activation, and in vivo microdialysis have been used to demonstrate that in male rats the use of place and response strategies in this task map onto discrete neural systems, i.e., hippocampus and dorsal striatum, respectively (Chang & Gold, 2003a; Packard & McGaugh, 1996; also see Kesner & Rogers, 2004; White, 2004). Whether analogous dissociations are found in females has not been shown directly. However, assuming that similar neural systems are involved, if estrogen influences hippocampal function, then rats with high circulating levels of estradiol would demonstrate differences in the use of place strategies relative to animals with low hormone profiles.

Training on this task involves allowing rats to choose between two arms of a T-maze, with food reward in the goal arm that remains in the same position relative to the start arm AND to the room cues throughout training (see Fig. 2A). In this way, rats can solve the task using either an egocentric, response strategy, i.e., turn this way, or an allocentric, place strategy, i.e., go there. Because the strategy used is not revealed by the rat's

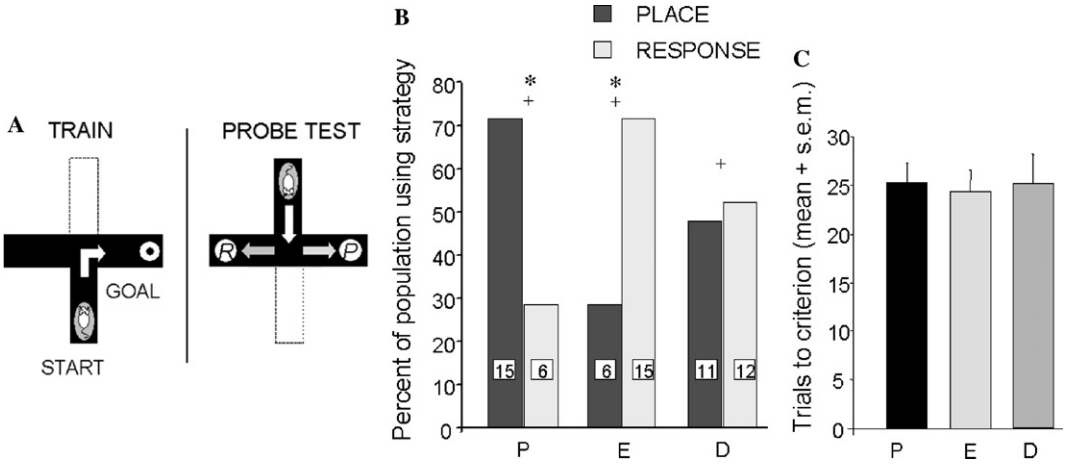

Fig. 2. (A) Dual-solution T-maze task used to assess place and response learning. During training, the start and goal arms remain constant, such that a rat can use a place (go there) or response (e.g., go right) solution. The strategy used during training is assessed with a probe trial during which the start arm is rotated 180°. (B,C) Effects of estrous cycle stage on (B) the proportion of rats using place or response strategies during the probe and (C) the trials to reach criterion. +, $p < .05$ within and *, $p < .05$ between cycle stages. From Korol et al., 2004.

behavior during training, a probe test to determine strategy is administered immediately after criterion (9/10 correct choices) is reached. Dramatic effects of the estrous cycle were noted when rats were trained and tested in a single day thereby confining learning to one phase of the reproductive cycle (Korol, Malin, Borden, Busby, & Couper-Leo, 2004; Fig. 2B).

Strikingly, rats at proestrus with high circulating hormones were significantly more likely to select place over response strategies, rats at estrus with low levels were significantly more likely to select response strategies, and rats at diestrus with intermediate levels of hormones showed no bias. Interestingly, learning speed was insensitive to hormonal status, with no differences in trials to criterion measured across estrous cycle stage (Fig. 2C). Further, in our paradigm, place and response approaches appear to represent equally effective solutions to the task. Thus, fluctuations in reproductive hormones across the cycle bias the learning strategy independent of general effects on learning ability or memory formation. The bias in strategy use across the estrous cycle is reminiscent of the shift in cognitive abilities measured in women (Hampson, 1990) and in rhesus monkeys (Lacreuse, Verrault, & Herndon, 2001) across the menstrual cycle, though the specific cognitive systems and tasks differ across species. At the midluteal phase of the menstrual cycle when ovarian steroids are highest, women demonstrate good performance on some verbal skills, such as articulation, but poor performance on visual–spatial skills such as mental rotation. Interestingly, the converse is true during the menstrual phase when hormones are low (Hampson, 1990), suggesting that fluctuations in reproductive hormones may alter the cognitive systems used to perform specific tasks.

The shift in learning induced by estrogen appears to be more than a simple shift in choice contingencies at the time of the probe test. In tasks designed to promote the use of one solution over others (Fig. 3A), estrogen enhanced learning when rats were tested on a place

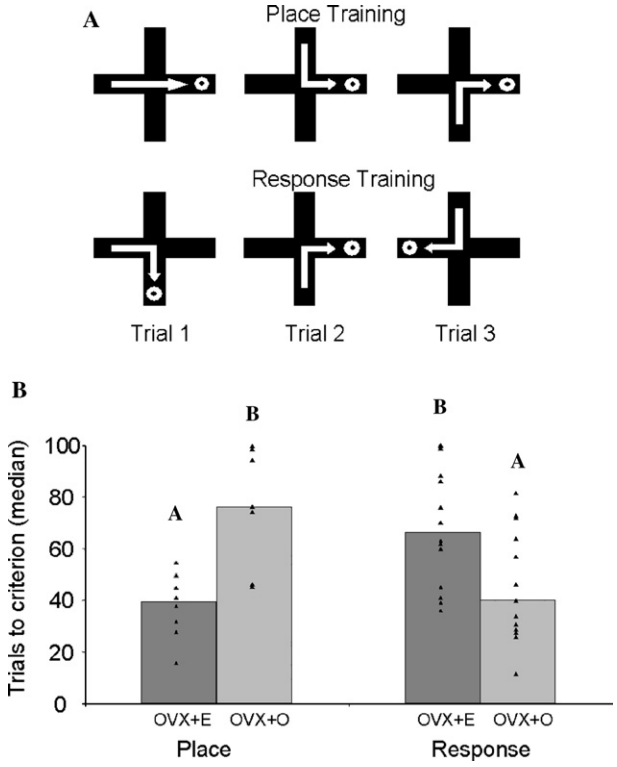

Fig. 3. (A) Graphic representation of training protocols for place and response tasks in the 4-arm plus-shaped maze. The goal arm is indicated by the food reward ⊙. (B) Number of trials to reach criterion in place and response tasks in ovariectomized young adult rats treated with 17-β estradiol-benzoate (OVX + E) or with oil vehicle (OVX + O). Estradiol treatment enhanced place learning and impaired response learning. Groups labeled with A and B are significantly different from each other. From Korol and Kolo, 2002.

learning task that relies on the integration of extramaze cues, but impaired learning when rats were tested on a response learning task requiring the use of a body turn (Korol & Kolo, 2002; Fig. 3B). Specifically, young adult female rats were ovariectomized and deprived of ovarian steroids for 3 weeks. Rats treated with acute systemic estradiol 48 and 24 h prior to training were significantly enhanced on place learning relative to hormone-deprived rats when tested on a four-arm maze. Equally compelling was the finding that rats deprived of hormones for three weeks were *enhanced* on a response-learning task in the same maze, but impaired in place learning (Fig. 3B). Thus, in place and response versions of the four-arm maze, i.e., versions that are apparently solved using different strategies, high estrogen resulted in both facilitation and impairment, i.e., of place and response learning, respectively. In a recent report using a version of the swim task in which both spatial and non-spatial (e.g., cued) strategies were effective (Daniel & Lee, 2004), young adult female rats receiving chronic estrogen exposure were relatively impaired on the non-spatial version of the task, whereas hormone-deprived rats were impaired during a probe test at which time the cue was removed. Thus, like our findings, estrogen-deprived rats excelled in a non-spatial paradigm (static cue present) during training, and were impaired during the no-cue probe tests when spatial strategies were most effective.

The finding that estrogen acts quite specifically on cognition, failing to confer a general enhancing effect on learning and memory, aligns well with past work using a range of species (for reviews see Dohanich, 2002) and provides a conceptual framework to help clarify a somewhat conflicted literature. What is emerging from the findings is the idea that the effects of estrogen can be dissociated by the cognitive demands and, perhaps, the brain areas required for effective task performance. At least in rodents, it is likely that moderate doses of estrogen facilitate hippocampus-sensitive cognitive functions, shown by improvements in learning spatial versions of radial maze (Daniel, Fader, Spencer, & Dohanich, 1997) in working but not reference memory (Fader, Johnson, & Dohanich, 1999; Holmes, Wide, & Galea, 2002), and place learning (Korol & Kolo, 2002). Importantly, estrogen deprivation appears to promote striatum-sensitive learning, such as in egocentric (Korol & Kolo, 2002) and cued win-stay (Galea et al., 2001) paradigms.

In a recent report, however, continuous treatment of estrogen for 30 days appeared to have no effects on navigational strategy (Gibbs, Gabor, Cox, & Johnson, 2004) when probed after 4 weeks of training. In this report, estradiol treatment did facilitate acquisition of a delayed matching-to-position working memory task in a T-maze. However, after several days of training, when rats were probe-tested for strategy used (e.g., place vs learning) by rotating the start arm 180° between the first and second trial of a pair, no group differences were detected. Failure to observe a hormone-related biases in strategy may reflect the type and duration of training used. In contrast to the dual-choice paradigm we (Korol et al., 2004; described above) and others have used, rats in the Gibbs et al. (2004) study were pre-trained and trained for several days in the working memory task before learning strategy was determined. Furthermore, for the working memory task, rats were required to encode which arm was visited during the initial forced trial of each trial pair in addition to the basic rule, win-stay. Thus, the task requirements differed substantially from those in the dual-solution task described above in which win-stay was the rule. Finally, a closer examination of the results suggests that all rats fell from ~94% accuracy at criterion before the probe to chance or below chance performance during the probe test (Gibbs et al., 2004), indicating that relatively few animals were using an allocentric or spatial strategy at the time of test; if so, performance would have resisted perturbation by altering the start position. In fact, the animals may have used an egocentric or striatal-based strategy to solve the task, a likely conclusion given that strategy was probed after extensive training, a point in acquisition when response or striatal-sensitive approaches tend to prevail (Chang & Gold, 2003a; Packard & McGaugh, 1996).

Taken together and placed into a neurobiological context, the results suggest that the effects of estrogen can be dissociated by the neural system engaged during learning. Within the neural systems framework, estrogen may somehow augment the relative participation of the hippocampus over the dorsal striatum, and the absence of estrogen may favor non-hippocampal systems.

4. Multiple memory systems

Mounting evidence points to the existence of multiple memory systems designed to manage different attributes of problem solving as shown by the breadth of approaches represented in reviews in this issue. Using functional or chemical lesions, double and triple dissociations have been made between hippocampus, striatum and amygdala for their involvement on tasks with different primary demands, such as place, response, or emotional learning, respectively (see Kesner & Rogers, 2004; White & McDonald, 2002; White, 2004, for reviews). That different task attributes map onto different neural systems is supported by recent work showing relative activation patterns across hippocampus and dorsal striatum that reflect place and response solutions when demonstrated with neurochemical markers such as acetylcholine in rats (McIntyre, Marriott, & Gold, 2003) or functional imaging in humans (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Poldrack & Packard,

2003). Though different cognitive taxonomies depending upon the specific structures and functions have been proposed (Kesner & Rogers, 2004; White, 2004), the basic principal is the same, i.e. that different task attributes or response requirements tend to map onto different neural systems.

The mapping can be somewhat independent, with clear dissociations between structures and function. Alternatively, there are instances in which manipulations of one system actually influence performance in an incompatible task, e.g., a task previously shown to rely on a different system. In male rats, lesions of the hippocampus impair learning in place and win-shift tasks (McDonald & White, 1993; White & McDonald, 2002) as predicted by many findings implicating hippocampus in place learning, but surprisingly enhance learning in response, cued, or win-stay tasks, tasks thought to rely on intact dorsal striatal functioning (White & McDonald, 2002). These sorts of relationships suggest that competitive interactions exist between these neural systems and that these interactions may result from up- or down-regulation of a competitor. Consequently, hippocampal participation, for example, in a task may actually compete with other structures for cognitive resources thereby producing less than optimal performance in tasks that rely on the intact functioning of those other structures.

The evidence of multiple memory systems has come in large part from studies that disrupt one structure through electrolytic or chemical lesions and measure the consequences on performance in various tasks with different cognitive attributes believed to rely on specific structures. Relatively less has been done to show that modulation of a given intact neural system influences the function of this and other memory systems in a manner predicted by the lesion work. However, Packard and colleagues have several demonstrations that specific manipulations of discrete neurochemical systems show task dependency (Packard, 1999; Packard & Teather, 1997a; Packard & White, 1991; Packard, Vecchioli, Schroeder, & Gasbarri, 2001). Double dissociations of the effects on memory of direct and indirect dopamine agonists have been found for the hippocampus and the dorsal striatum. Post-training administration of amphetamine as well as D1 and D2 agonists into the hippocampus enhanced retention on a win-shift task, leaving win-stay performance unaffected, while infusions of dopamine agonists into the dorsal striatum facilitated win-stay performance exclusively (Packard & White, 1991). Competition between memory systems may also be accomplished through modulatory influences. For example, glucose infusions into the dorsal striatum, theoretically enhancing striatal function, *impair* place learning in a food-motivated Y-maze task (Pych, Kim, & Gold, 2002). Microdialysis for ACh in amygdala and hippocampus, and single unit recording in hippocampus and striatum point to the possibility of collaborative interactions between neural systems that may not always be reciprocal (Gold, 2003; Mizumori, Yeshenko, Gill, & Davis, 2004). As such, it is becoming clearer using many learning paradigms at least in males, that complex interactions between memory and neurochemical systems exist and contribute to learning and memory.

5. Site of Estrogen's actions: independent or dependent systems?

Framed by the idea of multiple memory systems, the accumulating evidence that estrogen elicits task-dependent effects on learning and memory raises the possibility that estrogen acts to modulate learning and memory through site-specific effects. Increases in circulating estrogen may enhance place and impair response learning by enhancing hippocampal function and impeding striatal function via direct action at these two sites. Equally likely is the possibility that estrogen acts on one structure to confer good place learning performance and poor response learning performance through competitive interactions among participating structures. Central actions of estrogen have been implicated by studies showing that post-training infusions of estradiol into the hippocampus enhance memory for platform location in the spatial version of the swim task (Packard & Teather, 1997b). Furthermore, systemic elevations in estrogen can attenuate spatial learning deficits resulting from hippocampal cholinergic blockade (Fader, Hendricson, & Dohanich, 1998; Gibbs, 1999).

These sorts of studies address the possibility that estrogen acts at the hippocampus to modulate cognition, but fail to examine whether there is site specificity to estrogen's actions. To test the idea of site specificity, young adult ovariectomized rats prepared with bilateral guide cannulae aimed at either the hippocampus or the dorsal-lateral striatum were tested either on a place learning task or a response learning task similar to those used previously (Korol & Kolo, 2002). All rats received three 0.5 μl infusions of 0.5 μM 17β-estradiol-3-sulfate, a water soluble form of estrogen dissolved in aCSF vehicle (93.6 ng/0.5 μl) or vehicle alone directly to the hippocampus: 48, 24, and 2 h prior to training. Multiple infusions were used in attempt to mimic the duration of estradiol exposure to the brain following our systemic paradigm of two injections 48 and 24 h prior to training. Estradiol treatment enhanced place learning but was ineffective in modulating response learning relative to vehicle controls. Conversely, estradiol administration to the striatum had no effect on place learning but significantly impaired response learning when visual cues were made inaccessible by encircling the maze with a curtain (Zurkovsky & Korol, 2002; Fig. 4). It is unlikely that

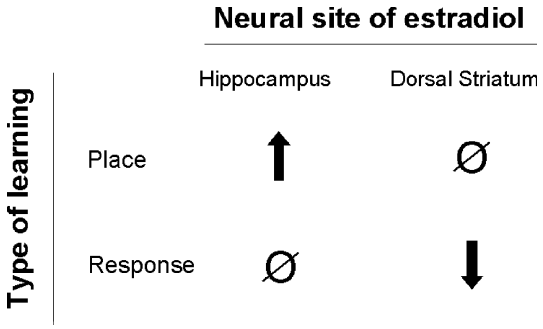

Fig. 4. Graphic depiction of the effects of central infusion of 17β-estradiol-sulfate on place and response learning in ovariectomized, young adult female rats. Specifically, intrahippocampal estrogen enhances place learning, without effect on response learning, while intrastriatal estrogen impairs response learning without effect on place learning. The site-specificity of estrogen's effects suggests that it acts independently on the caudate and hippocampus to regulate learning strategy.

our dose or specific estradiol compound was generally subeffective in the striatum in that unilateral intrastriatal infusions of the same dose of estradiol-sulfate enhanced rotation behavior contralateral to the hemisphere treated (results not shown) similar to previously reported findings using estradiol (Roy, Buyer, & Licari, 1990).

One conclusion that can be drawn from the data following direct brain infusions is that estrogen modulates the involvement of hippocampus and dorsal striatum in cognition independently, though the possibility of different dose–response functions for effects at competing sites or cognitive systems cannot be excluded. The apparent independence of estrogen's site-specific effects does appear different from interactions among memory systems in males. For example, lidocaine induced inactivation of the hippocampus enhanced response learning (Chang & Gold, 2003b). The property of independence may reflect the specific chemical system involved or manipulated, with the likelihood that estrogen modulates several different neurochemical systems that are distributed distinctly across different brain regions, thereby, adding another layer of complexity to estrogen's role in modulating multiple memory systems.

6. Neurochemical regulation

The precise cellular mechanisms of how estrogen orchestrates the balance between hippocampus-sensitive and striatum-sensitive learning strategies remain unclear. Information regarding the actions of estrogen at each independent site is important for understanding basic neural mechanisms of estrogen effects on cognition and for devising a working model to explore how estrogen influences the interactions among memory systems. The current state of the field is that much more is known about the effects of estrogen, as they relate to cognition, on hippocampal function than those on dorsal striatum function. This discrepancy notwithstanding, extensive advances have been made to elucidate the regulation of neurochemical properties of the dorsal striatum by estrogen and other estrogenic compounds, e.g., selective estrogen receptor modulators.

6.1. Hippocampus

A coherent working model of estrogen's modulation of the function of the hippocampus is evolving from the work of many laboratories (e.g., Daniel & Dohanich, 2001; Gibbs & Gabor, 2003; Rudick & Woolley, 2001; Murphy, Cole, Greenberger, & Segal, 1998; Woolley, 1999), implicating the actions of both cholinergic and GABAergic mechanisms. Through a somewhat simplified synthesis of this work, acute treatments of estrogen up-regulate cholinergic function and down-regulate GABAergic function in hippocampus, leading to diminished inhibition at early time points after estrogen exposure. Subsequent changes may include increases in NMDA receptor density and binding, in spine density, and in excitatory synaptic connections (Daniel & Dohanich, 2001; Murphy et al., 1998; Yankova et al., 2001). Interestingly, at longer time points after estrogen exposure, inhibitory currents in CA1 pyramidal cells return to baseline values, suggesting a compensatory response by hippocampal neurons to the initial loss of inhibition perhaps involving a sequence of events to balance excitatory and inhibitory tone (Rudick & Woolley, 2001).

Modulation of the medial septal cholinergic system may mediate estrogen's actions on GABA and subsequently NMDA systems. Estrogen treatment attenuates the memory impairing effects of cholinergic antagonists administered systemically or infused directly into the hippocampus (Fader et al., 1998; Gibbs, 1999). Likewise, sub-effective doses of cholinergic antagonists reverse the memory enhancing effects of estradiol while sub-effective doses of estradiol and cholinergic muscarinic agonists act synergistically to enhance memory (Packard & Teather, 1997c). Furthermore, intact cholinergic function in basal forebrain neurons or in afferents to the hippocampus is necessary for estrogen to decrease inhibitory post-synaptic currents (IPSCs; Rudick, Gibbs, & Woolley, 2003), to increase dendritic spines (Leranth, Shanabrough, & Horvath, 2000) and to enhance NMDA binding (Daniel & Dohanich, 2001) in CA1 pyramidal neurons.

In addition to regulation of learning and memory through the cholinergic system, estrogen may directly modulate GABAergic functions. Estrogen decreases IPSC's in cultured hippocampal neurons and down-regulates GAD synthesis shortly after exposure to estradiol in interneurons believed to have estrogen receptors (Murphy et al., 1998). However, it is also possible that estrogen regulates GABAergic tone

through its actions on the cholinergic system. Especially relative to hippocampal neurons, the basal forebrain cholinergic neurons are rich in estrogen receptors (Gibbs, 1996a; Shughrue, Lane, & Merchenthaler, 1997, 2000), supporting the possibility that estrogen acts at the basal forebrain to regulate the production and release of acetylcholine. The evidence of estrogen receptors at cholinergic terminals in the hippocampus (Towart et al., 2003) suggests that estrogen may also regulate the release of ACh. In turn, it is thought that the cholinergic fibers terminating on GABA interneurons regulate GABA release onto hippocampal pyramidal neurons (Daniel & Dohanich, 2001; Freund & Gulyas, 1997; Hajos, Papp, Acsady, Levey, & Freund, 1998).

Though the precise site of action remains to be determined, estrogen appears to have a disinhibitory effect on hippocampal pyramidal cells through GABAergic mechanisms that are under cholinergic modulatory control. It is thought that the excitation following disinhibition may lead to heightened plasticity of hippocampal pyramidal cells, such as increased LTP, NMDA receptor number and dendritic spine density (Woolley, 1999). Thus, one likely scenario for estrogen's action is that estrogen affects the cholinergic system, which in turn acts on the GABAergic system, which in turn influences pyramidal cell activity and hippocampal function. Though it remains unclear, it is likely that estrogen acts at both the medial septum, the site of the basal forebrain cholinergic input to the hippocampus, and the hippocampus to regulate cholinergic function. There is a wealth of findings suggesting that estrogen upregulates ACh synthesis through increases in ChAT activity in basal forebrain neurons including the medial septum (e.g., Gibbs & Gabor, 2003; Luine, 1985, for review). No conclusions can be drawn as to whether estrogen's action on the GABAergic system is necessary to observe changes in cholinergic function because the reciprocal tests, i.e., blocking GABAergic functions and measuring estrogen's action on cholinergic function, have not yet been conducted.

In an attempt to address cholinergic involvement in estrogen-induced shifts in strategy, levels of acetylcholine release in the hippocampus of ovariectomized females treated acutely with 17β-estradiol benzoate or oil (vehicle) were measured during place learning, performance for which was facilitated by direct intra-hippocampal estrogen application (Zurkovsky & Korol, 2002). In vivo microdialysis measurements of extracellular ACh were taken before, during and after acquisition (Marriott & Korol, 2003). Two consecutive days of 17β-estradiol treatment potentiated the typical maze-induced increase in extracellular ACh relative to baseline values (Ragozzino, Unick, & Gold, 1996). Levels remained significantly potentiated in hormone-treated rats throughout the first and second halves of the training period, including the final sample in which criterion was reached

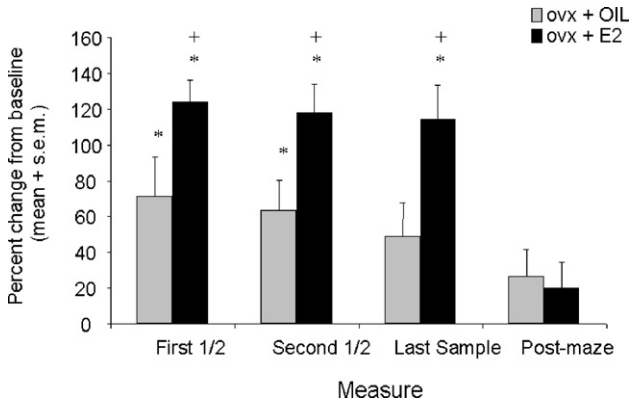

Fig. 5. Changes in hippocampal extracellular ACh levels during and after place learning on a 4-arm, plus-shaped maze. Data are expressed as percent changes from baseline values obtained 48 min prior to placement on the maze and training. Levels rose significantly from baseline during training (*) and returned to baseline following removal from the maze. Two days of systemic estradiol treatment in ovariectomized young adult rats significantly potentiated the maze-related increase (+). Estrogen effects were evident in the first and second halves of training, as well as during the last sample in which criterion was reached. From Marriott and Korol, 2003.

(Fig. 5). Immediately following training, rats were removed from the maze and ACh levels returned to baseline values in both estrogen and oil-treated animals.

Basal levels during rest in holding cages prior to training were unaffected by hormone treatment, suggesting that activation of the cholinergic system during learning was necessary to observe estrogen's modulatory effects. Potassium-stimulated ACh release in the hippocampus of untrained ovariectomized rats was also facilitated by acute estrogen exposure whereas basal levels were not (Gibbs, Hashash, & Johnson, 1997), corroborating further the idea that estrogen modulates neural and/or cognitive functions through cholinergic mechanisms. Alternatively, but not mutually exclusively, ACh output may *reflect* the participation of the hippocampal system in place learning, with estrogen acting to enhance hippocampal function indirectly through estrogen-sensitive sites distal to either the hippocampus or to the basal forebrain cholinergic input to the hippocampus, such as the amygdala (Womble, Andrew, & Crook, 2002), prefrontal cortex (Frick & Berger-Sweeney, 2001; Keenan, Ezzat, Ginsburg, & Moore, 2001; Kritzer & Kohama, 1999; Luine, Richards, Wu, & Beck, 1998; Wall & Messier, 2001) or the striatum (Becker, 1999; Poldrack & Packard, 2003).

While a solid model is being developed to explain the role of GABA in the cellular response of hippocampal neurons to estrogen, very little work has been done to elucidate the role of GABA in the cognitive effects of estrogen. If inactivation of the hippocampus leads to the use of response solutions (Chang & Gold, 2003b; Packard & McGaugh, 1996), then one might expect infusions of muscimol, a $GABA_A$ agonist, into the

hippocampus to produce biases toward the use of response strategies. Because measures of GABAergic function and inhibitory tone in hippocampal neurons fluctuate with different regimens of estradiol exposure (Hart, Patton, & Woolley, 2001; Murphy et al., 1998; Rudick et al., 2003; Schumacher, Coirini, & McEwen, 1989), it is likely that pharmacological manipulations of the GABA system would produce varying effects on learning strategy across the estrous cycle. If the hippocampus is relatively more excitable when ovarian steroids are high (Terasawa & Timiras, 1968), GABA agonists might produce functionally less inactivation at proestrus than during stages when hormones are low and when GABA tone is relatively high and excitability low. Because of heightened excitability or lower inhibition, higher doses of muscimol may be needed to produce the same strategy shifting effects in rat at proestrus than at other stages. Changes across the estrous cycle also produce differences in binding properties of $GABA_A$ agonists in the hippocampus (Schumacher et al., 1989), potentially altering the efficacy of muscimol in the hippocampus to modulate strategy.

When low (0.26 nmoles / 0.3 μl) or high (2.6 nmoles / 0.3 μl) concentrations of muscimol, a $GABA_A$ agonist, were infused into the hippocampus 20 minutes prior to training and testing on the dual-solution T-maze task, there was a treatment-related effect, with muscimol-treated animals in general demonstrating the predicted shift to response learning compared to saline treated controls (McElroy & Korol, 2002). However, the muscimol effect varied with estrous cycle. Rats at estrus and diestrus demonstrated a significant bias toward the use of response strategies regardless of muscimol dose whereas rats at proestrous, when progesterone and estradiol are elevated, did not (data not shown).

Specifically, in proestrous rats the low dose of muscimol produced an incomplete shift from place to response relative to control treatment, with ~70% of saline-treated rats at proestrous using place and ~30% using response, whereas in the low muscimol group, ~45% of proestrous rats used place and ~55% used response. Rats in the high muscimol proestrous group were biased toward response, mirroring the bias in saline treated rats. Rats at estrus showed no treatment-related effects, with both control and muscimol treated rats demonstrating biases towards response. Interestingly, rats at diestrus, when hormone levels are intermediate, demonstrated a bias towards the use of response strategies at both low and high muscimol doses.

When the effects of muscimol are viewed as a shift in strategy relative to control performance, approximately the same relative treatment-related shift appears to occur across proestrus and diestrus. It is as if the profile of strategy use in proestrous rats following infusions of low doses of muscimol becomes that of diestrous control rats, and following infusions of high doses of muscimol, becomes that of estrous control rats (Fig. 6). Further, the profile of the diestrous rat following low doses of muscimol shifts to that of the estrous control rat. The strategy profiles in estrous rats treated with both high and low muscimol were similar to those of saline-treated rats. The lack of effects may have resulted from decreased sensitivity to muscimol (Schumacher et al., 1989) or because estrous rats were already biased toward response after saline treatment as expected from previous work (Korol et al., 2004).

Importantly, all animals took the same trials to criterion regardless of drug treatment or estrous cycle phase, suggesting that these variables were acting on strategy selection and use, not on learning rate or on nonspecific factors such as locomotor activity or motivation. Taken together across estrous cycle and treatment groups, the data suggest a fairly consistent response-producing effect of muscimol, with profiles of high gonadal steroids

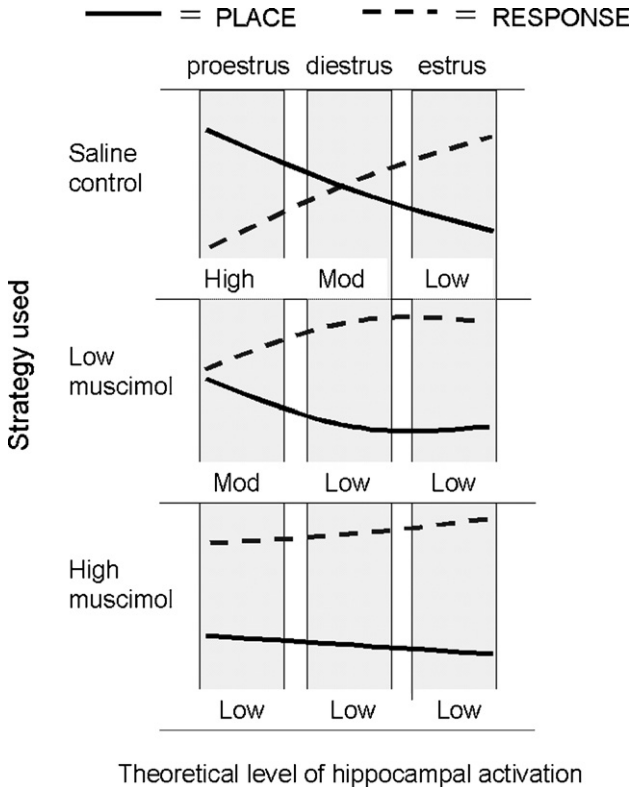

Fig. 6. Theoretical representation of the effects of estrous cycle and intrahippocampal muscimol on hippocampal activation and learning strategy. Based on unpublished data, graphs depict the relative use of place and response strategies in young adult female rats at proestrus, diestrus, or estrus under three intrahippocampal treatments: saline, low muscimol, and high muscimol dose. Note that in saline controls, a cycle-related shift in strategy bias is seen, with proestrous rats using place and estrous rats using response. With increasing doses of muscimol, and presumably increasing levels of hippocampal inactivation, strategy biases shift towards response solutions. The theory suggests that hormonal changes across the estrous cycle act through GABAergic means to change inhibitory tone and thus strategy selection.

predisposing rats to use place strategies. The additive effect of ovarian hormone level and muscimol suggests that the strategy shift observed across the cycle may reflect changes in inhibitory function.

These data represent the first demonstration that exposure of the hippocampus to $GABA_A$ agonists causes a shift to response solutions that is sensitive to estrous cycle stage. It is unclear whether the estrous cycle effects reflect changes in synthesis, release and / or receptor binding properties of GABA and its agonists to the $GABA_A$ receptor. Perhaps hormonal changes across the estrous cycle act through GABAergic means to change inhibitory tone of the hippocampus, shifting strategy selection. High levels of estradiol and / or progesterone seen at proestrus, possibly acting through reductions in hippocampal inhibition, may produce learning biases toward hippocampal-sensitive strategies such as place. Estrogen applied in vitro (Murphy et al., 1998) or in vivo (Rudick & Woolley, 2001) downregulates GAD synthesis in a population of hippocampal interneurons that are also ER positive (Hart et al., 2001; Su et al., 2001). However, no alterations in GABA activity measured as level of accumulation into medial septal or CA1 pyramidal neurons were found across the estrous cycle (Grattan et al., 1996). Application of muscimol in the hippocampus may have a greater effect in proestrous rats given findings that estrogen and progesterone enhance binding of ligands to the $GABA_A$ receptor (Schumacher et al., 1989) despite a decrease in the number of chloride ion channel receptor sites (Canonaco, Tavolaro, & Maggi, 1993). Changes at the receptor may provide one route for estrous cycle differences in effects of muscimol, a $GABA_A$ agonist that increases chloride conductance through its ligand-gated channel. Further analyses of the effects of both agonists and antagonists may lend insight into the contribution of GABAergic modulation to the effects of ovarian steroids on learning strategy.

6.2. Striatum

While models of the cognitive effects of estrogen in the striatum are not as well developed as they are for the hippocampus, several findings suggest that estrogen and other ovarian steroids can impact dorsal striatal function even though the striatum lacks classical cytoplasmic estrogen receptors of both α and β subtypes (Shughrue et al., 1997). Estrogen has been shown repeatedly to modulate neurochemical, especially dopamine (DA), function in the striatum and to provide robust neural protection against ischemia, 6-OHDA lesions, or dexamethasone-induced neuronal damage (for reviews see Becker, 1999; Di Paolo, 1994; Dluzen & Horstink, 2003).

Perhaps the most robust effect of estrogen on striatum is enhancement of dopamine release in the striatum and consequent behaviors. Facilitation of release has been shown in dissociated striatal cells, striatal slices and in awake, behaving animals. Cyclic changes in striatal dopamine release have been measured using in vivo microdialysis (Xiao & Becker, 1994) and in striatal slices (Cabrera, Bregonzio, Laconi, & Mampel, 2002). Specifically, extracellular DA levels are greatest during proestrus and estrus and lowest during diestrus and in ovariectomized rats (Xiao & Becker, 1994). Fluctuations in estrogen and progesterone across the estrous cycle appear to permit allopregnenalone potentiation of stimulated DA release (Cabrera et al., 2002), likely the result of pulsatile elevations in progesterone and estradiol (Dluzen & Ramirez, 1987). Estrogen administration to ovariectomized young adult females potentiates DA release from dorso-lateral striatum measured with in vivo microdialysis, with enhancements seen within 30 min of a 3-day estradiol exposure (Becker & Rudick, 1999). Whether ovarian steroids influence the synthesis, storage, release, or clearance of DA is not clear. Estrogen increases immunostaining for tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis, in neuronal processes in the striatum of primates (Kritzer, Adler, & Bethea, 2003) and impedes clearance of DA from striatum (Arvin, Fedorkova, Disshon, Dluzen, & Leipheimer, 2000).

Estrogen-induced changes in striatal function may also result from regulation of DA receptors. Fluctuations in D2 agonist binding sites can be observed across the estrous cycle with a change in the ratio of high to low affinity from proestrus to diestrus stages (Di Paolo, Falardeau, & Morissette, 1988). Estradiol application directly to the striaum increased D2 receptor binding in lateral but not medial striatum (Roy et al., 1990). Direct estrogen application in the absence of DA stimulating drugs also increased rotation behavior, shown to respond to increases in DA release and/or D2 receptor distribution, contralateral to the hemisphere of estrogen exposure (Roy et al., 1990). The modulatory effects of estrogen on dopamine processing in the striatum also manifest themselves in other behaviors sensitive to dopamine function such as pacing of sexual behavior, stereotypy, and running wheel activity (Becker, 1999). Chronic two-week oral exposure to specific estrogen receptor agonists, including estradiol and raloxifene, reversed an ovariectomy-induced decline in D2 receptor binding in dorso-lateral but, once again, not medial, striatum (Landry, Levesque, & Di Paolo, 2002). While ovariectomy had no effect on D2 receptor binding in dorso-medial striatum, estrogen had a tendency to enhance D2 binding.

Some of the changes described above are specifically localized to the lateral striatum (e.g., Landry et al., 2002; Roy et al., 1990). Importantly, dorso-lateral striatum is involved in integrating sensori-motor function important for stimulus-response learning (Packard &

Knowlton, 2002), representing a site through which estrogen could regulate striatal-sensitive cognitive functions such as egocentric (response) learning.

One working hypothesis for neurochemical regulation in the striatum (Becker, 1999) suggests that acute estrogen exposure acts directly (1) to decrease GABA release from the GABAergic spiny neurons that send collaterals to the DA terminals and (2) to increase DA release from DA terminals from the substantial nigra. Both actions lead to increased DA release. Cholinergic sensitivity to estrogen may contribute to its effects on DA function. The highest levels of ChAT mRNA staining in the striatum are observed following periods of high hormone levels (Gibbs, 1996b). Further, nicotine-induced DA release was elevated in striatal slices from ovariectomized rats treated with estrogen compared to rats deprived of hormone (Dluzen & Anderson, 1997). That there is estrogen-sensitive regulation of DA function at various loci is similar to effects in the hippocampus where estrogen may regulate ACh release through actions at the cholinergic terminals from medial septum, at the medial septum proper, and these both may control inhibitory tone by changing GABAergic input to the hippocampus from the medial septum or at the GABAergic interneurons (Freund & Gulyas, 1997; Hajos et al., 1998).

Given such effects of estrogen on striatum, and that amphetamines and other catecholaminergic agonists into the striatum enhance response learning (Packard & White, 1991) it is somewhat paradoxical that in our paradigm, estrogen treatment across 48 h impairs response learning. However, estrogen decreases NMDA receptor binding in striatum even in the presence of increased dopamine (Cyr, Ghribi, & Di Paolo, 2000). Perhaps this decrease in excitatory function translates into decreased performance on response learning tasks. The timing of estrogen exposure may also be important for this apparent inconsistency. When measurements were taken within 4 h following 2–4 days of estrogen exposure a potentiation of stimulated release of DA from striatum (c.f. Becker, 1999), occurred. However, when measured at least 24 h after treatment, precisely when we measured response learning in ovariectomized rats treated systemically with estrogen (Korol & Kolo, 2002), the potentiation, albeit present, was attenuated (Becker, 1999). This possibility fails to account for the impairing effects on response learning we observe when estradiol is administered centrally (Zurkovsky & Korol, 2002); in this paradigm, estrogen was infused 48, 24, and 2 h prior to training.

7. Conclusions

Increased profiles of estrogen shift learning toward place but away from response strategies. Importantly, relatively low profiles of estrogen do the opposite, i.e., shift learning style toward response and away from place strategies. Findings using direct, site-specific infusions demonstrate that hippocampal treatments are effective at enhancing place learning, but ineffective at impairing response learning. Conversely, striatal treatments impair response learning, leaving place learning intact. These data support the hypothesis that estrogen effects on these two memory systems are independent and that the estrogen-related impairment in response learning is not simply a result of increasing the competitive edge of the hippocampus over the striatum, such as what might be suggested by data from hippocampal lesions in male rats. For example, in males functional inactivation of the hippocampus enhances striatal function (Chang & Gold, 2003b) and glucose into the striatum impairs hippocampus-sensitive place learning (Pych et al., 2002). It is unclear whether estrogen deprivation, which facilitates response learning, acts in a similar direct fashion, that is on the hippocampus and striatum independently, e.g., down-regulating hippocampal function and up-regulating dorsal striatal function. Of course, in the gonadally intact state, estrogen is distributed throughout the nervous system acting at multiple memory systems concurrently and thus may produce effects different than those seen with extirpation and replacement paradigms.

Numerous neurochemical systems in the hippocampus and striatum have been implicated in the cognitive effects of estrogen, including excitatory and inhibitory amino acid transmitters, GABA and glutamate, catecholamines, acetylcholine and serotonin to name a few. Thus, in addition to its role in orchestrating memory systems, estrogen may also regulate the relative balance of specific neuromodulators in and across these neural systems. While some of the effects of estrogen demonstrated in females have been reproduced in males (Packard, Kohlmaier, & Alexander, 1996; Sherwin, 2003a, for review), there are sex-related differences that, in some cases, rely on developmental exposure to gonadal steroids. However, many of the effects simply have not been tested in males.

Though estrogen produces plastic changes in function of both hippocampus and striatum, it is unknown whether that the effects are through similar or different receptor or subcellular mechanisms. The hippocampus contains both ER α and ER β, whereas the striatum lacks classical receptors (Shughrue et al., 1997). However, neurons in both structures respond extremely rapidly to estrogen (Mermelstein, Becker, & Surmier, 1996; Wong & Moss, 1992), suggesting non-genomic effects through cytoplasmic signaling pathways following membrane/extracellular receptor activation. The mitogen-activated protein kinase (MAPK) is one pathway may play a key role in estrogen's action on cognition (Bi, Foy, Vouimba, Thompson, & Baudry, 2001).

The effects of estrogen are made more complex by the evidence that dose and duration of estrogen exposure, as well as length of deprivation, are all believed to play important roles in determining the neural and cognitive

efficacy of estrogen. Using the dual solution task, chronic, continuous administration of estrogen to young adult rats for eight weeks was ineffective in producing the strategy bias seen following shorter (1 and 4 weeks) exposures (unpublished data). Surprisingly, animals deprived of hormones for eight weeks also failed to show the expected bias towards response strategies, suggesting, perhaps that estrogen's actions on the balance between neural systems changes over time. Differential effects of hormone duration have been observed in paradigms using older animals. Cyclic or short-term regimens in older animals are more effective in stimulating spine changes (Miranda, Williams, & Einstein, 1999), modulating cholinergic function (Gibbs, 2000) and learning and memory (Markowska & Savonenko, 2002; Rapp, Morrison, & Roberts, 2003).

In sum, by further investigating the neural mechanisms through which estrogen acts we will gain greater understanding of how estrogen orchestrates the contributions of many neural systems to learning and memory. Studies of these neuroendocrinological effects on memory may provide a rubric for understanding individual differences in learning styles and cognitive changes during aging, perhaps fostering the development of treatments for neurodegenerative diseases such as Alzheimers and Parkinson's disease. The notion that estrogen has distinct actions on specific neural systems and cognitive processes may moderate the interpretations of recent findings reported through the Women's Health Initiative Memory Study investigations, showing no cognitive improvements—and perhaps even impairments—in post-menopausal women taking estrogens (Espeland et al., 2004). It is possible that the composite measure used in these investigations, i.e., the modified mini-mental state exam, is insensitive to the task-specific actions of estrogen on cognition shown to exist in humans (Sherwin, 2003b). Independent analysis of the subtests or use of a full neuropsychological battery of tests may produce a different set of findings in which both improvements and impairments by estrogen are observed. Hopefully, further exploration into estrogen and memory systems will provide solid answers to the specificity of steroid effects on cognition and brain function.

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