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Estrogen enhances the retention of spatial reference memory in the open field tower task, but disrupts the expression of spatial memory following a novel start position

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ABSTRACT

Estrogen's (E) involvement in cognition has been difficult to characterize; numerous studies show that E can both enhance and impair learning and memory. One difficulty may be that experimental paradigms often examine only a single aspect of E's involvement in cognition, for example, the role E plays in the expression of memory after learning has taken place. In addition, the effect of aversive and/or stressful features inherent to many cognitive tests may contribute to the contradictory findings. The present experiment aims to examine the effect of estradiol (E2) on several elements of cognition in a specific experimental setting. We investigated the within-subject effects of long-term E2 replacement in ovariectomized (OVX) female rats on the acquisition and retention of a hippocampal–mediated spatial reference memory task in a familiar non-threatening environment. Results show that E2-replaced rats and OVX sham-replaced rats acquired the ability to navigate an open-field tower maze in order to obtain a food reward at the same rate. Subsequent to acquisition, both E2-replaced and OVX rats performed the task at comparable levels. However, following a 21-day retention interval, non-replaced rats exhibited a significant impairment in spatial memory when returned to the maze environment, while E2-replaced rats exhibited no change in maze performance. When the OVX group was performing once again at asymptote, test trials were administered during which the rats were placed in a non-experienced start location within the maze. This novel condition significantly reduced correct responses in E2-replaced females whereas OVX controls remained unaffected. These results suggest that while the presence of E2 is not important for acquisition of spatial memory in a safe familiar environment, it improves retention of spatial memory. Data further suggests that E2 disrupts the expression of spatial reference memory following an alteration of the test conditions sustaining a habitual response, possibly by the induced emotionally-arousing state of stress.

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1. Introduction

Estrogen (E) has been shown to modulate brain regions essential for cognitive function such as the neocortex, hippocampus, basal forebrain, and amygdala (Becker, Breedlove, Crews, & McCarthy, 2002, p. 562). However, whether E actually provides beneficial effects on human cognition has been a subject of great debate. Many attempts have been made to reconcile inconsistent data related to E's effect on learning and memory. Some research suggests that the time-course of E treatment following menopause, or OVX in animal studies, is of particular importance. Specifically, E treatment must be initiated shortly after menopause or OVX in order to exert beneficial effects on memory in women, female monkeys and aged rats (Gibbs, 2000; Lacreuse, 2006; Sherwin, 2006). In addition, differences in E compounds, route of administration, cyclic vs. continuous regiments, and the simultaneous use of progestins also play a role in the disparate effects of E on cognition (Gibbs & Gabor, 2003; Sherwin & Henry, 2008). Although research using rodent models can provide greater control over many aspects of methodology, significant inconsistencies in rodent studies examining the effect of E on learning and memory remain (Diaz-Veliz, Butron, Benavides, Dussaubat, & Mora, 2000; Diaz-Veliz, Urresta, Dussaubat, & Mora, 1991; Fader, Hendricson, & Dohanich, 1998; Frye, Duffy, & Walf, 2007; Gibbs, 2000; Gibbs, Burke, & Johnson, 1998; Hruska & Dohanich, 2007; Marriott & Korol, 2003; Ping, Trieu, Wlodek, & Barrett, 2008; van Haaren & van de Poll, 1984). One suggestion has been that the contradictory effects of E on cognitive functioning are due to the use of cognitive tasks that may or may not involve the hippocampus (Daniel, 2006). However, studies that use similar tasks involving hippocampus-dependent memory (i.e. spatial learning) still show different effects of E. For example, E enhances performance in the radial-arm maze (Daniel, Fader, Spencer, & Dohanich, 1997), yet impairs performance in the Morris water maze (MWM) (Warren & Juraska, 1997).

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Studies often involve examination of a specific stage of cognition. For example, many experimental designs involve training subjects on a particular task to a previously determined criterion. Upon reaching that criterion, the training is discontinued, thus targeting exploration of E's effects specifically on the acquisition stage of learning (Daniel et al., 1997; Fader et al., 1998; Frye et al., 2007; Gibbs, 1999; Hammond, Mauk, Ninaci, Nelson, & Gibbs, 2009; Korol, Malin, Borden, Busby, & Couper-Leo, 2004; Luine, Richards, Wu, & Beck, 1998; Ping et al., 2008; Sinopoli, Floresco, & Galea, 2006; Warren & Juraska, 1997). Other tests do examine E's effect on expression of learned behavior, or test memory shortly after acquisition has occurred (Dachtler, Fox, & Good, 2011; Daniel & Lee, 2004; Pompili, Tomaz, Arnone, Tavares, & Gasbarri, 2010; Sutcliffe, Marshall, & Neill, 2007), but do not examine memory retention following a longer period of delay. Therefore, it may be informative to examine the effects of E on retention of acquired behavior over a greater duration of training.

The aversive and stress-producing elements of a particular cognitive test must also be considered. Scientists investigating effects of stress (for review see: Beck & Luine, 2010) on learning and memory realize that a complex relationship exists between the neural reaction to the stressor and the current endocrine state in females. Similarly, the effects of E on cognitive function could presumably be mediated by the concurrent emotional state of the animal. Studies reporting the lack of, or impairing, effects of E generally employ tasks that involve aversive stimuli, such as footshock-induced avoidance learning. Tasks like these generally show that female rats and mice in proestrus, or those treated with E following OVX, exhibit decreased avoidance responses and increased escape failures compared to their respective controls (Diaz-Veliz, Soto, Dussaubat, & Mora, 1989; Diaz-Veliz et al., 1991, 2000; Farr et al., 1995; Sfikakis, Spyraki, Sitaras, & Varonos, 1978; Van Oyen, Van De Poll, & De Bruin, 1979). Moreover, Diaz-Veliz et al. (2000) demonstrated that treatment with diazepam significantly improved the conditioned response on avoidance learning in female rats with high levels of E, suggesting that the stress-inducing aspect of the task may play a role in retention impairment. In addition, tasks of spatial memory that use the MWM (which tends to be of an aversive nature) show either lack of an effect, or impaired performance following E treatment (Chesler & Juraska, 2000; Warren & Juraska, 1997). On the other hand, researchers who report enhancing effects of E utilize tasks that are rarely stressful (Fader et al., 1998; Frye et al., 2007; Gibbs, 2000; Hruska & Dohanich, 2007; Ping et al., 2008). Thus, it is likely that E enhances cognitive performance in non-stressful tasks, but impairs it in aversive behavioral paradigms. In support of this argument, a review by Morgan, Schulkin, and Pfaff (2004) suggested that E's effects on cognition are context-dependent; E's arousal effects in a safe environment are conducive to learning and memory, while the same arousal effects under aversive conditions are deleterious (Morgan et al., 2004).

A considerable amount of research is still required in order to clarify E's role in cognition. The present investigation has three objectives: (1) to employ a novel task that assesses spatial learning in a slow acquisition, non-threatening low-stress open arena maze that is equivalent to a water maze; (2) to differentiate the effects of E2 on acquisition and on retention of memory following a 21-day retention interval; (3) and to test the stability of acquired spatial memory under novel test conditions. For this study, we operationally define 'Acquisition' as the initial stage of learning during which the response is gradually strengthened, until the animal reaches asymptote, 'Retention' as performance on the spatial memory test following a period of delay during which the animal is not exposed to the learning task, and 'Expression' as observed performance on the task following any given manipulation.

The present experiment was designed to determine the within-subject effect of E on acquisition and retention of a hippocampus-dependent spatial memory task specifically designed to lack aversive features. The task used here is an open-field tower maze (adopted from (Cole, Clipperton, & Walt, 2007)), which is equivalent in complexity to the MWM. However, this task does not require the animal to swim, therefore removing the stressful and anxiety-provoking features inherent to the water maze. In addition, there are a number of strengths in this particular methodology that aid in the characterization of the effects of E on spatial learning. The probability of making the correct choice based on chance alone is 25% lower than in most tests of spatial learning, such as T-maze and radial arm maze. Also, rather than being forced to make one choice from a limited number of predetermined directions (as is required by many spatial strategy paradigms), the path a subject takes is not restricted in the open-field tower maze. Thus, the rat's direction is independent, and the correct choice depends on the use of intra and extra maze cues during spatial navigation within the maze. Overall, we believe that this task provides a good measure of navigational skills and spatial learning. Proficient performance in this maze relies on spatial reference memory acquired over several days, and does not depend on a choice-making decision required by learned response tasks, hence limiting the evaluation of E's effects to a hippocampal-dependent memory system. Taking advantage of the fact that the open-field tower maze is maximally designed to be stress free, we evaluated whether a change in test conditions induced by a switch in the initial start position of the subject in the maze will disrupt peak memory performance in our OVX and OVX E-replaced rats.

2. Materials and methods

2.1. Subjects

The subjects were 16 naive, OVX female Sprague–Dawley rats obtained at Charles River Laboratories, St. Constant, Quebec. They were approximately 3 months old at the time of treatment and were housed with ad lib water and rat chow. Because it has been reported on a number of anxiety tests that single-housed female rats display anxiety like behavior compared to those housed together (Lunga & Herbert, 2004), rats were double-housed throughout the duration of this experiment. The cage room was maintained at 23 °C with a 12:12-h light-on:light-off cycle. The experiment was carried out during the light-on phase. All rats were on restricted feeding throughout the experiment. This was accomplished using a daily assessment of their body weight to calculate the appropriate amount of food needed to be administered in order to keep them at 85% of their free-feeding weight.

2.2. Apparatus

As shown in Fig. 1, the apparatus consisted of four food towers set 60 cm apart in the center of a circular arena 2 m in diameter. The boundary wall was constructed from white laminate, and was 40 cm high. The inside of the walls were painted with different patterns, such that one quarter of the wall was painted with black and white stripes, one quarter was solid black, one quarter was white with black circles, and the last quarter was solid white. The floor of the maze was beige vinyl used for floor surfaces. The food towers, indicated by letters A, B, C, and D in Fig. 1, were $8 \times 8 \times 20$ cm wooden blocks, coated with polyurethane. A plastic food cup, 2.5 cm in diameter and 2 cm deep, was created from a 35 mm film canister, and was attached to the center of the top of each tower with a small screw. Due to the height of the towers, a rat could not investigate the contents of a food cup without rearing