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Sex differences and the role of acute stress in the open-field tower maze

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ABSTRACT

Many studies provide evidence that differences in spatial learning exist between males and females. However, it is necessary to consider non-mnemonic factors that may influence these findings. The present experiment investigated acquisition, retention, and the effects of stress on response- and place-learning in male and female rats. Rats were trained in an open-field tower maze. Procedures were used to minimize stress in the rats, and their ability to solve place- or response-learning in the maze was determined by analyzing a response variable (i.e., first choice correct response) that was not influenced by general locomotor activity. The results revealed that male and female rats acquire place- and response-learning at the same rate even though females moved significantly faster in the maze. However, females showed better retrieval of place-, but not response-learning compared to male rats. This effect appeared to be enhanced when the rats were tested immediately following an acute restraint stress. Furthermore, both female and male rats that were exposed to acute restraint stress showed less impairment than controls when subsequently tested in a novel situation. These findings have clinical implications that a mild physiological stress response can make one more cognitively resistant to adversities later in life.

1. Introduction

Do males and females learn differently? Many researchers have attempted to answer this question using human and non-human animal models, and while there is an abundance of literature about this topic, a consensus is not entirely clear. Evidence suggests that various non-mnemonic processes can influence an animal's performance, thus making it difficult to accurately measure whether a sex difference in spatial learning is observed [19,21,31]. For example, male rats outperform female rats in the radial arm maze, but only when learning is determined using measures that are affected by their level of locomotor activity [49]. Another factor that can influence maze performance is a subject's stress level. Female rats, for instance, are more sensitive to the stress of swimming in a water maze than male rats and therefore tend to spend more time swimming by the maze perimeter and travel longer distances which causes them to find the target more slowly [2,31]. Therefore, in order to study sex differences in spatial learning it is important to use a task that minimizes stress and measure variables that do not depend on rats' level of locomotor activity. An aim of the present experiment was to address these issues.

Spatial learning and memory tasks such as the Morris Water Maze (MWM) and Barnes Maze have been found to induce an automatic stress response in rodents [18]. While male rats have been shown to outperform female rats on the MWM [21], this sex difference appears to be stress specific. If stress is reduced by giving rats pretraining trials prior to acquisition, then the difference in learning found between the sexes is reversed [38]. Moreover, female rats travel longer distances and need more time to reach a hidden platform in the MWM than male rats because females spend more time in the periphery of the maze, which is indicative of a greater stress response [2]. When the stress response was eliminated, either through an experimental training manipulation or adrenalectomy, no sex differences in performance were found. Beiko et al. [2] concluded that female and male rats may have similar spatial learning capabilities, but their abilities may be differentially affected by a MWM generated stress response.

Differences in general locomotor activity can also affect how males and females perform in commonly used spatial mazes, such as the radial arm maze. Some studies report that males outperform females in the radial arm maze, but others do not [19]. Van Harren, Wouters, and Van De Poll (1987) postulated that sex differences observed in rats trained in a radial arm maze may be due to differences in general motor activity and not visuospatial memory abilities [50]. Thus, a possible explanation for the sex differences observed in spatial learning is that female rats exhibit greater levels of activity and exploratory behavior than male rats [49].

The present experiment used the Open-Field Tower Maze (OFTM) to assess spatial learning in male and female rats. The OFTM is a land-based maze designed in such a way that performance is measured

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independent from an animal's general level of activity and lacks the averseness, but not the complexity, of the MWM [27]. The OFTM measures learning by calculating the percent of first-choice correct responses a rat makes to find an appetitive reward. This dependent measure is not affected by a rat's speed or distance traveled because ample time is provided for the rat to retrieve the reward on each trial and the time, speed or distance a rat travels to retrieve the reward is not used as a performance indicator. There are other advantages that the OFTM has for measuring spatial learning compared to some other mazes. For example, the probability of making the correct choice based on chance alone is 50% lower in the OFTM than in tests of spatial learning in a T-maze. Also, rather than being forced to make one choice from a limited number of predetermined directions (as is required by a T-maze and a radial arm maze), the path a rat can take in the OFTM is not restricted.

Another issue that arises when assessing spatial learning is that males and females tend to use different behavioral strategies when navigating [19,25,31,43,44,52]. Specifically, females are more inclined than males to use landmarks for navigating and males tend to navigate using geometric information and cardinal directions more often than females [11,52]. For example, female rats solve a cued-version of a MWM as well as male rats, but males outperform females in the non-cued version of the maze [40]. It is possible that males and females rely on separate brain regions (i.e., the hippocampus and striatum) to solve different types of spatial navigation tasks. These brain regions are thought to process information related to either place-learning, which corresponds to navigation using landmarks, or response-learning, which is similar to the use of cardinal directions (see [39] for review). The hippocampus is responsible for place-learning, which involves learning to approach a particular place in a maze using only spatial cues; and the striatum is responsible for response-learning, which requires the subject to follow a specific direction and disregard spatial cues [36,37]. It has been shown that naturally high levels of estrogen cause female rats to use a place-learning strategy rather than a response-learning strategy to solve a T-maze [24], and cycling estrogen treatment enhance place-, but not response-learning in the OFTM [26]. Therefore, we predicted in the present experiment that females would acquire place-learning better than males, and males would acquire response-learning better than females.

In addition to examining sex differences in acquisition and retention of place- and response-learning, the present experiment also tested how an acute stressor affects memory retrieval following a retention interval. Acute response to a moderate stress has been generally reported to enhance hippocampus dependent cognitive function [23,32,42]. However, the effect of stress on learning is sex-specific [1]. For example, exposure to acute restraint and intermittent tail-shocks on the day before training enhances acquisition of eyeblink conditioning in male rats and impairs acquisition in female rats [53,54]. Exposure to acute stress has also been shown to increase hippocampal spine density in male rats and decrease hippocampal spine density in female rats [46]. A separate issue is whether the experience of acute stress differentially affects male and female rats during retrieval of an established hippocampus-dependent spatial memory. In male rats, acute stress appears to have a differential effect on various memory phases. For example, both endogenously stress-induced and exogenous elevations of glucocorticoids enhance consolidation, yet impair retrieval of long-term spatial memory [13,41].

To our knowledge, the differential effect of stress response on various memory phases has not been explored in female rats. Moreover, the number of experiments that have compared how acute stress affects spatial memory retrieval in males versus females is limited. One study found that females showed better spatial recognition memory on the Y-maze following an acute restrained stress than stressed male rats [10]. Based upon these findings, we hypothesized that the stressor given to the rats in the present experiment would impair memory retrieval in male, but not female rats. We also hypothesized that this effect would only occur in place-learners because hippocampus-dependent tasks (e.g., place-learning) are thought to be more vulnerable to stress effects than striatum-dependent tasks (e.g., response-learning) [1].

The present investigation had two main objectives: (1) to test sex-differences in a task that assesses spatial acquisition and retention of place- and response-learning, and measures performance independent of stress and general motor activity levels, and (2) to examine how an acute stressor affects memory retrieval following a retention interval in male and female rats.

2. Materials and methods

2.1. Subjects

The subjects were female (n = 26) and male (n = 26) naïve Sprague-Dawley adult rats obtained from Charles River Laboratories. The rats were pair-housed in the animal care facilities at Christopher Newport University on a 12-hour light/dark cycle. The rats began training between 12:00 pm and 1:00 pm daily, which was approximately 5 h following the onset of the light phase. All experimental procedures were approved by CNU's Institutional Animal Care and Use Committee and carried out during the light-on cycle. Rats were handled by the experimenters for 2 mins each day during the week prior to training. All rats were maintained on a restricted feeding schedule throughout the duration of training. The rats were given 1 h of free feed daily following the completion of all training sessions for that day. This method of food restriction allowed us to keep the rats pair-housed, which was needed because social isolation is known to produce stress in female rats (e.g., [51]). This feeding regimen maintained all rats at ~85% of their growth-adjusted free feeding weight.

2.2. Apparatus

The apparatus and procedures used in this experiment have been previously described in detail [27]. The floor of the OFTM was a circular piece of black laminate (diameter = 183 cm) that was surrounded by a laminate perimeter wall (height = 40 cm). The interior portion of a perimeter wall was divided into four visually-distinct 90° sections: solid white, solid black, black and white stripes, or black dots against a white background (Fig. 1). Four white PVC towers (8 cm × 8 cm × 20 cm) topped with black laminate were located inside the maze. These towers were arranged in a square-shape (54 cm × 54 cm). A small food cup with a screw-top plastic lid (height = 1.75 cm and diameter = 3.75 cm) was fixed to the top of each tower. The testing room was illuminated by a lamp (60 W light bulb) that was directed toward the ceiling and a sound generator (HoMedics, Commerce Township, MI) provided a constant white noise (~70 dB) in the background. All pretraining and training trials were recorded with a Monochrome GigE video camera and Media Recorder Software (Noldus, Leesburg, VA). The videos were

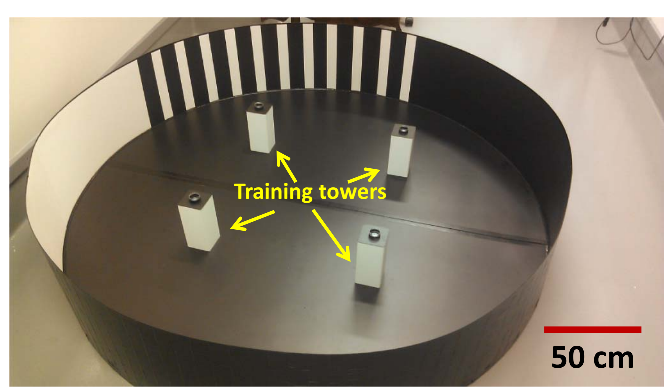

Fig. 1. Photograph of the Open Field Tower Maze.