Video Article

Place and Response Learning in the Open-field Tower Maze

Olga Lipatova[1], Matthew M. Campolattaro[1], Donna J. Toufexis[2], Erin A. Mabry[1]

[1]Department of Psychology, Christopher Newport University

[2]Department of Psychological Science, University of Vermont

Correspondence to: Olga Lipatova at olga.lipatova@cnu.edu

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Abstract

This protocol describes how the Open-field Tower Maze (OFTM) paradigm is used to study spatial learning in rodents. This maze is especially useful for examining how rats learn to use a place- or response-learning to successfully navigate in an open-field arena. Additionally, this protocol describes how the OFTM differs from other behavioral maze paradigms that are commonly used to study spatial learning in rodents. The OFTM described in this article was adapted from the one previously described by Cole, Clipperton, and Walt (2007). Specifically, the OFTM was created to test spatial learning in rodents without the experimenter having to consider how "stress" might play a role as a confounding variable. Experiments have shown that stress-alone can significantly affect cognitive function[1]. The representative results section contains data from an experiment that used the OFTM to examine the effects of estradiol treatment on place- and response-learning in adult female Sprague Dawley rats[2]. Future studies will be designed to examine the role of the hippocampus and striatum in place- and response-learning in the OFTM.

Video Link

The video component of this article can be found at http://www.jove.com/video/53227/

Introduction

The open-field tower maze (OFTM) can be used to examine the behavioral and neurobiological mechanisms of spatial learning in rodents. Importantly, the OFTM allows researchers to study both "place-based" and "response-based" learning types. During *place-learning* an animal navigates through a maze using the spatial cues in the surrounding environment (*e.g.*, a food reward is located next to a tall beacon). During *response-learning* the animal makes a specific turn response regardless of its position relative to spatial cues (*e.g.*, make a left or right turn to find a food reward). It has been previously reported that response-learning and place-learning rely on two different memory systems[3, 4] and mapping their neural mechanisms has been an ongoing scientific pursuit[2, 5-7]. The design of the OFTM was adapted from the one previously described[8].

Open field paradigms (a component of the OFTM) are commonly used to investigate anxiety in rodents[9]. During the typical open field anxiety test rats that spend more time in the center of an open field have lower stress and anxiety levels than rats that spend more time near the perimeter. In the OFTM, a rat must enter the center of the maze to find the food reward. Therefore, correct navigation in the OFTM indicates that these rats are non-stressed. One reason why the rats are non-stressed during the training is because unlike standard open-field tests of anxiety training the OFTM requires pre-training phase during which the rat is pre-exposed to the maze over a long period of time. In addition, the training occurs in a dimly lit environment further reducing the anxiety-inducing aspect of an open field which is typically brightly lit.

Another unique feature of the OFTM, compared to some other mazes, is how learning is measured. Experimenters using the Morris Water Maze or Barnes Maze typically measure learning by analyzing the speed and/or path length a rat travels to reach its target location. These dependent measures can be affected by non-learning factors, such as changes in a rat's general motor activity. However, the OFTM measures learning using the percent of first-choice correct response a rat makes to find the food reward. This dependent measure is not vulnerable to changes in motor performance and therefore, more accurately assesses learning than measurements of speed and distance. Nevertheless, the experimenter can also measure a rat's speed and distance traveled in the OFTM using video tracking software.

Other maze-types, such as the T-maze, Morris Water Maze and Barnes Maze can be used to study place- and response-learning. However, the OFTM is unique in a few notable ways. First, the OFTM is a more sensitive behavioral assay than the T-maze because the OFTM has a chance performance of 25%, whereas the T-maze has a chance performance of 50%. Second, a rat can only turn in one of two ways in the T-maze, but has unrestricted route possibilities when navigating in the OFTM. Third, unlike the Morris Water Maze and Barnes Maze tasks (which have unrestricted route possibilities like the OFTM), experiments using the OFTM do not require rats to navigate through an aversive situation. Rats are motived to navigate in the Morris Water Maze to escape swimming in water and they are motivated to navigate in the Barnes Maze to avoid being in an open, brightly-lit environment. It has been demonstrated that exposure to the Morris Water Maze or Barnes Maze induces the release of stress hormone (*i.e.*, corticosterone) in rodents[10]. However, rats navigate in the OFTM because they are motivated to find a food reward and training is conducted with dim ambient lighting. Thus, the OFTM is a non-aversive appetitive task. Results from experiments that use a stressful

maze paradigm to examine the effects of manipulations such as drug, hormone, exercise, or diet on learning and memory mechanisms can be difficult to interpret because “stress”, by itself, may influence cognitive function[11].

Protocol

This protocol is approved by the Institutional Animal Care and Use Committee of Christopher Newport University.

1. Construction of the OFTM Apparatus

1. Construct the boundary wall (40 cm high and 183 cm diameter) from three pieces of white laminate. Construct the circular maze floor (183 cm diameter) from black laminate and glue it to a plastic table top. Secure the boundary wall to the edge of the table with screws and glue.
2. Decorate the interior surface of the boundary wall: Leave one quarter solid white; Paint one quarter solid black; Paint one quarter with black stripes; Paint one quarter with black circles.
3. Build four “food towers” (8 cm x 8 cm x 20 cm; **Figure 1A**) cut from a square-shaped white PVC post. Glue a piece of black laminate (8 cm x 8 cm) to the top of each tower. Secure them to the maze floor with crazy glue 54 cm apart from each other.
4. Build three “pre-training towers” (5 cm, 10 cm & 15 cm high respectively; **Figure 1B**) from a square-shaped white PVC post. Glue a piece of black laminate (8 cm x 8 cm) to the top of each tower. These towers are taped to the maze floor only during the pre-training phase (described below).
5. Glue one black opaque plastic food cup with a screw-top lid (= a clear plastic bead container painted black; 1.75 cm high and 3.75 cm diameter) to the top of each food tower. Drill three small venting holes (3 mm diameter) in each lid. The holes ensure that the rat cannot locate the “correct” food tower using olfactory cues. The height of the training towers ensures that the rat cannot locate the “correct” tower using the uncapped food cup as a visual cue.

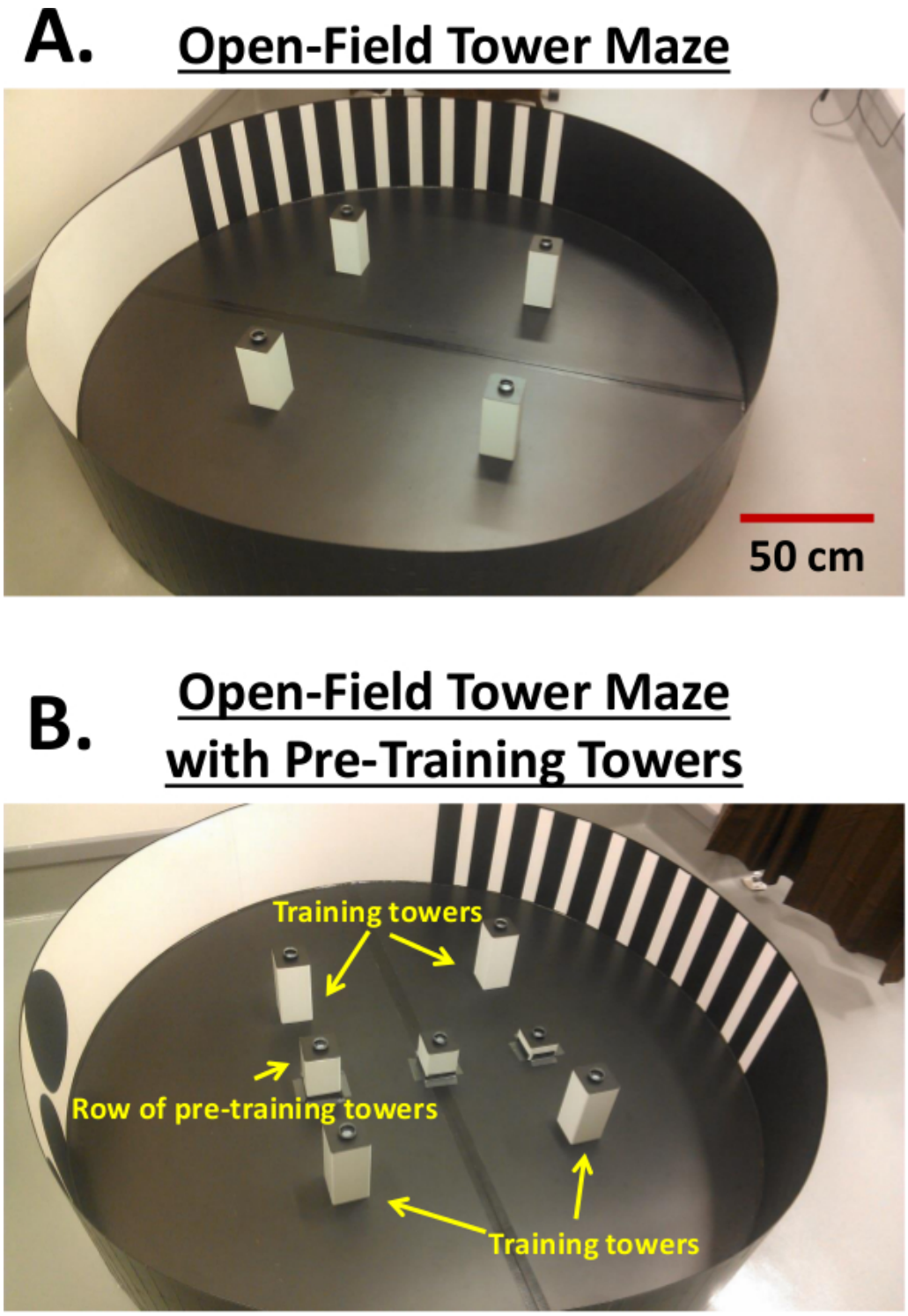

Figure 1. **Photographs of the Open-field Tower Maze (OFTM).** (**A**) The rat is able to find and retrieve a food reward from only one reward-baited "training tower" during acquisition, as well as all subsequent training and testing. (**B**) Three "pre-training towers" are placed in the center of the maze arena during pre-training. Please click here to view a larger version of this figure.

2. The OFTM Maze Room

1. Use a lamp with a 60 W light bulb (Lumens: 800) to dimly illuminate the maze room. The lamp is located 3 ft above the floor and 2 ft to the side of the maze, facing toward the ceiling. Play white noise in the background (~70 dB) using a sound machine.
2. Mount a digital video camera to the ceiling above the maze to transmit video to a computer. Hang an opaque curtain to separate the maze from the computer monitoring area.

3. Rat Handling, Food Restriction & Housing

1. Have each experimenter handle all rats for seven days (4 min per day) prior to pre-training.
2. Place rats on a food restricted diet (1 hr of free-feeding per day). This diet ensures that rats will be motivated to retrieve rewards during training, while maintaining a healthy weight (~90% of free-feeding weight).
3. Double-house rats (if using females) throughout the duration of the experiment. Pair-housed female rats are less anxious than single-housed female rats[12].

4. Pre-training Procedures

1. Bait each uncapped food cup on the seven towers with a food reward (*e.g.*, one piece of fruit cereal) inside.
2. Place a rat into the maze in a random location until it finds and consumes all seven food rewards before it is removed.
    1. If the rat does not retrieve all of the food rewards within 10 min, then remove it from the maze and give pre-training procedures again the following day. Note: some rats will take longer than others to initially learn to retrieve the food rewards from the top of the towers.
    2. If a rat does not retrieve and consume all seven food rewards from the towers within the first two days of pre-training, give it additional 30 min sessions in the OFTM until the food rewards are retrieved. Typically, the rat will find and consume all the food rewards after one or two of these 30 min sessions.

5. Place-training & Response-training Procedures

1. Assign each rat two of four start locations. Counterbalance the following: the start location release point within and between each training day; the type of learning (place vs response); the “correct tower” for all the place learners; and the turn each response-learner is trained to make (right vs. left).
2. At the start of each training day turn on the noise machine and open the video recording program. Bait all four towers and cover three out of the four food cups, leaving the food reward on the “correct” tower exposed.
3. On each given trial, start video recording (refer to manufacturer’s user manual for instructions), then place the rat in the maze at its assigned start location. Then, go behind the curtain to observe the rat’s behavior on a computer monitor. Remove the rat from the maze immediately after it retrieves the reward or after 3 min have passed and stop video recording.
    1. For **place-learning** rats, always use the same “correct” food tower, and place the rat in one of two start locations. A place-learner solves the OFTM by finding a specific location using the spatial cues provided in the maze. For example, bait tower D (= the “correct” tower) and release the rat from start location ‘2’ or ‘3’ (solid arrows in **Figure 2A**, left), or bait tower A and release a rat from start location '1' or '4' (dashed arrows in **Figure 2A,** left).
    2. For **response-learning** rats, switch the “correct” food tower depending on the start location. Response-learners solve the OFTM by learning to make a specific turn (*e.g.*, always turn right), regardless of its starting location in the maze. For example, bait tower D and release the rat from start location ‘3’, or bait tower B and release that same rat from a start location ‘2’ (solid arrows in **Figure 2B**, left). For a different rat, bait tower B and release the rat from location ‘1’, or bait tower A and release that rat from location ‘4’ (dashed arrows in **Figure 2B**, left).
4. Give all rats a total of 48 training trials across 12 days (four trials per day).

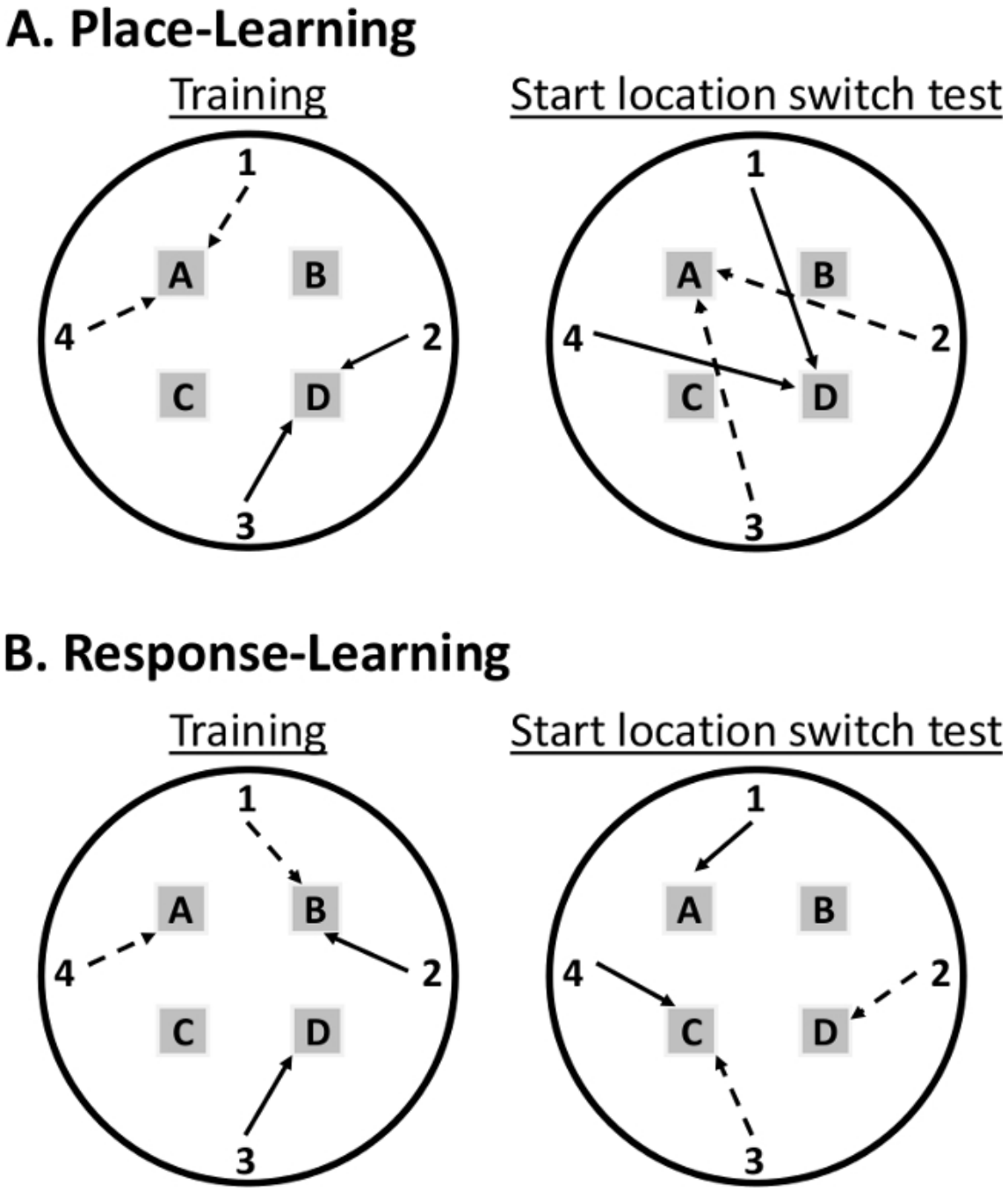

Figure 2. **Overhead Schematic Showing Place- and Response-Training & Testing Procedures.** This figure shows the start and food reward locations for training place-learners (**A, Left**) and response learners (**B, Left**), and also the start and reward locations used during the start location switch test for place-learners (**A, Right**) and response learners (**B, Right**). Numbers indicate a rat's starting location; gray squares represent food towers; solid and dashed lines point to the baited food tower. Start locations are counterbalanced within each training condition. Please click here to view a larger version of this figure.

6. Start Location Switch Testing Procedures

1. After all the rats perform at their asymptotic level (~80% of correct first choice responding) carry out a "Start Location Switch Test" to test the persistence of the learned behavior.
2. Counterbalance the novel start locations (*i.e.*, the start locations that have not been previously used for the rat).
3. Follow the procedures for each training trial described in protocol section 5 with the new start locations.
    1. For a place-learning rat that originally was released from location '2' or '3' and had tower D as its "correct" tower, place the rat in either of the new start location '1' or '4' , while still baiting tower D (**Figure 2A**, right).

2. For a response-learning rat that was originally released from location '2' or '3' and learned to turn right to receive the reward (on towers B and D, respectively), place the rat in either of the new start location '1' or '4' and bait either tower A or C, respectively (which would still require the rat to turn right in order to find the food reward) **Figure 2B**, right.
3. Administer all rats eight start location switch test trials across two days (four trials per day).

7. Data Analysis

1. Have an experimenter who has not trained rats and does not know the treatment of each rat score video-taped trials by counting the number of responses a rat makes to find the "correct" tower on each trial (indicated by the rat rearing up over the food cup).
2. Calculate the percent of times that a rat finds the reward on its first choice (% of first choice correct responses) within each training day. Construct learning curves using the percent of first choice correct responses across training days. Use the percent of first choice correct response for the statistical analysis.
3. Calculate the number of trials it took the rat to reach the *a priori* set criterion to acquire the task (*i.e.*, first choice correct responding on 8 out of 10 consecutive trials). Exclude rats from analysis that do not reach the *a priori* criterion.

Representative Results

The representative results described here have been previously published in the Neurobiology of Learning & Memory, Elsevier[2]. In this experiment the OFTM was used to test the effects of chronic and cycling estradiol treatments on place- and response-learning in female Sprague-Dawley rats (250 – 300 g; N = 48). There were two important reasons why the OFTM was used to conduct this experiment. First, estradiol has been shown to induce differential effects on place- and response-learning[7]. Second, it was necessary to test the effects of estradiol on learning in a non-stressful environment, because gonadal hormones have differential effects in humans exposed to stressful situations[13]. In the Lipatova *et al.* (2014) experiment ovariectomized female rats were administered daily subcutaneous injections of estradiol (10 µg/kg) or vehicle solution (peanut oil). Rats in the "Continuous" condition received daily injections of estradiol and rats in the "Vehicle" condition received daily injections of the vehicle solution. Rats in the "Cycling" condition were given injections of estradiol every 4th day and vehicle solution on the other days. Half the rats in each condition were trained with place-training procedures and half were trained with response-training procedures. Six rats did not reach the *a priori* acquisition to criterion and thus were not included in the analysis. The final groups were: Vehicle-Place (Vehicle-P; n = 9), Vehicle-Response (Vehicle-R; n = 6), Continuous-P (n = 7), Continuous-R (n = 7), Cycling-P (n = 7) and Cycling-R (n = 6).

Acquisition to Criterion: Place-Training vs. Response-Training

After pre-training, each rat was given 48 acquisition trials on the OFTM. A 2 x 3 (training type x treatment) ANOVA was performed using the number of trials the rats took to reach the *a priori* acquisition criterion, which revealed a significant main effect of treatment [$F(2, 36) = 5.6$, $p < 0.01$] and training type [$F(1, 36) = 5.09$, $p < 0.04$]. A follow up test (HSD) showed that rats given cycling estradiol-replacement took fewer trials to reach the acquisition criterion for place-learning than rats given cycling injections or vehicle injections, $p < 0.01$. Estradiol treatment had no effect on the number of trials it took the rats to reach the acquisition criterion for response learning (**Figure 3**).

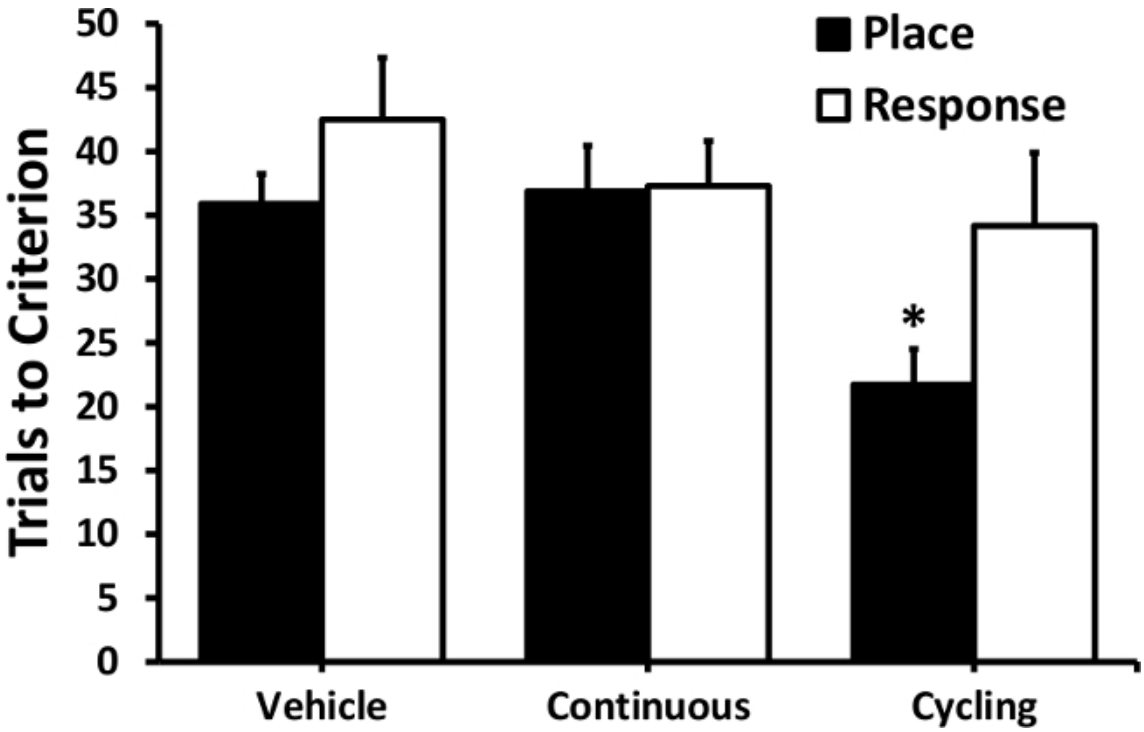

Figure 3. **Trials to Criterion for Place- and Response-training.** This graph shows the average number of trials for rats given place (black bars) and response (white bars) training needed to reach 8 out of 10 consecutive first choice correct responses. Female rats given cycling estradiol

replacement required fewer trials to reach criterion for place-learning than rats given continuous estradiol replacement and vehicle-treated rats. There was no significant difference in acquisition of response learning across the different treatment conditions. [Modified from Lipatova *et al.* 2014 and reprinted with permission from Elsevier] Please click here to view a larger version of this figure.

Acquisition in Place-Learners

Figure 4 shows acquisition curves for the vehicle and estradiol-treated rats that were given place-training. A 3 x 12 (treatment x trial block) repeated-measures ANOVA revealed a significant within-subject effect of trial block [$F(11, 220) = 22.47$, $p < 0.01$], indicating that performance improved during training. Additionally, the analyses revealed a significant between-subject effect of treatment [$F(1,20) = 3.76$, $p < 0.05$] (**Figure 4**). A follow up test (HSD) showed that rats given cycling estradiol treatment (Cycling-P) had higher percentages of 1st choice correct trials than vehicle (Vehicle-P) and continuously (Continuous-P) estradiol treated rats, $p < 0.02$. There was no difference in the percent of 1st choice correct responses between the Vehicle-P and Continuous-P group. These results showed that cycling estradiol treatment enhanced acquisition of place-learning.

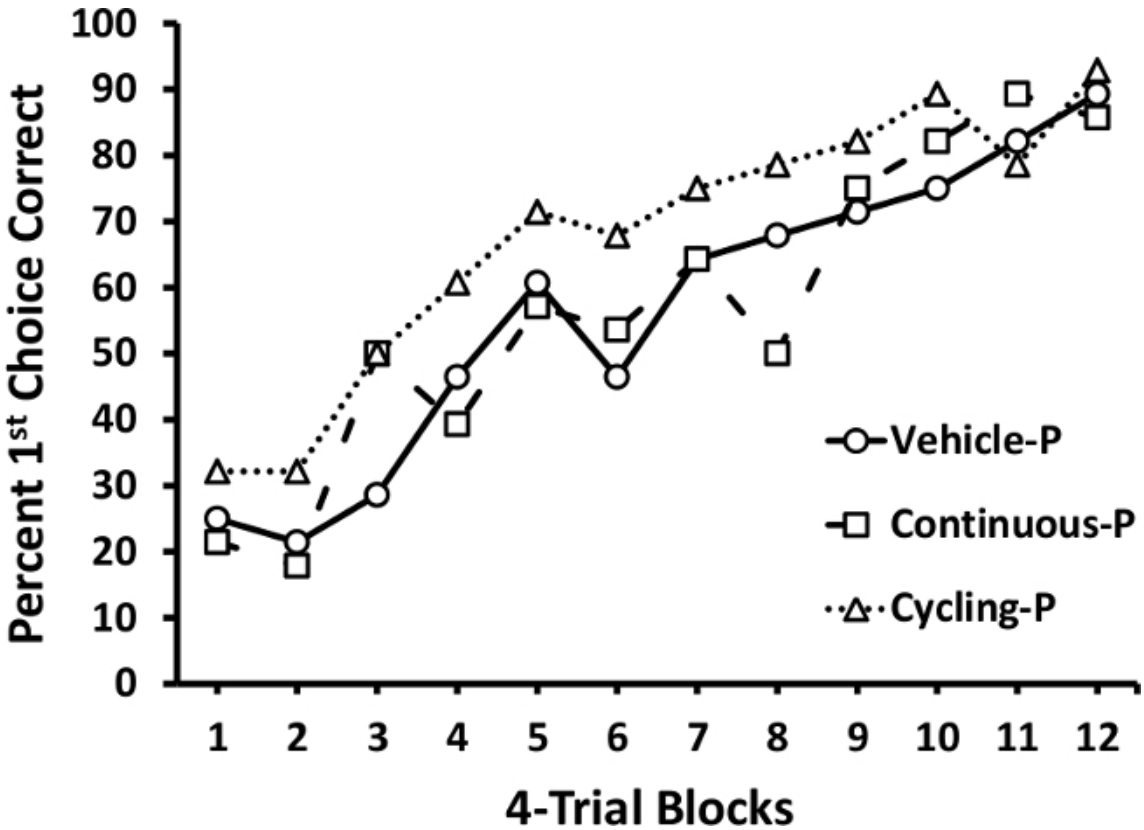

Figure 4. Acquisition Rate for Place-Learning. This graph shows the rate of acquisition for rats given place-training based on the percentage of first choice correct responses made within blocks of four trials. After 48 trials all rats reached ~80% first choice correct responding. Cycling estradiol replacement rats (Cycling-P; white triangles) acquired place-learning significantly faster than continuous estradiol replacement rats (Continuous-P; white squares) and vehicle treated rats (Vehicle-P; white circles). [Modified from Lipatova *et al.* 2014 and reprinted with permission from Elsevier] Please click here to view a larger version of this figure.

Acquisition in Response Learners

Figure 5 shows acquisition curves for the vehicle and estradiol-treated rats given response-training. A 3 x 12 (treatment x trial block) repeated-measures ANOVA revealed a within-subject effect of trial block [$F(11, 176) = 12.59$, $p < 0.01$], showing that performance improved throughout training. However, treatment type had no significant effect on the rate of response learning.

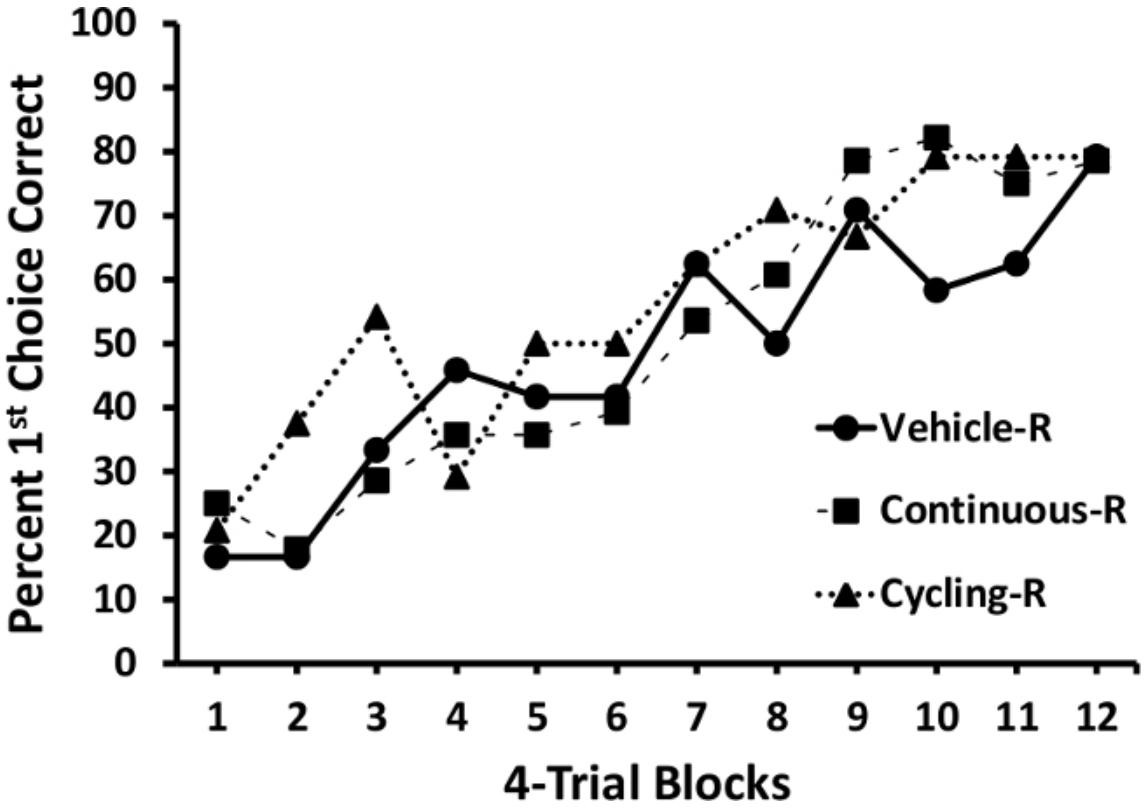

Figure 5. Acquisition Rate for Response-Learning. This graph shows the rate of acquisition for rats given response training based on the percentage of first choice correct responses made within blocks of four trials. After 48 trials of training all rats reached ~80% first choice correct responding. There was no significant difference in acquisition rate across the different treatment conditions (Cycling-P; black triangles vs. Continuous-P; black squares vs. Vehicle-P; black circles). [Modified from Lipatova *et al.* 2014 and reprinted with permission from Elsevier] Please click here to view a larger version of this figure.

Start Location Switch in Place-Learners

Place-learners were initially impaired when the start location was switched, regardless of treatment. A 2 x 3 (last trial block on the original start location vs. the first trial block on the switch start location test x treatment) repeated measures ANOVA revealed a significant effect of start location [$F(1,18) = 9.68$, $p < 0.01$] (**Figure 6**). There was no significant interaction or between-subjects effect. However, previous findings have shown that vehicle-treated place-learners are less impaired than the estradiol-treated rats during a start location switch test[14]. Therefore, pairwise comparisons were performed to compare percent of 1st choice responses between each group's last block on the original start location and the first trial block on the switch start location. Estradiol-treated rats had lower 1st choice response percentages during the switch start test compared to their original start location, $p < 0.05$. As previously reported, there was no significant decline in performance found for vehicle-treated rats. The difference in performance between vehicle-treated and estradiol-treated rats became larger on the second trial block of the switch start location test (**Figure 6**). A 2 x 3 (last block on the original start location vs. the second trial block on the switch start location x treatment) repeated measures ANOVA revealed a significant effect of start location [$F(1,18) = 20.69$, $p < 0.01$] (**Figure 6**), showing that performance in vehicle-treated rats on the second block of the switch start location test was the same as their performance on the original start location and estradiol-treated rats displayed a prolonged deficit. Pairwise comparisons showed that Continuous-P and Cycling-P rats had significantly reduced performance on the second day of the new start location compared to their performance during the last day of original start location, $p < 0.01$. All rats returned to pre-switch test levels of performance when they were subsequently trained on their original start location (**Figure 6**). This finding was confirmed with a 2 x 3 (original start location before switch vs. original start location after switch x treatment) repeated measures ANOVA that revealed no significant within-subject or between-subjects effect.

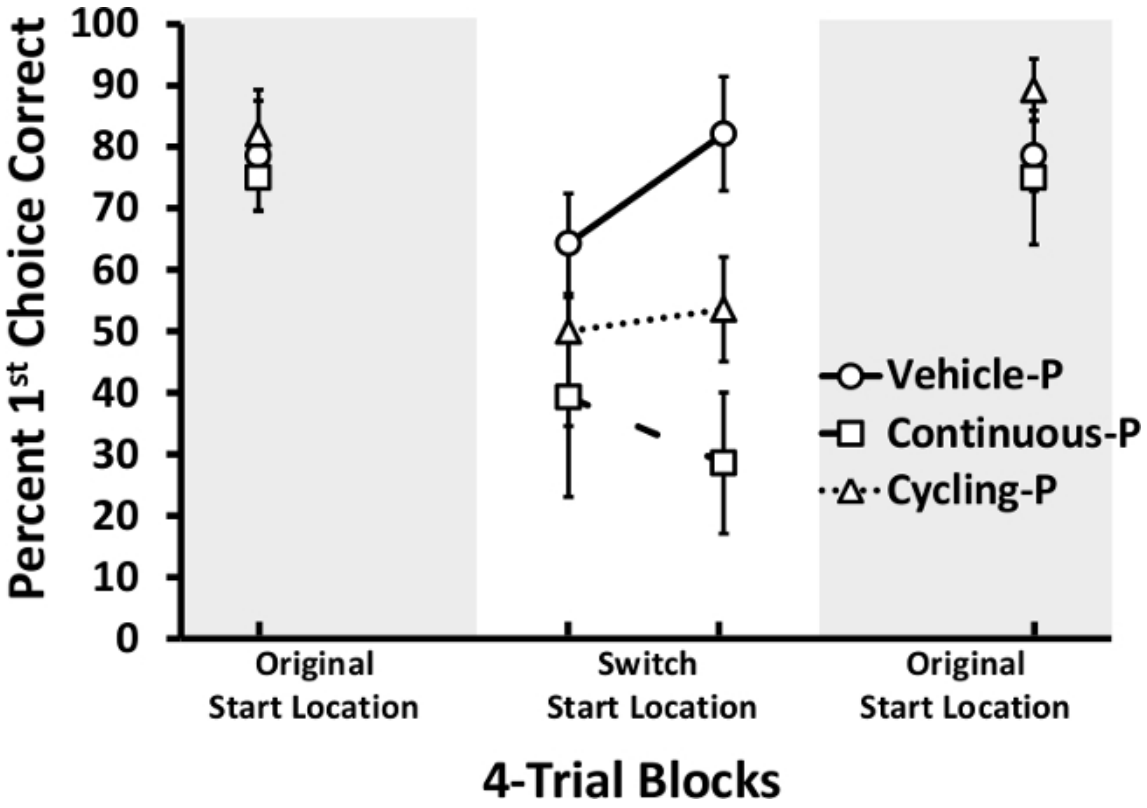

Figure 6. **Start Location Switch Test for Place-Learners.** This graph shows the percentage of first choice correct responses in four-trial blocks for place-learners on the last day before the start location switch (**left panel**), during the start location switch test (**middle panel**) and back with the original start location (**right panel**). Estradiol-treated rats (white squares & white triangles) had overall lower percentages of 1st choice correct responses than vehicle-treated rats (white circles). [Modified from Lipatova *et al.* 2014 and reprinted with permission from Elsevier] Please click here to view a larger version of this figure.

Start Location Switch in Response Learners

Response-learners were impaired when given the switch start location test. A 2 x 3 (last block of the original start location vs. first trial block of the new start location x treatment) repeated measures ANOVA revealed a significant effect of start location [$F(1,16) = 10.28$, $p < 0.01$], but no interaction or main effect of treatment. Therefore, the decline in performance during the first block of the switch start test was equivalent across each treatment condition (**Figure 7**). However, unlike in the case of place-learners, pairwise comparisons revealed that performance in estradiol-treated response-learners recovered to pre-switch test performance level on the second trial block of the switch start location test, while vehicle-treated rats continued to show impaired performance, $p < 0.04$. Therefore, vehicle-treated response-learners were more impaired on the switch start location test than estradiol-treated response-learners. All rats returned to pre-switch test levels of performance when they were subsequently tested with their original start location (**Figure 7**). This finding was confirmed with a 2 x 3 (original start location before the switch test vs. original start location after the switch test x treatment) repeated measures ANOVA did not reveal any significant within-subject or between-subjects effects.

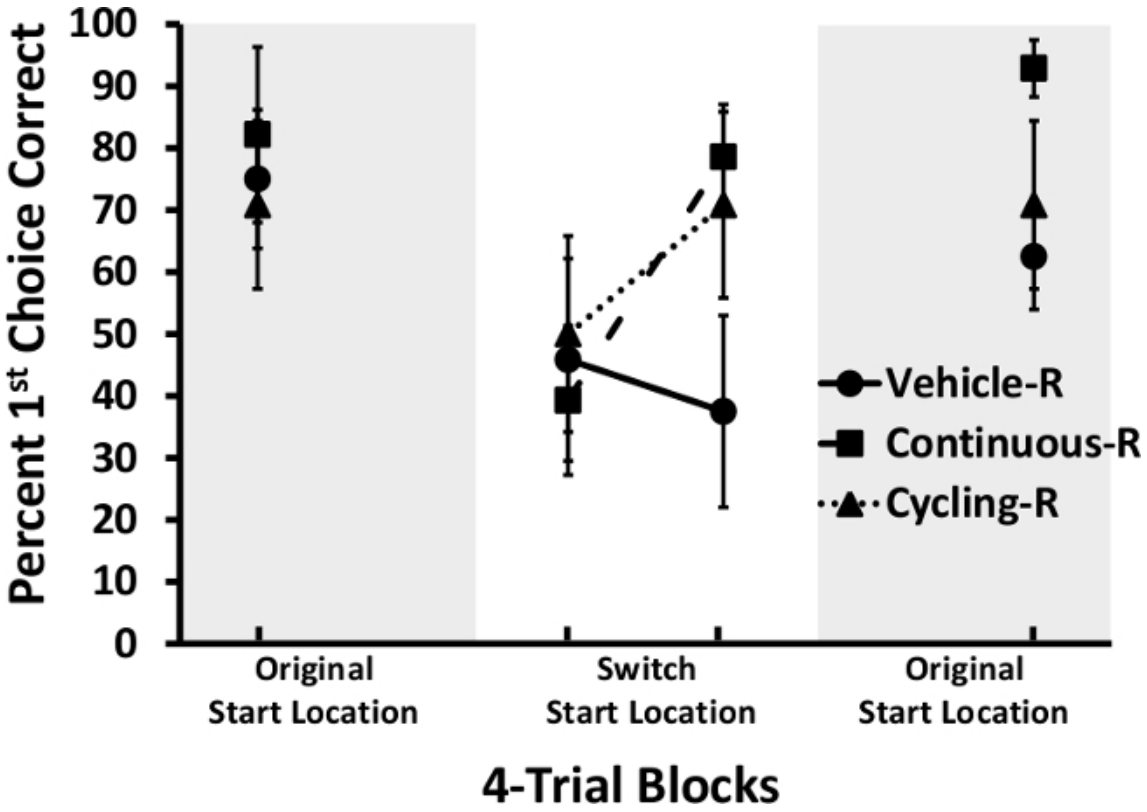

Figure 7. **Start Location Switch Test for Response-Learners.** This graph show the percentage of first choice correct responses in four-trial blocks for response learners on the last day before the start location switch (**left panel**), during the start location switch test (**middle panel**) and back with the original start location (**right panel**). Estradiol-treated rats (black squares & black triangles) overall had higher percentages of 1st choice correct responses than vehicle-treated rats (black circles). [Modified from Lipatova *et al.* 2014 and reprinted with permission from Elsevier] Please click here to view a larger version of this figure.

Discussion

Numerous paradigms can be used to investigate learning and memory in rodents, and each has important steps that experimenters should follow. In the OFTM, it is important that maze conditions (*e.g.*, position of maze, intra- and extra-maze cues, dim lighting and background noise level, daily time of training) are kept constant throughout the duration of the experiment. It is also necessary to minimize stress in rat subjects to ensure continuous performance in the OFTM. Stress can be kept to a minimum in female rats by pair-housing them and also through routine handling by experimenters prior to training. In order to accurately score a rat's performance during training and testing (*i.e.*, when a rat makes a correct or incorrect tower choice), it is important to use food towers that are tall enough so the rat must "climb up" the tower and rear over the food cup to retrieve a reward. The lid of the food cup is not visible to the rat until it "climbs" the tower. The food tower that the rat chooses, therefore, is unambiguous and can be reliably scored by the experimenter. The maze floor must be constructed from material that has high contrast relative to the rat's color if the experimenter wants to analyze the rat's velocity, distance traveled and/or time spent in a specific portion of the maze using video tracking software.

Long-term memory retention of place and response learning could be examined using the OFTM task. Following the completion of 48 training trials, all rats may spend 21 days in their home cages without any handling. This 21-day interval is commonly used to test for retention of a long-term memory[15-17]. The rats could be taken off food restriction at the beginning of this memory retention period and subsequently returned to food restriction a week prior to testing. All rats then could receive 12 reacquisition trials across three days (four trials per day) of training (during the reacquisition trials, follow the protocol described in this manuscript). If an experimenter needs to assess long-term memory retention, then rats should not be handled during the retention interval because retrieval cues, such as handling, tend to block long-term forgetting[18, 19]. Experiments that require handling during the retention interval should be designed to include a retention interval longer than 21 days to avoid this confound. In addition to testing for long-term memory retention, the OFTM can also be used to examine rat's ability to learn a new maze rule (*e.g.*, reversal learning).

The OFTM was designed to specifically assess spatial learning (*e.g.*, place- and response-learning in rodents, but only adult Sprague-Dawley rats have been used in actual experiments with this maze. However, it is certainly possible to use other types of rodents in the OFTM, such as other rat strains and mice. It is also possible to test rodents of different ages in the OFTM, although it may be necessary to scale the maze dimensions up or down depending on the size of the subject tested. The OFTM is not currently available for purchase on the open market, so experimenters will need to construct their own maze. It is unlikely that minor differences in construction materials (*e.g.*, texture and/or color) or maze size deviating from the OFTM described in the present protocol will significantly influence how a rat performs in the maze; however, this hypothesis has not been tested. It is also recommended that experimenters conduct pilot work before they begin an experiment.

There are a few notable reasons why the OFTM is a useful paradigm for studying the behavioral and neurobiological mechanisms of spatial learning. The OFTM is similar in complexity to the Morris Water Maze; however, the rat is not forced to swim in this task. Thus, the OFTM can be used to assess learning in a non-stressful situation, unlike the Morris Water Maze which inherently evokes a stress response in rodents[10]. Additionally, the probability for a rat to make a correct response by chance is 25% lower in the OFTM than in a T-maze. Also, rather than being forced to make one choice from a limited number of predetermined paths (as is required in some spatial paradigms), the rat's navigation path is not restricted in the OFTM.

Prior studies have shown that place-learning depends on the hippocampus and response-learning depends on the striatum (reviewed in [5]). This brain-region distinction between place- and response-learning has been found using the T-maze apparatus[4], a radial-arm task[20], as well as the Morris Water Maze[3, 21]. Future experiments will be conducted to test whether the hippocampus and striatum are necessary for place- and response-learning in the OFTM. If this is the case, additional experiments will be able to confidently test the effects that hormones, drugs, diet, *etc.* have on hippocampal- vs. striatal-dependent learning pathways in a non-stressful environment.

Disclosures

The authors have nothing to disclose.

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