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Sex Differences and Latent Place Learning in a Novel Water Maze Environment

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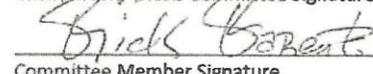
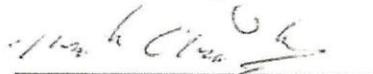
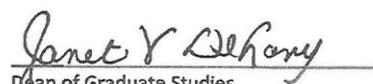
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Abstract

Sex Differences and Latent Place Learning in a Novel Water Maze Environment

Elizabeth Tobin

Results of research involving sex differences when solving spatial learning and memory tasks are often inconsistent as some studies report significant sex differences, while others do not report any difference. Latent learning is often studied both with and without motivation in male animal subjects. The current study investigated sex differences and latent learning in rats tested in the Morris water maze using a two-room design. The results showed a significant sex difference whereby females were more likely to go to the new location while males preferred the old location. These results likely derive from interaction effects between known sex differences in factors such as cue use and individual differences in working memory. It has been reported that female rats have superior working memory. Working memory, therefore, could result in more efficient processing of novel cues during passive placements allowing them to perform more accurately after being placed into the pool.

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Chapter One:

Introduction

Early studies show that various brain regions contribute to sex differences with regards to spatial cognition (Kimura, 1992). For example, Kimura (1992) reported a male advantage on mental rotation with humans, which has been shown to correlate with spatial performance in the virtual water maze (Astur, Tropp, Sava, Constable, & Markus, 2004). Significant sex differences in rats concerning spatial cognition have also been reported (Jonasson, 2005; Keeley, Tyndall, Scott, & Saucier, 2013), although, other studies have found no significant sex differences in spatial cognition (Devan, Tobin, Dunn, & Magalis, 2016; Healy, Braham, & Braithwaite, 1999; Jonasson, 2005). Indeed, sex differences have also been reported in relation to other characteristics such as hormonal factors (Hawley, Grissom, Barratt, Conrad, & Dohanich, 2012; Sava & Markus, 2005), susceptibility to stress (Burke et al., 2013; McFadden et al., 2011), enriched environment (Chamizo, Rodríguez, Sánchez, & Mármol, 2015), landmark use along with strategy preference (Kanit, Koylu, Erdogan, & Pogun, 2005; Keeley et al., 2013), latent learning (Stouffer & Barry, 2014) and other neurobiological factors (Chow, Epp, Lieblich, Barha, & Galea, 2013; Grissom, Hawley, Hodges, Fawcett-Patel, & Dohanich, 2013).

The broad range of sex differences previously reported concerning spatial performance is likely due to individual differences combined with interaction effects from other factors and variables. One such factor is strategy preference which often relies on landmark availability and may, therefore, be influenced by latent learning. Latent learning is a form of incidental, response independent learning where no intention

to learn was made (Blodgett, 1929; Stouffer & Barry, 2014) and is often studied using some form of motivation (Stouffer & Klein, 2013; Whishaw & Pasztor, 2000). However, incidental latent learning has also been studied without motivation, just exploring an environment or without movement, passively observing the cues from the above or from the goal location. This form of learning is reported to improve performance in rats after varying numbers of passive platform placements (Sutherland & Linggard, 1982; Horne, Gilroy, Cuell, & Pearce, 2012; Jacobs, Zaborowski, & Whishaw, 1989;).

Although the relationship between sex, latent learning and spatial cognition is of interest, most latent learning studies have reported findings regarding solely male subjects. The number of platform placements is also of interest when considering sex differences and response independent learning because both are associated with landmark use and therefore strategy preference. Although the Morris water maze will be used to measure spatial cognitive performance (Morris, 1981); the following literature review focuses on the relevant research regarding cognitive processes related to differences in both biological sex and latent learning. Specific attention is paid to sex differences related to cognitive processes which utilize brain regions associated with spatial cognition.

Sex Differences and Spatial Cognition

Small effect sizes and inconsistent sex differences in spatial cognition are typically reported (Perrot-Sinal, Kostenuik, Ossenkopp, & Kavaliers, 1996) and a variety of explanations have been proposed to account for the differences. For example, studies often report sex differences in level of performance, strategy preference, landmark use and stress level (Burke et al., 2013; Chamizo, Rodríguez, Torres, Torres, & Mackintosh,

2014; Hamilton et al., 2008; Kanit et al., 2005; Keeley et al., 2013). In rats, a male performance advantage on spatial tasks such as the water maze and radial arm maze is often reported (Jonasson, 2005). This advantage is most often observed during early water maze training when males find the platform more quickly than females (Beiko, Lander, Hampson, Boon, & Cain, 2004; Blokland, Rutten, & Prickaerts, 2006).

Beiko et al. (2004) reported that male and female rats were trained in the water maze in three different learning conditions; place learning with a fixed hidden platform, cue learning with a visible platform and egocentric learning with a hidden platform at a specific angle from the start position. Rats were first trained in place learning, then cue learning, and finally, egocentric learning. Results revealed improved performance of male rats in the place condition and no sex differences in either the cue or egocentric conditions. The male advantage during the place learning condition resulted from female rats display of more thigmotactic behavior during the first three days of the place condition as they spent more time near the pool wall. However, when Beiko et al. (2004) reversed the order of the learning conditions so that rats had egocentric learning first and place learning last, results no longer revealed any significant sex difference in any learning condition. This implies that sex differences are less evident after pre-training and also indicate different search strategies may be used by male and female rats, as evidenced by no additional time being spent in the training quadrant by female rats during the probe test.

Although improved male performance is commonly cited in the literature, the difference has not been consistently replicated. For example, in a meta-analysis by Jonasson (2005), the male advantage in spatial navigation was described as “robust” even

though only 7 water maze studies found significant male advantage while 11 of the other water maze studies included in the analysis found no difference. This variability could be due in part to individual differences in spatial navigation because the advantage in performance was modifiable by pre-training in addition to various other factors that might also alter sex differences in spatial tasks.

Sex differences affect stress in spatial tasks and stress is known to affect cognitive performance in both humans and rats (Arnsten, 2009; Burke et al., 2013). In rats, sex influences the effect of stress; stress is known to increase thigmotaxis and impair retrieval of long term spatial memory in females (Burke et al., 2013; McFadden et al., 2011). Perhaps one way that pre-training influences performance is by reducing stress thereby decreasing thigmotactic behavior in female rats (Beiko et al., 2004). By decreasing stress to the animals, many sex related differences in performance are also reduced because differences in thigmotaxis are abridged. It is, therefore, necessary to reduce stress on the animals in order to reduce the stress effect on cognition.

Enriched environments have been shown to reduce stress in rats, therefore, increasing spatial performance (Chamizo et al., 2015; Harris, D'Eath, & Healy, 2009). For example, in the study done by Harris et al. (2009) both male and female rats were housed in either enriched or non-enriched environments and then trained in a standard water maze protocol. Results indicated improved performance of enriched rats because they were less thigmotactic than non-enriched rats. Additionally females were overall found to be more thigmotactic than males. The enhanced performance seen in the enrichment group was suggested to be a result of reduced anxiety during testing as enrichment has been associated with a reduced stress response (Harris et al., 2009). A

study by Chamizo et al. (2016) also found that enrichment increased spatial cognitive performance and reduced thigmotaxis in a snow cone maze. A sex difference was found regarding cue information used by rats to reach the platform as males tended to rely on geometric cues and information such as pool geometry, while females preferred to use information concerning landmarks. The preference for different cue types in the sexes could influence strategy selection and consequently spatial navigation in rats.

Search strategy is another factor that differs between the sexes (Grissom et al., 2013; Hawley et al., 2012; Kanit et al., 2005; Sava & Markus, 2005) which could be influenced by interactions with cue use preference. Several common search strategy types are used by rats in water maze paradigms, including place responding and cue or directional responding. Place responding strategies occur when rats swim directly to the old platform location where they were trained to go; whereas cue or directional responding occurs when rats swim directly to the new platform location (Grissom et al., 2013). Recent studies have found sex differences in both the cues used and strategies preferred by rats. Males often prefer place navigation by using geometric and allocentric cues; whereas females tend to prefer response navigation by using landmark and egocentric cues (Blokland et al., 2006; Chamizo et al., 2015; Keeley et al., 2013). Although this finding is common throughout the literature, not all studies have found that male rats initially prefer place responding (Hamilton et al., 2008).

The interaction between cues use and strategy selection is further evidenced by results from Hamilton et al.'s (2008) study which consisted of only male rats and found evidence of spatial navigation being predominated by directional responding. The study revealed that directional responding was preferred by rats even when a variety of pool

and platform placements were used. Only when the water level in the water maze pool was filled to a depth which obscured the salience of the pool wall, did the rats prefer a place strategy response and swam to the old location in the pool relative to the distal cues. Distal cues and the visibility of the pool wall interacted to regulate responding, which supports the interaction of complex brain systems during spatial navigation. The interactions were observed when multiple brain systems were activated and coordinated to produce a navigational response. Therefore, these differences in search strategy preference are also affected by other factors such as brain structure and hormones.

Recent studies examining the influence of brain structure in biological sex differences related to spatial navigation have implicated female hormones as a probable factor (Chow et al., 2013; Cimadevilla et al., 1999; Healy et al., 1999; Keeley et al., 2013). The estrus cycle has been reported to affect female rat performance in the water maze depending on what stage of the cycle the female rat was in. However, additional findings report that spatial performance was not affected by estrus cycle even though increased spatial learning has been correlated with high levels of estrogen (Healy et al., 1999). For example, when estradiol levels were higher, and females were in proestrus, they preferred place navigation and geometric cue use as opposed to directional responding while spatially navigating (Keeley et al., 2013). Estradiol has been known to influence behavior and increase spatial learning during high hormone levels and could be the result of the change in response strategy preference found in females from directional to place responding (Cimadevilla et al., 1999). This behavioral shift is connected to estradiol as estradiol has also been shown to influence the hippocampus (Cimadevilla et

al., 1999) which facilitates the use of place responding (Grissom et al., 2013) because the hippocampus is one brain structure associated with spatial learning and memory.

The acquisition of spatial information is associated with the hippocampus (Chow et al., 2013; Koss & Frick, 2017; Grissom et al., 2013) and has been indicated in sex differences related to strategy selection. For example, sex differences observed in the use of cues and learning strategies may influence the differences in hippocampus based navigation (Chow et al., 2013). Females less often used hippocampus based place response strategies and experienced less activation of hippocampal neurons. These results suggest that activation of neurons in the hippocampus is influenced by learning strategy (Chow et al., 2013). Similar results were found by Grissom et al., (2013) that linked strategy preference to hippocampus binding ratios. Results indicated that when a responding strategy was preferred by rats, lower hippocampus binding ratios were observed in relation to binding ratios of both the amygdala and striatum. Further support for the role of the medial portion of the dorsal striatum has been reported by Devan, McDonald and White (1999) when the striatum was suggested to contribute to the control of cognition through connections between the limbic system with some striatal areas. The striatal areas may be responsible for the integration of signals from various parts of the brain to produce a behavioral response. For example, it has been suggested that the limbic circuit interacts with basal ganglia strengthening the cognitive control of behavior (Devan, Magalis, & McDonald, 2015; Devan, Hong, & McDonald, 2011).

Another brain system integrated with spatial learning is the entorhinal cortex (EC); its functioning has been correlated with improved performance in the water maze (Keeley et al., 2013). Although male and female hippocampal volumes were equal, links

between the entorhinal cortex and spatial memory were revealed when heading in males was correlated with the volume of the entorhinal cortex. These results suggest geometric cue based navigation relies upon the entorhinal cortex. The use of different brain systems for different types of strategy preferences suggests that the environmental cues chosen by rats for spatial navigation could activate different neural structures as well as play a role in latent learning.

Latent Learning

Learning is a continuous process, and whether purposeful or not, the brain is always responding to stimuli, making decisions and storing information as memories. Even during response independent learning, these complex processes occur simultaneously, influencing multiple brain systems as well as behavioral responses such as spatial navigation (Sutherland & Linggard, 1982; McNamara, Long, & Wike, 1956; Devan et al., 2002). Previous research has indicated that spatial performance has been improved by latent learning in rats after passively placing subjects on the target platform location prior to a swim trial (Sutherland & Linggard, 1982; Sutherland, Chew, Baker, & Linggard, 1987; Devan et al., 2002; Jacobs et al., 1989; Keith & McVety, 1988). For example, in Sutherland and Linggard's (1982) original study involving latent learning in the water maze, rats were passively placed multiple times a day for five days in either the correct platform position, the incorrect platform position or they remained naive with no placements. Results showed that rats placed in the correct platform position demonstrated improved performance with regard to several specific aspects such as acquisition, swim path, latency and initial heading error. Although much of the literature

reports a positive relationship between latent learning and improved performance, there is little consensus regarding the nature of the performance.

Devan et al. (2002), observed that increased spatial performance and improved initial heading error resulted from passive placement and swimming from a novel start point in a more direct path to the goal (Keith & McVety, 1988; Keith 1989) improving initial heading error. Meanwhile, others have reported that although passive placements do improve acquisition performance compared to controls, the performance never reaches the same level as animals permitted to swim throughout the environment (Sutherland et al. 1987; Whishaw, 1991). Additionally, the number of passive placements necessary to observe a benefit to performance has not been consistently reported (Devan et al., 2002; Horne et al., 2012; Keith & McVety, 1988; Jacobs et al., 1989; Whishaw, 1991). For example, the inconsistencies reported regarding the number of passive platform placements required before observing any improved performance has varied from a single placement (Devan et al., 2002; Whishaw, 1991) to more than five placements being required (Horne et al., 2012; Jacobs et al., 1989). For instance, Horne et al. (2012) reported that improved performance was observed in male rats after as few as 7 placement trials and the improvement was suggested to be the result of increased stimulus-stimulus (S-S) associations. Similarly, Jacobs et al. (1989) reported that although latent learning was possible by male rats, more than five passive placements were needed before this type of learning was observed. In contrast to these findings, results reported by Devan et al. (2002) and Wishaw (1991) indicate that a single passive placement was enough to improve performance.

A single passive placement was used by Devan et al. (2002) in two experiments regarding latent learning in the water maze in male rats. In experiment 1, rats were pre-trained in one room to a specific location, before being given one passive placement trial in another room with a new platform location, which was then followed by 4 swim trials to the new platform location and a probe test. Rats preferred the place they were previously trained to go to which also happened to be close to the same salient adjacent landmark cue in the previous room: the door. The procedure was then replicated in a second experiment with a curtain hung to cover the door since salient cues have been known to influence navigational responding (Hamilton et al., 2008; Sava & Markus, 2005). Experiment two revealed that performance was improved by latent learning in the absence of the salient cue. These results give further support to the importance of both the cooperation between brain systems and interactions between factors, such as cue use, with regard to specific types of behavioral responding.

The types of cues used by rats have been reported to influence latent learning concerning strategy selection as well as activation of specific brain structures (Chow et al., 2013; Grissom et al., 2013; Keeley et al., 2013). For example, as reported by Devan et al. (2002) the observation of latent learning was dependent on the salience of environmental landmarks available for use as cues which resulted in different strategy preferences. Such strategy preferences are often determined by different brain structures simultaneously processing interactions between various memories and brain systems. Although brain structures have been studied in connection with latent learning, most are reported using dry land mazes in combination with some type of motivation. For instance, recent lesion studies have suggested the relevance of cue availability to latent

learning because both the entorhinal cortex and the dorsal hippocampus have been reported to be associated with spatial learning and memory in dry land mazes using motivation (Stouffer, 2010). So long as latent learning did not require multiple environmental cues to be associated together, the entorhinal cortex appears to play a central role; otherwise, the dorsal hippocampus is required to process multiple cues. Another example of the importance of the entorhinal cortex is suggested by the impairment in acquisition training or testing observed in a radial arm maze using food motivation after temporary deactivation of the entorhinal cortex (Gaskin & White, 2010). The results of these studies imply that the hippocampus, striatum and entorhinal cortex work together to produce spatial learning and cognition.

Although there are many previous studies regarding latent learning, all but a few include implications of sex differences because most studies included solely male subjects. Two studies were found relating sex differences to latent learning. One study reported that the onset of latent learning was at an earlier age in females than males (Stouffer & Barry, 2014). Meanwhile, the other study was related to the strength of long term spatial memory that has been reactivated by latent learning (Flint, Valentine & Papandrea, 2007). In the study, a reactivation of memory treatment, in the form of passive placement on the platform in its original training location, was implemented and suggested that the reactivation treatment was more beneficial to females than males (Flint et al., 2007).

The Present Study

Due to the mixed results reported in the literature regarding both sex differences and latent learning in spatial navigation, a clear understanding of the factors has not been established yet. The present study was designed to examine the effect of biological sex and latent learning on spatial cognition which was examined through the use of passive placement of male and female rats in a novel two room Morris (1981) water maze conducted in a previous study (Devan et al., 2002). After all the rats completed place acquisition training in room A, they next completed passive placement training and trials in room B before completing a single probe trial in room B which was used to measure spatial cognition and indicate latent learning. Due to the biological sex differences in cue types attended to and strategy preference, it was expected that males would outperform females. There were a couple factors of interest here; were two passive placements enough to indicate improved performance due to latent learning and would biological sex influence any differences? It was hypothesized that performance of all rats would be improved from passive placement through latent learning, that animals who were good latent learners would outperform others on the probe test and that males would outperform females in the Morris water maze.

Chapter 2:

Method

Subjects

The subjects used for this experiment were 16 Long-Evans hooded rats (Harlan Sprague-Dawley Inc.). The sample of 8 females and 8 males weighed 300-350 grams (\approx 9 months of age). All animals were singly housed in hanging wire mesh cages with ad libitum access to food (Lab Diet 5001 Rodent Diet) and tap water. The holding cages were located in an environmentally controlled colony room which includes a 12:12 hr. light-dark cycle (room temperature \simeq 23 degrees Celsius). Behavioral training and testing was all completed during the light cycle and was approved by Towson University Institutional Animal Care and Use Committee (see Appendix A).

Apparatus

The specific environment and apparatus used in this study were modeled after Devan et al. (2002). Additional details pertaining to available distal cues as well as the configuration of both room A and room B are reported by Devan et al. (2002). Spatial learning was assessed by performance in the Morris water maze (Morris, 1981), which consisted of two circular reinforced steel tanks. The steel tanks were each located in a different room, and each had their interior surfaces painted white. In Room A, the tank had a wall height of 59 cm, a diameter of 171 cm and was located slightly off-center in the room sitting on top of cinderblocks raising it 20 cm from the floor

Room B measured was located adjacent to room A along its west wall. The steel tank in room B was also positioned on cinder blocks and was slightly smaller than the tank in Room A with a diameter of 166 cm and wall height of 59 cm. The tank was

positioned in approximately the center of the room, slightly towards the east wall. Both rooms contained several distal cues that were visible both during transport of subjects to start positions and from inside the pool. Details regarding the description of distal and added cues in both room A and room B are reported by Devan et al., (2002).

White shower curtains were hung from ceiling to floor in both rooms to hide the salient cue: the door. The curtain in room A was hung diagonally covering the southwest corner of the room allowing an unobstructed view of the sink and towel dispenser. Two curtains were hung in room B obstructing the view of the door, sink and towel dispenser from inside the room and covering the entire south wall.

Water tanks in both rooms were filled with water (temperature $\simeq 23.5 \pm 1.5$ degrees Celsius) to an approximate depth of 32 cm which was clouded with white, non-toxic water-based paint ($\simeq 100\text{mL}$) to conceal a PVC-constructed escape platform. The escape platform was constructed of white PVC piping with a diameter of 13 cm, height of 30 cm and was placed approximately 2 cm below the surface of the water. A camera was in each testing room recessed above the tank. The camera was connected to a VHS recorder as well as a computer located in the same room as the tank. The system relayed video input to a VHS recorder and VP118 tracking system (HVS Image Ltd., Hampton, UK) located in the main laboratory area which measured all indices of spatial learning during each phase of testing.

Procedure

The various testing phases in this study are a follow up to and variation of those used by Devan et al. (2002). Testing took place over 12 days and was divided into three

particular phases: an acquisition phase, a passive placement / latent learning phase and a probe test phase.

Place acquisition phase (room A). Subjects underwent four acquisition swim trials per day for ten days. The areas of the pool were divided into four quadrants, North, South, East, and West; these were not actual compass-based headings. The pool area was further partitioned into three equal concentric Zones (A, B and C). The Zones included; the area defining the center third Zone A, the middle third containing platform locations in the center of the quadrants while forming a ring Zone B and the outer third around the pool wall Zone C. The amount of time spent near the pool wall in Zone C has previously been reported as % Peripheral pool time (Devan et al., 1999)

The escape platform was placed in a set location in the center of the northeast quadrant (Location 1). The top of the platform was submerged 2 cm below the surface of the water. During acquisition trials, the experimenter gently placed the animals inside the tank facing the wall in a starting position. Each of the four start positions (N, S, E, or W; not true compass headings), were identical for all rats and determined randomly via block randomization. For each trial, the animals were individually released in the pool and given 60 seconds to swim in the tank to locate the submerged escape platform. The experimenter lightly guided the subjects by hand if they did not locate the platform within the allotted time. Once located, the subjects were kept on the platform for an interval of 20 seconds. Animals were held by the experimenter for approximately 5 seconds between trials. These testing procedures were repeated each day for a total of 40 trials per animal (four trials per day over the ten days of this testing phase).

Passive placement and latent learning phase (room B). On day 11, the day after the last day of place acquisition, all animals underwent passive placement and latent learning trials. The submerged platform was located in the approximate center of the northwest quadrant (Location 4) opposite from the platform location during the initial ten day acquisition phase. Rats were each given two 60 second passive placements on the platform. Each rat was returned to their holding cage for five minutes in between the two passive placements. This was modified from Devan et al.'s (2002) study because rats were leaving the platform during the extended passive placement. After the second passive placement, rats were removed from the platform and held for about 5 seconds before beginning latent learning trials. For the first trial, all animals were placed in the tank at the south start point and given a total of four trials. Similar to the acquisition phase, all subjects were able to attempt to locate the platform.

Probe test phase (room B). On the day following passive placement and latent learning, the animals were exposed to a single probe test in room B. The platform was removed from the tank for this phase of testing. Animals were placed near the wall in the south start position and allowed to search for the missing platform for 60 seconds. Specific spatial learning indices comparing navigational behavior between either the original place (Location 1) versus the new latent learning place (Location 4) platform locations was assessed during this specific testing phase. Additional general dependent measures such as Escape Latency (time to reach platform in sec), Preference Score (difference score for quadrant preference), Cumulative Distance (total distance of deviation from straight route to goal), Swim Speed (path length/time in sec), Absolute Heading Error (deviation from straight route to goal after moving 20 cm from start), time

spend in Zone B and % Peripheral Pool Time (Zone C) were also measured during all trials of all phases.

Performance Measures and Group Assignments

Two of the measures used to assess spatial learning during place acquisition and latent learning, escape latency and cumulative distance, were used to divide the animals into groups. The groups consisted of Fast or Slow place learners in room A and Good or Poor latent learners in room B. Although cumulative distance may be a better indication of spatial learning (Gallagher, Burwell, & Burchinal, 1993/2015); escape latency is also a good measure as it is well reported in previous studies; therefore, both measures were used to determine groups.

Statistical Analyses

Results for all phases were analyzed using both SPSS as well as Excel statistical software. Excel was used initially to determine descriptive statistics such as the mean and standard error of the means (SEM). SEM was computed by dividing the standard deviation by the number of subjects to determine variance in the sample. Excel was then used to plot the data. The data was further screened for statistical assumptions with regards to homogeneity of variance, normality and sphericity. Due to the nature of the variables in addition to small sample size, it is not surprising that some assumptions were violated. Although equality of variance was not violated in all cases, most of the data was significantly skewed and Mauchley's test of sphericity was violated. As a result of these violations both parametric and non-parametric analysis were computed.

Chapter 3:

Results

During day 2 of the study, tracking data for two male rats were lost due to computer error. Thus, the mean for the other six males on day two was computed for each dependent measure and substituted for the missing data. Additionally, the Greenhouse-Geisser corrected value was reported for all mixed ANOVAs described below to adjust for degrees of freedom as a correction for violated repeated measures assumptions described above.

Groups of fast and slow place learners were assigned by rank ordering and splitting the sexes into equal groups. The average escape latency for each animal over the ten days of place acquisition was used to determine the four fastest and slowest males (fast means 10.9, 11.8, 13.6, and 14.6; slow means 16.5, 16.8, 18.5 and 19.4) as well as the four fastest and slowest females (fast means 10.6, 12.0, 12.2 and 12.2; slow means 13.7, 14.0, 14.9 and 15.1). The same rank order procedure of group assignment was applied using the mean cumulative distance and produced identical fast and slow place learning groups (see left side of Figure 1 below). Groups of good and poor latent learners were also determined by the same rank ordering procedure. Escape latency and cumulative distance were used from the first swim trial of the latent learning phase to determine good vs poor group assignment, as this trial best assesses latent learning since it is independent of prior active swimming in room B (see right side of Figure 1 below).

Group membership between fast and slow place learners as well as good and poor latent learners was compared. Half of the females who were fast learners were good latent learners (rats 1 and 7) while the other fast learners were poor latent learners (rats 5

and 13). Similarly, the slow female place learners also redistributed into good latent learners (rats 3 and 9) and poor latent learners (rats 11 and 15). When considering the male learning groups, three slow place learners were also poor latent learners (rats 2, 10 and 14) while only one slow place learner was a good latent learner (rat 16). Whereas three fast place learners were good latent learners (rats 4, 6 and 8) and only one fast place learner was a poor latent learner (rat 12). The relationship between the two types of learning was further compared using both parametric and nonparametric analysis and neither revealed any significant results (Pearson Correlation, $r = .224$, $p = .403$).

Mixed design ANOVAs with two between (Learners: Fast, Slow; Good, Poor) and one within (trial block) were independently computed for each of the dependent measures acquired during the acquisition phase in room A and latent learning phase in room B.

The analysis for escape latency revealed a significant main effect of Fast / Slow place learners, $F(1, 8) = 28.837$, $p < .005$, partial $\eta^2 = .783$, observed power = .996. Cumulative distance analysis revealed significant main effects of both sex, $F(1, 8) = 5.732$, $p < .05$, partial $\eta^2 = .417$, observed power = .557, and Fast / Slow place learners, $F(1, 8) = 24.059$, $p < .005$, partial $\eta^2 = .750$, observed power = .989. Significant within subjects main effects were also found for trial blocks [escape latency: $GGF(3.379, 27.033) = 50.344$, $p < .005$, partial $\eta^2 = .863$, observed power = 1.00; cumulative distance: $GGF(3.273, 26.182) = 46.520$, $p < .005$, partial $\eta^2 = .853$, observed power = 1.00; swim speed: $GGF(3.235, 25.881) = 5.706$, $p < .005$, partial $\eta^2 = .416$, observed power = .924; heading error: $GGF(3.449, 27.593) = 14.892$, $p < .005$, partial $\eta^2 = .651$, observed power = 1.00; time in zone B: $GGF(4.160, 33.278) = 7.493$, $p < .005$, partial η^2

= .484, observed power = .993; time in zone C: $GGF(3.598, 28.786) = 10.789, p < .005$, partial $\eta^2 = .574$, observed power = 1.00]. Mean escape latencies for Fast / Slow and Good / Poor learners are shown in Figure 2. Groups were assigned per the best performance overall as Fast/Slow and Good/Poor learners as well as the best performance of learners within each sex.

Figure 1. Group Assignment of Fast/Slow Place and Good/Poor Latent Learners

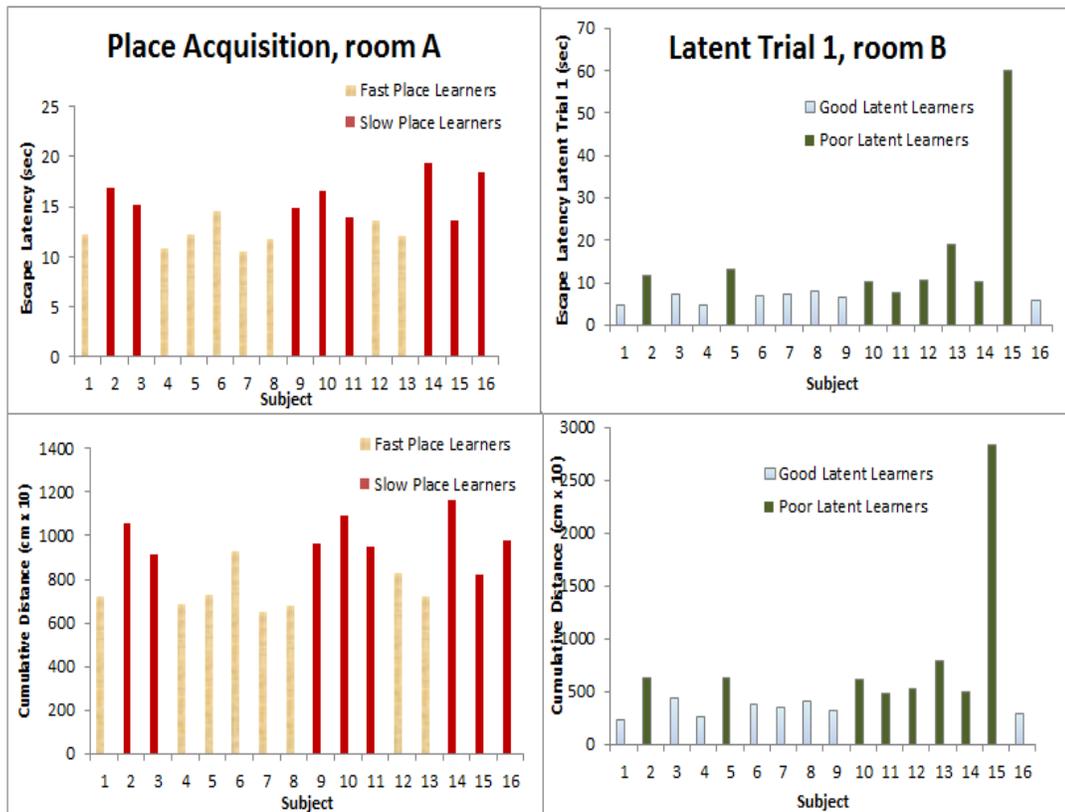


Figure 1: The chart above shows group membership. Fast and Slow place learners in room A were rank ordered based off mean escape latency (sec) and cumulative distance (cm x 10) then assigned into groups (above left). Similarly, Good and Poor latent learners in room B were also rank ordered, using data from only the first latent trial, and assigned into groups (above right).

Figure 2. Learning Group Comparisons of Place Acquisition in room A

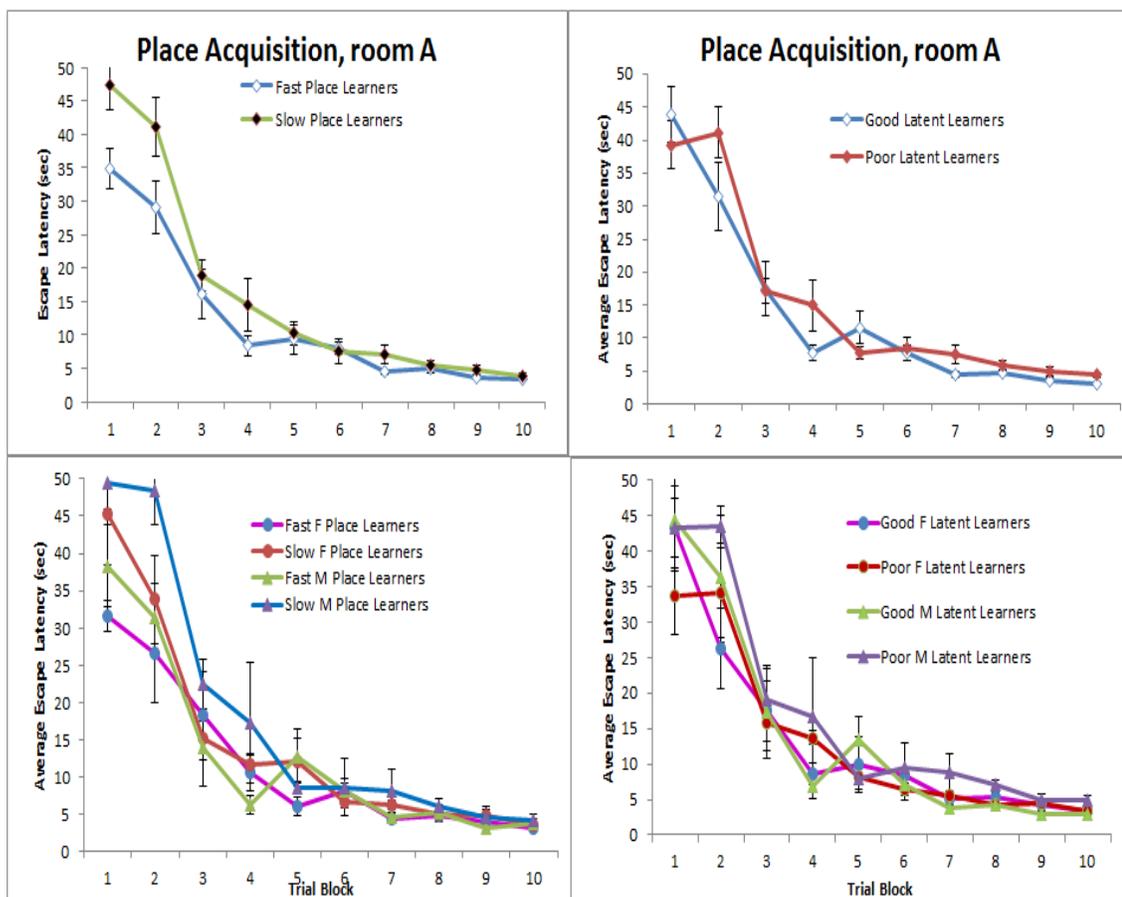


Figure 2: The chart above shows mean escape latencies (+/- SEM) for Fast / Slow place learning group assignment (top left) and Good / Poor latent learning group assignment (top right) across the 10 days of place acquisition. Latencies for Fast / Slow groups (bottom left) as well as Good / Poor groups (bottom right) were further split by sex.

Mixed two-way ANOVAs with one between (sex) and one within (trial block) were independently computed for each of the dependent measures acquired during the acquisition phase in room A as well as the latent learning trials on day 11 in room B. Analysis concerning escape latency revealed a significant within subjects effect for latency according to Greenhouse-Geisser, $F(3.973, 55.619) = 57.274, p < 0.0005$, partial $\eta^2 = .804$, observed power = 1.00, a nonsignificant interaction, $F(3.973, 55.619) = 0.752, p = .560$, partial $\eta^2 = .051$, observed power = .226, and a nonsignificant main effect of sex, $F(1, 14) = 3.211, p = .095$, partial $\eta^2 = .187$, observed power = .386. Cumulative distance analysis also revealed a significant within subjects effect $GGF(4.034, 56.474) = 59.832, p < .005$, partial $\eta^2 = .810$, observed power = 1.00, as well as a main effect of sex that approached significance, $F(1, 13) = 4.286, p = .059$, partial $\eta^2 = .284$, observed power = .483. Male and female performance on dependent measures of escape latency, cumulative distance, swim speed and absolute heading error are represented as group means in regard to place acquisition in room A and can be seen below in Figure 3.

Figure 3. Dependent Measures of Males and Females during Place Acquisition

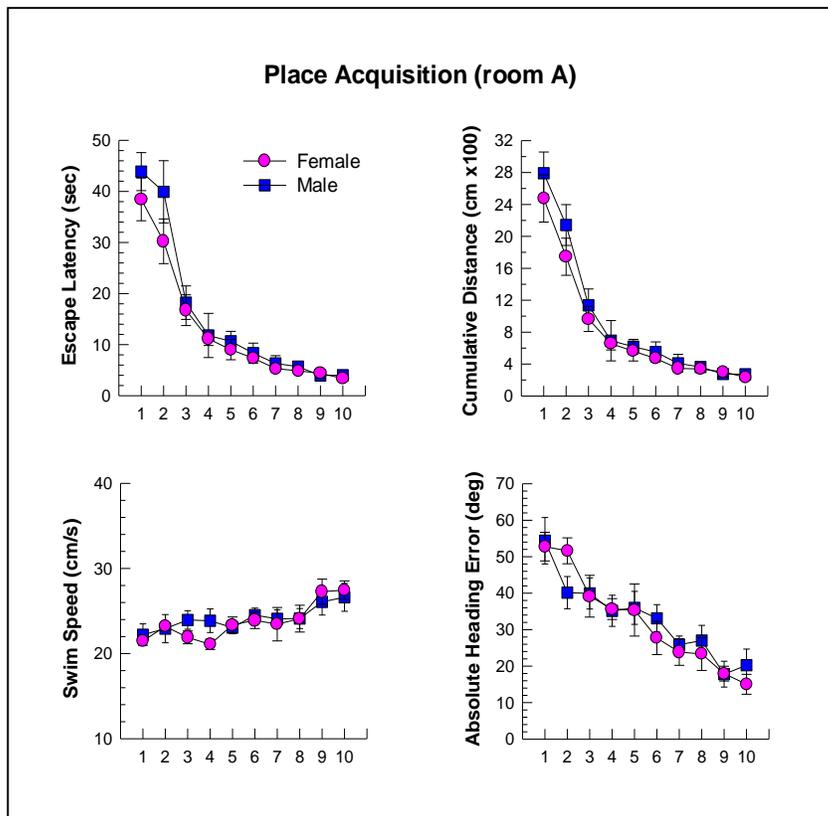


Figure 3: The figure above compares the main dependent measures of place acquisition in room A for each sex. Data are shown as means per group (male, female) of each trial block for every day of acquisition.

Time spent in Zone B was analyzed for the place acquisition phase and showed a significant main effect of sex, $F(1, 14) = 5.199, p < .05$, partial $\eta^2 = .271$, observed power = .565; which revealed a females spent more time in zone B than males (Figure 4). Analysis of time spent in zone B also revealed significant within subjects effect *GGF* ($5.947, 88.260$) = 10.285, $p < .005$, partial $\eta^2 = .424$, observed power = 1.00. Analysis concerning all other dependent measures only revealed significant within subjects effects [heading error: *GGF* ($4.460, 62.434$) = 16.226, $p < .005$, partial $\eta^2 = .537$, observed power = 1.00; swim speed: *GGF* ($3.894, 54.517$) = 5.356, $p < .005$, partial $\eta^2 = .277$, observed power = .958; time spent in zone C: *GGF* ($4.479, 62.709$) = 17.376, $p < .005$, partial $\eta^2 = .554$, observed power = 1.00]. Analysis was also completed with dependent measures from day 11, but no significant results were found. Due to violations of assumptions mentioned above, nonparametric analysis were run for all measures and were found to be in agreement with these reported parametric results.

Figure 4. Time Spent in Zone B by Males and Females during Place Acquisition

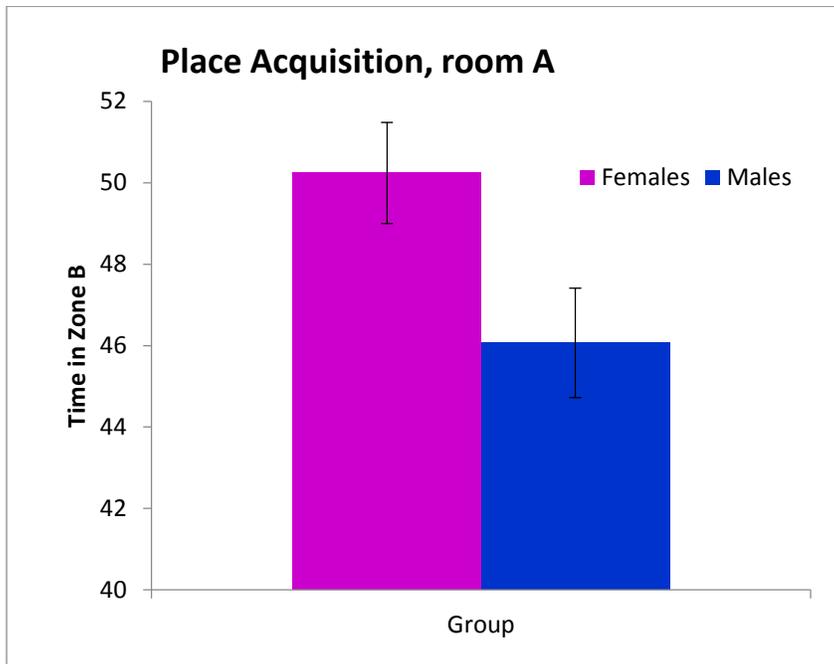


Figure 4: The above graph shows significant sex differences for amount of time spent in Zone B as female rats spent more time than males in zone B on all days except one.

Multiple two-way ANOVAs were computed for phase three data from the 60 sec probe test in room B to assess the relationship between place learning in room A versus latent learning by passive placement in room B. Results from the analysis revealed significant main effects for sex in regard to heading error, $F(1, 14) = 5.560, p < .05$, partial $\eta^2 = .284$, observed power = .593. The overall sex difference in heading error can be seen below in Figure 5.

Although no significant results were revealed in relation to overall quadrant preference, results do show a significant main effect of sex when considering solely the quadrants which previously held platform locations. There was a significant main effect of sex for preference for quadrant 1 (Location 1), $F(1, 14) = 4.604, p = .05$, partial $\eta^2 = .247$, observed power = .515. The main effect of sex with regard to preference of quadrant 4 (Location 4) approached significance, $F(1, 14) = 3.591, p = .079$, partial $\eta^2 = .204$, observed power = .423. Analysis regarding the number of annulus crossings of each previous platform location revealed results similar to quadrant preference. Results revealed a significant main effect of sex with regard to passes through the new location, $F(1, 14) = 7.585, p < .05$, partial $\eta^2 = .351$, observed power = .726; as well as a significant preference for the new platform location $F(1, 14) = 6.302, p < .05$, partial $\eta^2 = .310$, observed power = .647. Sex differences in amount and preference of annulus crossings along with differences in the quadrant time can be seen below in Figure 6.

Figure 5. Heading Error of Males and Females during Probe Test

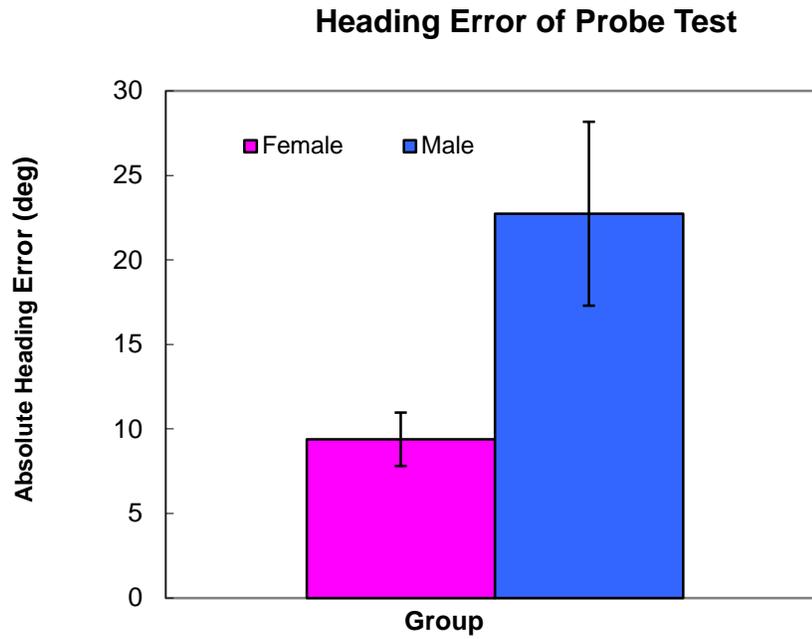


Figure 5: The above graph shows means (\pm SEM) for absolute heading error of males and females on the probe test; significant main effect of sex revealed more precise females.

Figure 6. Quadrant Preference and Annulus Crossing of Males and Females during Full Probe Test

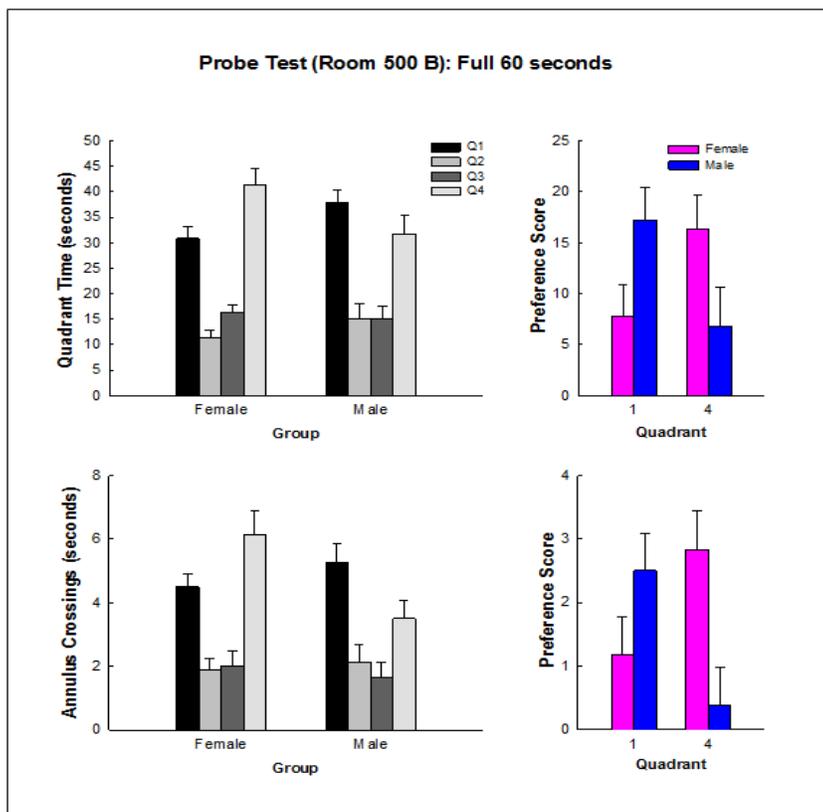


Figure 6: The above graph illustrates results for quadrant preference and annulus crossings by group. Males prefer quadrant 1 with trained location 1 while females prefer quadrant 4 with the new passive placement location 4.

Data from the probe test (day 12) was broken down into 20 second time bins for use with bin analysis. This was done in order to help uncover differences in spatial behavior and was completed using the same method reported by Devan et al. (2003). Mixed two way ANOVAs were independently computed for time bins concerning both the old and new target quadrants. Results were consistent with those reported above in relation to quadrant preference as a significant main effect of sex was found with regard to preference of quadrant 1 $F(1, 14) = 4.627, p < .05$, partial $\eta^2 = .248$, observed power = 1.00; while preference for quadrant 4 remained insignificant. The nature of the sex differences reported above in relation to quadrant preference becomes clearer when viewing the spatial behavior broken down into time bins (Figure 7).

Figure 7. Time Bin Analysis for Probe Test Quadrant Preference of Males and Females

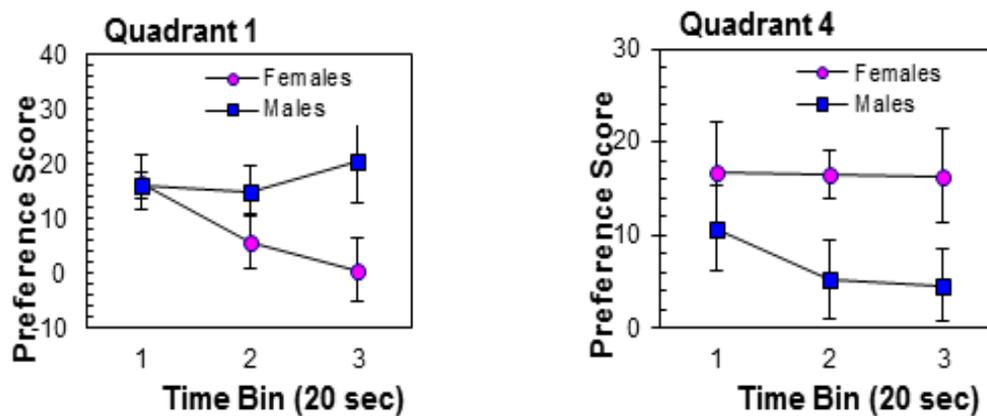


Figure 7: The above graph shows the time bin analysis by quadrant during the probe test for male and female rats, which revealed individual preferences according to sex.

Overall females preferred quadrant 4 while males favored quadrant 1.

Results of within subjects effects were also revealed in relation to quadrant time and preference as well as annulus crossings and annulus preference. Significant interactions between passes through the annulus and sex were revealed in relation to both overall passes through, $GGF(2.346, 32.841) = 3.804, p < .05$, partial $\eta^2 = .214$, observed power = .697; as well as passes through prior platform location 1 vs location 4, $GGF(1.00, 14.00) = 7.438, p < .05$, partial $\eta^2 = .347$, observed power = .718. A significant interaction between sex and preference for quadrant one versus quadrant four was also revealed, $GGF(1.00, 14.00) = 6.126, p < .05$, partial $\eta^2 = .304$, observed power = .634. These differences can be seen in Figure's 5 and 6.

Additional independent mixed ANOVAs were performed with the dependent measures in relation to fast/slow and good/poor learners. Results did not reveal any significance in relation to latent learning trials; however, analysis of learning type groups with probe test data revealed some significant results. Significant within subjects interactions were revealed for several probe test measures in relation to good / poor latent learners along with: passes through target annulus, $GGF(2.220, 17.758) = 8.759, p < .005$, partial $\eta^2 = .523$, observed power = .953; preference for pass through annulus, $GGF(2.100, 55.955) = 6.405, p < .05$, partial $\eta^2 = .445$, observed power = .851; quadrant time $GGF(1.369, 10.948) = 6.296, p < .05$, partial $\eta^2 = .440$, observed power = .703; quadrant preference $GGF(1.367, 10.939) = 5.082, p < .05$, partial $\eta^2 = .388$, observed power = .608. Results regarding annulus and quadrant preference also revealed significant main effects of good / poor latent learners, $F(1, 8) = 31.989, p < .005, \eta^2 = .800$, observed power = .998, and $F(1, 8) = 13.183, p < .05, \eta^2 = .611$, observed power = .887 respectively which can be seen below in Figure 8.

Figure 8. Quadrant Preference and Annulus Crossing of Good/Poor Latent Learners during Full Probe Test

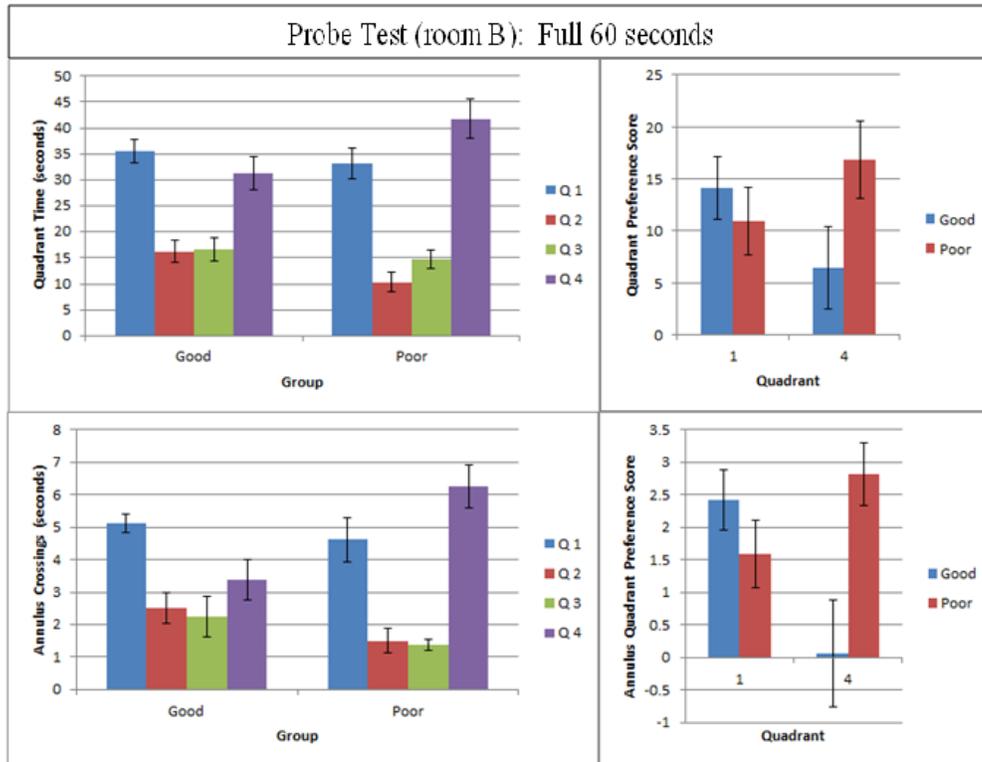


Figure 8: The figure above illustrates results showing significant differences in passes through annulus and preference of quadrant 4 among good vs poor latent learning groups.

Discussion

The results revealed a sex difference in spatial navigation on a latent learning task in the water maze. While most of the literature reports a sex difference in place acquisition (Jonasson, 2005; Keeley et al., 2013), no sex differences relating to the acquisition phase were found in escape latency, swim speed, cumulative distance, heading error or Zone C (% peripheral pool time) in this current study and so the hypothesis that males would outperform females was not supported. Although individual differences were found in respect to place learning (fast and slow) and latent learning (good and poor), the only significant main effects found during place acquisition with regard to fast vs slow place learners were concerning escape latency and cumulative distance. As such these results should be interpreted cautiously because both of these measures were used to create the group assignments; they were highly correlated with speed of learning. Furthermore, acquisition performance on latent learning trials was not significantly influenced by passive placement; however, a clear sex difference emerged during the probe test. Probe test data revealed a significant main effect of sex with regard to heading error, where females had more accurate trajectory towards the passive placement platform location (Location 4, in quadrant 4).

These results gave partial support for the hypothesis that the performance of all rats would be improved by passive placement as improved heading was only observed in female subjects. This outcome was further supported by significant sex differences in quadrant preference as well as preference for annulus crossings as females preferred the new platform location in quadrant four, whereas males preferred the old location used during place acquisition training in quadrant one.

These results suggest that females were more likely to use response independent information gained during passive placement's to show a preference for the new passive placement location. This outcome could be in part due to sex differences previously reported in cue use and behavioral strategies applied during spatial navigation (Blokland et al., 2006; Sava & Markus, 2005). Some studies suggest performance is based on individual strategy selection and presence of cues. One explanation for males and females using different cues when in room B, could be linked with the finding that female rats interact more with novel objects (Sutcliffe Marshall & Neill, 2006). If the new location of some distal cues in room B were treated as novel objects by the female rats in this current study, then they could be more receptive to those new cues and latent learning by passive placement on the goal platform.

One possible explanation for females outperforming males during probe test of the current study could be due to working memory. The sex difference found is consistent with previous research regarding working memory that also found that female rats performed better on an object location memory task (Saucier et al., 2008). Increased working memory of object location would aid performance during the probe test and could enable females to be more sensitive to environment changes such as changed cues. Conversely, males may not notice the subtle differences in cues as they have previously been reported to rely more on geometrical features and not as much on specific characteristics of landmarks when spatially navigating (Chamizo et al., 2014; Chamizo et al., 2016). This difference in cue usage has been linked with differences in strategy selection which is observable as increased preference for the new location in female but not male rats. These results were consistent with previous studies that also reported that

female rats demonstrated a preference for cue/directional responding when swimming to a new place, while the males preferred using geometric cues for place responding to the old place (Blokland et al 2006; Chamizo et al. 2015; Keeley et al., 2013). Although measures were taken in the current experiment to reduce the number of salient cues, for example: covering the view of the door, the possibility still exists that the pool wall was acting as a prominent, salient feature that influenced strategy selection and navigational responding.

Hamilton et al. (2008) investigated the relationship between cue use and types of spatial responding in male rats and reported that until the water level in the water maze pool was filled to remove the view of the pool wall, the animals preferred the old platform location relative to the pool wall over the new location relative to the room. Devan et al. (2002) also found support for male rats using the relationship between distal cues along with a salient cue to influence directional navigation. The results from the present study are consistent with Hamilton et al. (2008) and Devan et al. (2002) in that the male rats preferred responding to the place they had been previously trained to go to during place acquisition relative to the location of the pool wall in the new room. These previously reported relationships along with results from the present study suggest that males and females are paying attention to different cues during passive placement which are then influencing navigational behavior.

There is a possible explanation for this sex difference in navigational behavior, as multiple studies have evidenced superior working memory in female rats (Saucier et al., 2008; Sutcliffe et al., 2006). The increased working memory could help females start keeping track of differences in landmarks and cues while being carried to, and then

placed on the platform during the passive placement and latent learning trials. This could allow females extra time to remember more novel differences in the environment and thus prefer responding strategies to the new place they had been trained to escape to in room B as opposed to the male preference of the old place location from room A.

Results reported by Devan et al. (2002) indicated a correlation between latencies during latent learning trials in room B and place acquisition training in room A in male rats; however, those results were not replicated in this present study. Individual correlations were completed for each group of subjects (all subjects, males and females) and although they did not reveal any significant correlations between the variables in this study, there were some differences in performance between good and poor latent learning groups. Poor latent learners were shown to significantly prefer quadrant 4, which conflicted with the prediction that good latent learners would perform better on the probe test. One reason these results conflict with the expected could be due to the plethora of variability surrounding good and poor learning groups. The variability contained within the sample is thought to be due to interactions between individual differences, but there could also be a relationship between good vs poor latent learning and sex that was not observable in the small sample size used in this study. Another possible component to increased variability is the number of passive placements necessary to improve performance. If too few passive placements are given and not all rats engage in latent learning, then variability within the sample would increase.

Females in this current study demonstrated latent learning by preferring the quadrant of the new location of passive placements after two individual 60 second platform placements while males did not show this preference in their behavior. It is

possible that males needed more than two passive placements to improve performance. Although as few as one extended passive placement was previously reported to improve performance in male rats (Devan et al., 2002; Whishaw, 1991), it has also been reported that as many as five to seven passive platform placements were necessary to improve performance (Horne et al., 2012; Jacobs et al., 1989). This current study does not completely align with previous findings concerning number of passive placements as it was found that 2 passive placements were enough to improve performance in females but that it was not enough to produce the same effect in males. A limitation to the current study, the incomplete removal of the salient cue, could have influenced the behavior of some subjects. Although the door was covered by curtains, merely entering in through the doorway with the animals may have acted as a strong enough salient cue to influence behavior for some subjects.

Another explanation for this sex difference seen in male rats preference of quadrant 1 is due to competing brain structures. For example, Devan et al. (1999) propose that if alternative responses are possible, then the hippocampus (cognitive map formation) and striatum (habit formation) may interact in a way that causes behavioral changes. These behavioral changes can often be seen as sex differences. One such behavioral difference is time spent in zone B or zone C of the water maze pool.

A sex difference in time spent in zone B was found to be significant in this study which was unexpected and revealed that females spent significantly more time in zone B compared to males. No differences were found concerning zone C (% Peripheral pool time); which was unexpected because much of the literature reports sex differences in measures of anxiety during the water maze task (Devan et al., 2016; Beiko et al., 2004;

Burke et al., 2013; McFadden et al., 2011). Stress is known to increase anxiety related behavior and is sometimes introduced inadvertently during testing settings. In this current study, all animals were handled throughout the entire experiment by a single researcher, which may have helped to reduce stress during testing.

It is speculated that previous studies that report significant findings related to zone C (% Peripheral pool time) utilize multiple experimenters to handle the rats and may inadvertently introduce other possibilities of stress during testing thereby causing a change in behavior. Devan et al. (2016) suggested that the increased peripheral pool time reported in the study could be due to the strategy response implemented by females during a competitive place probe task; however, the present findings are not in agreement with those findings since time in zone C was not significant for any phase of the current study. Indeed, several other studies have also reported no sex difference in a thigmotactic response (Mendez-Lopez et al., 2009a; 2009b). However, the increased time spent in Zone B may represent a tendency to alter the peripheral response over time that is still guided by the pool wall.

Much of the current literature concerning sex differences as well as the literature reporting on latent learning is not in agreement and does not consistently report the same measurements. Based on evidence provided by previous studies that included estrus cycle information; the present study may have been able to determine additional sex differences had a measure of estrus cycle phase been included. Depending on the phase of the estrus cycle that the female rats were in, the results may have been affected. Future studies should be sure to include female subjects as well as measurements of the estrus cycle when attempting to determine sex differences. The relationship between

brain structure and latent learning in the water maze should also be a focus of future studies. Although there have been reports linking brain structures to latent learning, these occurrences have not been studied in the water maze. Future water maze studies that investigate latent learning should also include measures of brain structure activation in order to assess if the same structures are utilized during water maze completion as have been found in dry mazes (Stouffer, 2010; Gaskin & White, 2010).

In conclusion, results from the present study indicate a sex difference in relation to the quadrant preference during a probe test after passive platform placements. Results also indicate that other findings concerning latent learning are not in agreement as the findings reported vary and do not often include female subjects, especially in the water maze. Differences noted in this study are likely due to interaction effects from sex, working memory and cue use. The specific cues attended to by the rat during passive placements were important as the same cues were used to choose a navigational strategy in latent learning trials as well as the probe test.

Appendix

Appendix A:



IACUC PROTOCOL: 07082014BD-01

To: Bryan Devan, PhD

From: Towson University Institutional Animal Care and Use Committee
Louis DeTolla, VMD, PhD, DACLAM, IACUC Chairperson

Date: July 8th, 2014

RE: **IACUC PROTOCOL # 07082014BD-01**
Cognitive enhancement of learning and memory in rats

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This is to certify that the Institutional Animal Care and Use Committee has reviewed your protocol and granted FULL APPROVAL. The approval date for this protocol is July 8th, 2014.

Your protocol is approved for a period of 3 years; an annual report must be submitted to the IACUC six weeks before each anniversary of the protocol. Please note your protocol will expire July 7th, 2017. If you need to extend the protocol beyond this date, you must submit an Animal Care and Use form at least three months prior to the expiration.

If you have any questions, please do not hesitate to contact the IACUC Coordinator by email (ospr@towson.edu) or by phone (410.704.4488).

Louis J. DeTolla, VMD, PhD, DACLAM
Chairman, IACUC

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Degrees:

Towson University, Towson Maryland
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Bachelors of Science in Chemistry with MB3 minor
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Towson University, Towson Maryland
Bachelors of Science in Psychology, Magna Cum Laude
Graduation Date – May 2007

Frederick Community College, Frederick Maryland
Associate of Arts in General Studies
Graduation Date – May 2002

Research Interests:

Neuroscience, learning, memory, sex differences, stress and anxiety

Awards and Honors:

Member of Golden Key International Honor Society
Member of Towson University's Student Affiliates of the American Chemical Society (SAACS)
Completed International Scholar Laureate Certificate Program

Publications:

Devan, B.D., **Tobin, E.L.**, Dunn, E.N., & Magalis, C. (2016). Sex differences on the competitive place task in the water maze: The influence of peripheral pool time on spatial navigation performance in rats. *Behavioural Processes*, 132, 34-41. doi: 10.1016/j.beproc.2016.09.009.

Presentations:

Towson University Research Expo Poster Presentation
The Relationship Between Complex Post-Formal Thought (PFT) and Attachment Styles.
Elizabeth Tobin, Edyta Chrzanowska, Shelby Hilton, Luke Boardman, Dr. Jan Sinnott. April 20, 2016

Kennedy Krieger Hagopian Grant Poster Presentation
Examining contingency control deficits in children with and without autism. Hagopian, I. P., Toole, L. M., Boelter, E. Jennett, H. K., Lieving, G. A., MacWhorter, K. J., & **Tobin, E. L.** March 2007.

Experience:

- Teaching Assistant, Towson University September 2013 – Present
- Courses: Research Methods in Psychology
- Towson University, Psychology Research Assistant September 2013 – Dec 2014
- Aided in the design and implementation of several experiments in psychology while working in a group of peers along with our faculty mentor, Dr. Jan Sinnott.
- Kennedy Krieger Internship in Research. (6 credits) September – December 2006
- Assisted research with the Hagopian Grant: scheduled participants, scored behavior analysis forms, aided in data collection as well as dissemination.
- Towson University, Chemistry lab assistant.
- Independent use of the H-NMR (proton magnetic resonance) spectrometer to aid in the analyzation and identification of chemical compounds.

Special Skills:

SPSS, R, & SAS knowledge for computing statistics and basic understanding of Tableau
H-NMR Efficiency

Employment:

- Towson University, Towson, Maryland September 2010 – May 2012
Science Center Tutor for Chemistry & Biology
- Room With A View, St. Thomas, Virgin Islands March 2005 – July 2008
Server, hostess
- Mealey's Restaurant, New Market, Maryland. September 2003 – May 2005
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