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Cooperation & Competition Between Navigation Systems in the Rat Brain: The Role of the Hippocampus and Striatum During a Dissociative Maze Task.

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University of Connecticut Honors Thesis

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Abstract

While many tend to think of memory systems in the brain as a single process, in reality several experiments have supported multiple dissociations of different forms of learning, such as spatial learning and response learning. In both humans and rats, the hippocampus has long been shown to be specialized in the storage of spatial and contextual memory whereas the striatum is associated with motor responses and habitual behaviors.

Previous studies have examined how damage to hippocampus or striatum has affected the acquisition of either a spatial or response navigation task. However even in a very familiar environment organisms must continuously switch between place and response strategies depending upon circumstances. The current research investigates how these two brain systems interact under normal conditions to produce navigational behavior. Rats were tested using a task developed by Jacobson and colleagues (2006) in which the two types of navigation could be controlled and studied simultaneously.

Rats were trained to solve a plus maze using both a spatial and a response strategy. A cue (flashing light) was employed to indicate the correct strategy on a given trial. When no light was present, the animals were rewarded for making a 90º right turn (motor response). When the light was on, the animals were rewarded for going to a specific goal location (place strategy). After learning the task, animals had a sham surgery or dorsal striatum or hippocampus damaged. In order to investigate the individual role of each brain system and evaluate whether these brain regions compete or cooperate for control over strategy, we utilized a within-animal comparisons. The configuration of the maze allowed for the comparison of behavior in individual animals before and after specific brain areas were damaged.

Animals with hippocampal lesions showed selective deficits on place trials after surgery and learned the reversal of the motor response more rapidly than striatal lesioned or sham rats. Unlike previous findings regarding maze learning, animals with striatal lesions showed deficits in both place and response trials and had difficulty learning the reversal of motor response. Therefore, the effects of lesions on the ability to switch back and forth between strategies were more complex than previously suggested. This work may reveal important new insight on the integration of hippocampal and striatal learning systems, and facilitate a better understanding of the brain dynamics underlying similar navigational processes in humans.

Introduction

Upon entering a novel environment, organisms navigate using a variety of cues (Morris, 1981). Previous studies (Tropp and Markus, 2001; Gruenbaum et al., 2003) suggested that the way in which environmental cues are utilized change with increasing exposure to that environment. For example, a college student will likely use different environmental cues to locate a classroom on the first day of the semester compared with finding the same classroom several weeks later.

While many tend to think of navigational systems in the brain as a single process, in reality several experiments have supported multiple dissociations of different forms of learning, such as spatial learning and response learning (Packard & McGaugh, 1996; White & McDonald, 2002). The actual experiential mechanisms underlying these navigational changes are complex and ill-defined. Scientists have argued that when learning a navigation task these different systems compete and while one initially uses spatial and contextual cues to navigate the environment, over time there is a shift to a more habitual form of navigation involving repetitive motor responses less dependent on spatial cues (Packard & McGaugh, 1996; Packard, 1999; Canal et al., 2005; Chang & Gold, 2003).

Interestingly, spatial navigation and motor response navigation are governed by two distinct systems in the brain. In both humans and rats, the hippocampus has long been shown to be specialized in the storage of spatial and contextual memory (O'Keefe & Nadel, 1978; Winocur and Olds, 1978; Wan et al., 1994; Jarrard, 1995; Eichenbaum, 1999; Li et al., 1999; Richmond and Colombo, 2002), whereas the striatum is associated with motor responses and habitual behaviors (Packard and Knowlton, 2002; Christie & Dalrymple- Alford, 2004; Yin & Knowlton, 2006; Daberkow et al., 2007; Robertson, 2007; Graybiel, 2008).

Under controlled laboratory conditions, these two navigational systems can produce conflicting output. This has been demonstrated using a task, such as a T-maze (Figure 1), that can be solved by either navigating to a specific place using contextual cues, or navigating to a specific place habitually (Tolman, 1946).

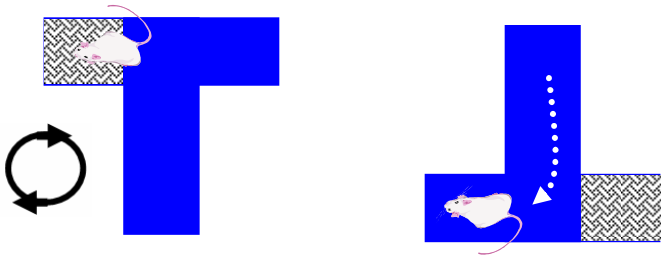

Fig. 1. Using a T-maze, Tolman showed that rats under certain conditions used a place strategy while in under other conditions used a motor response strategy.

Packard and McGaugh (1996) demonstrated the dissociation of the hippocampus and striatum systems using Tolman's (1946) T-maze paradigm. Rats were placed in the south arm and trained them to enter the west arm for a food reward. He then rotated the maze 180º such that the south arm now faced north. The same rats were then placed in the north arm of the maze, and were examined to see if they would continue to enter the west arm or if they would enter the east arm. Rats that entered the west arm of the maze used spatial cues to navigate and were designated as "place learners". Rats that entered the east arm made a habitual response and were designated as "response learners". During probes early in training, rats were shown to predominately exhibit place learning, however this behavior was blocked by hippocampal inactivation. With continued experience, however, rats began to demonstrate response learning. Yet, when the striatum was inactivated, rats tended to continue using the place strategy. Thus, it is suggested that with training there is a shift from using a place to a motor-response strategy (Figure 2).

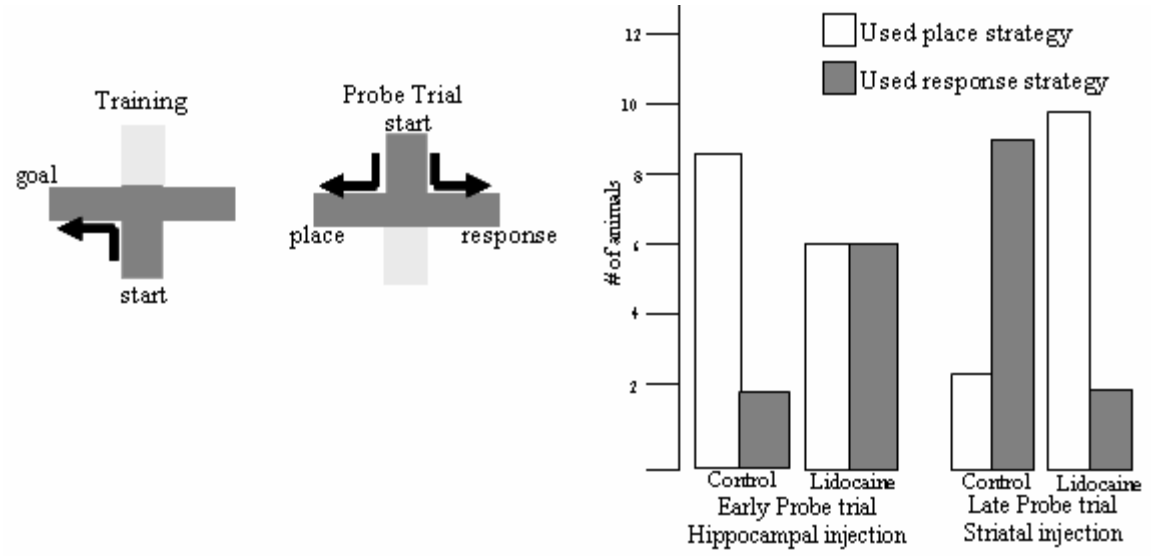

Fig. 2. Adapted from Packard & McGaugh (1996). While rats initially used spatial and contextual cues to navigate the environment, over time there was a shift to a more habitual form of navigation involving repetitive motor responses less dependent on spatial cues

Compton (2004) showed that inactivating either the hippocampal or striatal navigational system with a local anesthetic resulted in the other brain system taking control of the behavior. Using a Greek Cross apparatus in a Morris water maze, rats with an anesthetized hippocampus navigated using the striatum exclusively. Similarly, rats with an inactivated striatum navigated solely using the hippocampus. In addition, however, Compton also showed that hippocampus lesioned animals actually accelerated learning of the response task, and to a smaller effect striatal lesioned animals showed improved performance on the place task. The results suggest competition among systems when selecting a correct navigational strategy.

Similarly results were seen using a 4-arm plus maze (Chang & Gold 2003) that can be solved either using a place strategy (where animals were rewarded for going to a specific goal location) or a response strategy (where animals were rewarded for making the same motor response from the start arm). Hippocampal inactivation impaired acquisition of a place task but facilitated acquisition of a response task.

Currently, studies have only examined how damage to hippocampus or striatum has affected the acquisition of either a spatial or response navigation task. However even in a very familiar environment organisms must continuously switch between place and response strategies depending upon circumstances. The current research investigates how these two brain systems interact under normal conditions to produce navigational behavior. Rats were tested using a plus maze task developed by Jacobson and colleagues (2006) in which the two types of navigation could be controlled and studied simultaneously. After reaching peak performance the animals received either a lesion of the hippocampus, the striatum, or sham procedure and were tested on the same maze. The configuration of the maze allowed for the comparison of behavior in individual animals before and after specific brain areas were damaged.

It was hypothesized that: (1) hippocampal lesioned rats would make more errors post-surgery on a place task in which the goal arm changes every session, as well as when the goal arm is at a fixed location, compared to the amount of errors made on those respective tasks during training. The amount of errors performed by the hippocampal lesioned animals on a motor response task would be unaffected by the surgery. In addition, hippocampal lesioned animals would have an easier time learning a new motor response compared to both the striatal lesioned and sham group. (2) Rats with striatal lesions would make more errors post-surgery on the motor response task. The amount of errors performed by the striatal lesioned animals on a place task in which the place location is switched every session, or when the goal arm is at a fixed location between sessions, would be unaffected by the surgery. Furthermore, striatal lesioned rats would have a harder time learning a new motor response than the other two groups. (3) The sham group would not differ in the amount of errors made in either place or response tasks compared to training, and would have slightly more difficulty in learning a new motor

response task than the hippocampal lesioned animals. The sham group would learn the new response task faster than rats with striatal lesions. (4) There would be no difference in the number of trials made pre and post-surgery on any of the tasks.

Materials and Methods

Subjects:

A total of 16 female (approximately 7-11 month old at the beginning of training) Fisher 344 rats (Harlan, IN) were used in this experiment. Rats were individually housed in transparent, plastic cages (43.5 x 23 x 20.5cm) with a pine wood shaving floor, metal grate cover and unrestricted access to water. Rats were kept to a light/dark cycle of 12:12 hours in a vivarium kept at a constant temperature of 23.8°C with 35% humidity. All animals were weighed daily and extensively handled before any behavioral training. Animals were fed Harlan 2018 18% protein diet pellets to adjust and maintain a weight of about 85% of their *ad libitum* weight. Research protocols were approved by IACUC through the University of Connecticut Office of Research Compliance.

Materials:

A triangular maze, with the longest runway measuring 71cm x 11cm and the remaining two runways measuring 61.5cm x 11cm, resembling arms of the plus maze were used for pre-training. The maze was suspended 10.5cm off the table.

The modified version of the plus maze used in this experiment consisted of a black Plexiglas surface measuring 112.4cm long, 10.8cm wide, and 15.9cm off the table. Four black Plexiglas runways were constructed to form a perimeter around the plus maze, which may be

raised at the end of a trial. The perimeters allowed the rat to continuously run to the next start arm without being handled, thus minimizing stress for the rat (Figure 3).

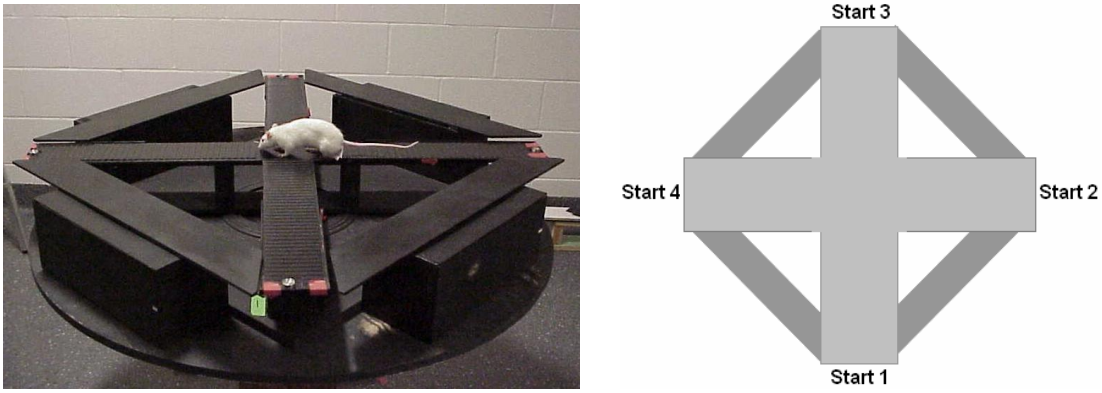

Fig. 3. The plus maze used to control which navigational system is driving an animal's behavior.

Arms were baited with chocolate sprinkles (Univ. of CT Dairy Barn) in small (1cm x 0.5cm) metal dishes. Animals were timed with the use of a digital timer (Fisher Scientific).

Drugs and Surgical Procedures:

Rats were anesthetized with a ketamine cocktail (i.m. ketamine 12.9 mg/ml; acepromazine 0.1 mg/ml; xylazine 1.3 mg/ml). Each rat received an initial dose of 28.67mg/kg ketamine, .2mg/kg acepromazine, and 2.89mg/kg xylazine with additional boosters to maintain the total absence of leg withdrawal reflex (total dosage given did not exceed double the initial dose). A midline incision was made and 2 holes drilled bilaterally above either the dorsal hippocampus (3 mm posterior and 4mm posterior, ± 2.5 mm lateral, 3-3.5 mm ventral from bregma) or the dorsal striatum (0.3 mm anterior and 0.3 mm posterior, ± 4 mm lateral, 5-6 mm ventral from bregma) (Figure 4). Ibotenic acid (MP Biomedicals; Aurora, OH) was dissolved in .1M PBS for a concentration of 10mg/ml. Infusion cannula (Plastics one; Roanoke, VA) securely attached to the stereotaxic device were lowered into the brain for infusion. At each site, 0.5µl was infused using a dual infusion pump (KD Scientific; Holliston, MA) and microsyringe (Hamilton; Reno, NV) at a rate of 0.15µl/min. Seven rats were randomly selected to receive a

lesion in the dorsal hippocampus, seven rats were randomly selected to receive a lesion in the dorsal striatum, and two rats were randomly selected as the sham group.

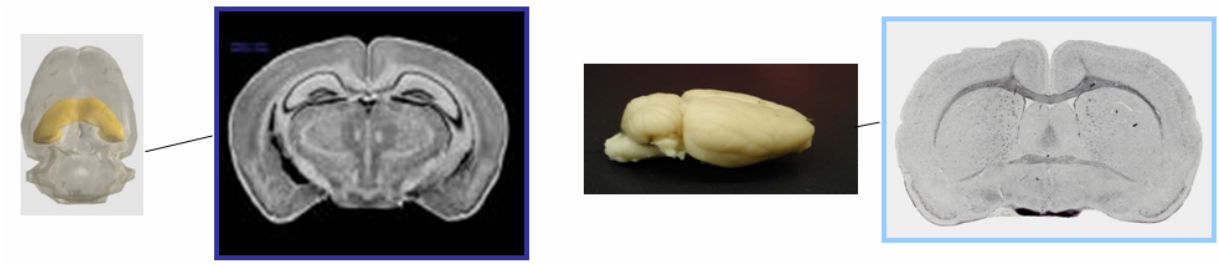

Fig. 4. Coronal cross sections of the dorsal hippocampus (left) and the dorsal striatum (right).

Behavioral Procedure:

Prior to the start of training, rats were handled, weighed, and acclimated to chocolate sprinkles. Food rations were adjusted daily in order to maintain consistent weights of about 85% of their *ad lib* weight. During pre-training, rats were trained to run down a triangle maze for chocolate sprinkle rewards. 2 Rats ran at a time, as each rat was placed facing inward towards the baited end. Distant food dishes were baited with sprinkles covering the base of the dish. Once the rat found the reward and continued down the next arm, food dishes were re-baited with sprinkles. If the rats showed signs of freezing, turning the wrong way or grooming, experimenters would coax the rats towards the correct direction. Latency of running the pre-training ramps was recorded. Rats were pre-trained on one of the 2 triangle mazes until they reached criteria. The criterion was defined as completing 5 trials (including eating the sprinkles) within 5 minutes.

Rats were trained on a modified plus maze one session per day. Sessions lasted up to 20 minutes if the 32 trials were not completed. Rats were initially placed at the end of the start arm behind a clear block. Each trial began as soon as the clear block was lifted and lasted until the rat reached the end of the arm, where it was blocked from re-entering the maze by a black block. The perimeter runway was then lifted for the rat to run to the next start arm. If an error was

made, the arm choice was recorded and the rat retuned to the same start arm to repeat the trial until a correct choice was made. The maze was cleaned with 30% isopropyl alcohol solution between sessions. The training procedure was broken up by Stages that slowly incorporated using both strategies on the same maze. Figure 5 outlines the training and testing procedure used.

Training				**Testing**		
Stage 1	Stage 2	Stage 3		Stage 4	Stage 3	Stage 5
Right turn motor response	Introduce fixed place	Random mix of fixed place and response	**Surgery**	Random mix of place and response New place goal each session	Random mix of fixed place and response Same place goal as during training	Reversal of motor response (left turn) Same place goal as during training

Fig. 5. Overview of training and testing procedures.

During the first stage of the procedure following pre-training, rats learned the response task only. Rats were trained on a motor response task using a plus maze in a dimly lit room, in which a 90º right turn lead to a chocolate sprinkle reward. Rats that choose an incorrect arm were blocked off and returned to the appropriate arm by a runway connecting each arm. When the rats achieved 80% correct responses on 2 consecutive days, they began the second stage.

In Stage 2, the rats were introduced to a context cue: a flashing light. When the light was on, a place strategy (in which the goal arm containing the chocolate sprinkles is always in the same location) is the correct choice. Thus, when the light was on, the place strategy was the correct choice and while the light was off, the response strategy is the correct choice (Figure 6). Initially each session is divided into half/half or quarter/half/quarter chunks of place trials and response trials consisting on one or two strategy switches respectively. Rats again had to achieve 80% correct responses on 2 consecutive days to proceed to the third stage.

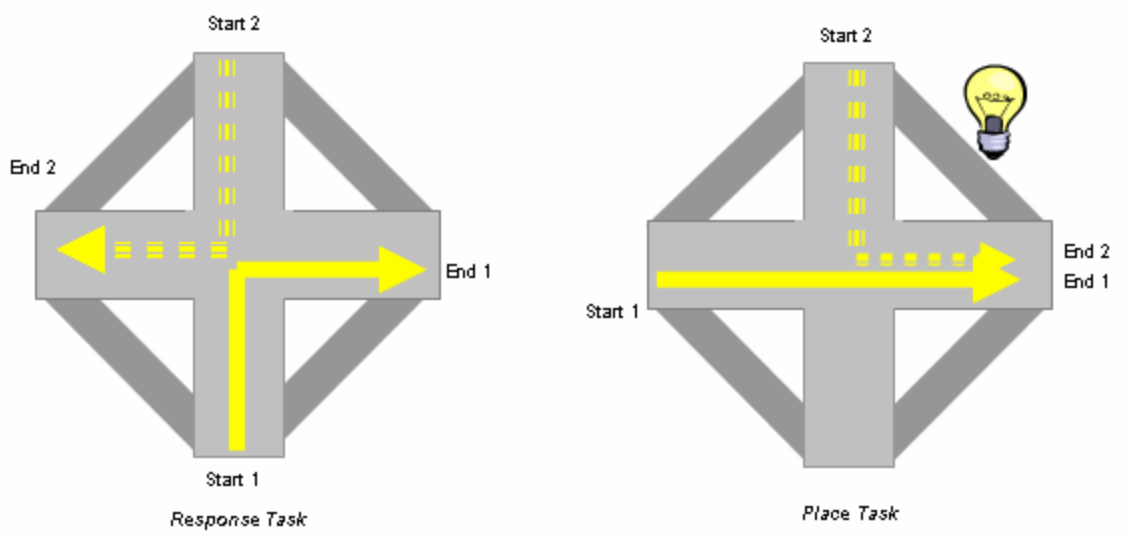

Fig. 6. The modified plus maze configuration. During Stage 3, the reward location was always a 90° turn for a response trial and the reward location was always at the east arm for a place trial.

During the third stage, place and response trials are mixed in a pseudorandom fashion such that there is roughly equal representation of both trial types and start arms. At this stage of training there are no more than 3 consecutive trials of one strategy. Rats continued to navigate the maze in Stage 3 until they reached 80% correct level of performance switching between strategies within a session.

In Stage 4, the place location is switched every session and the animals must remember the location of the goal arm within each session. At the beginning of each session, the rat was placed on the goal arm with food reward and the flashing light on for 20 second to serve as an indicator of the day's goal location. Criterion for this stage was 60% correct on place trials and 80% correct on response trials for three consecutive days.

Each animal then underwent surgery to lesion their caudate nucleus (a structure of the dorsal striatum), hippocampus, or a sham procedure. After a week of recovery, the ability of the rats to learn a new goal location was examined for four days (Stage 4), followed by two days with a fixed goal location as during the initial training (Stage 3). Rats then began Stage 5 for

seven days in which the reward for the response task is now switched to the opposite (now 90° left turn) arm.

Analysis:

The configuration of the maze allows for the comparison of brain activity on correct and erroneous trials. When the rats are placed on an arm that allows only a response strategy, this is considered a "single strategy trial". When either strategy would lead the rat to choose the same goal arm, this is considered a "cooperative strategy trial". When each strategy indicates different goal arms, this is considered a "competitive strategy trial" (Figure 7).

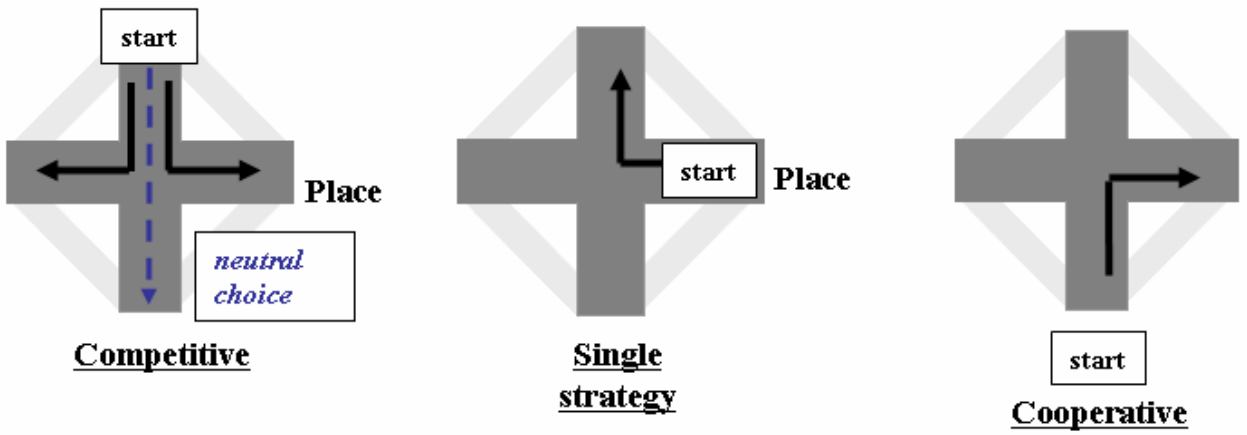

Fig. 7. Trial configuration for error analysis. The configuration of the maze allows for identifying three types of errors.

In order to investigate the individual role of each brain system and evaluate whether these brain regions compete or cooperate for control over strategy, the use of within-animal comparisons was necessary. For within animal comparisons of performance pre and post lesion, a baseline measure was calculated for Stage 4 (where each session there is a new goal location) and Stage 3 (with a fixed goal location that was introduced during training). Baseline was calculated as the average percent of correct trials of all days at criteria performance during training, before surgery.

For statistical comparisons of performance (percent correct) before and after lesions within groups on Stage 3 and Stage 4, a one-tailed paired t-test was used. For statistical

comparisons of the percent of correct trials between groups for Stage 5 post-surgery, single factor analysis of variance test (ANOVA) was used. In order to compare between groups for Stage 5, a Tukey post hoc test was performed. For analysis of total number of trials before and after surgery for Stage 3 and Stage 4, a two-tailed t-test for equality of means (assuming equal variances) was used. For analysis of total number of trials across days after surgery for Stage 3, Stage 4 and Stage 5, single factor analysis of variance test (ANOVA) was used.

Results

For the place trials on Stage 4 post-surgery, the sham group showed no significant change in performance. Rats that had a lesion to their striatum showed a change in the percent of correct place trials compared to baseline on all sessions of testing post surgery (one-tailed paired t-test session 1 $t_{(6)} = 1.96$; $p< 0.05$, session 2 $t_{(6)} = 5.49$; $p< 0.01$ session 3 $t_{(6)} = 2.97$; $p< 0.05$ session 4 $t_{(6)} = 2.26$; $p< 0.05$). Rats that had a lesion to their hippocampus also showed a change in the percent of correct place trials compared to baseline on all sessions of testing post surgery (one-tailed paired t-test session 1 $t_{(6)}= 2.09$; $p< 0.05$, session 2 $t_{(6)}= 3.71$; $p< 0.01$, session 3 $t_{(6)}= 4.24$; $p< 0.01$, session 4 $t_{(6)}= 1.92$; $p= 0.05$). As observed in Figure 1, rats with either hippocampal or striatal lesions were consistently impaired post lesion.

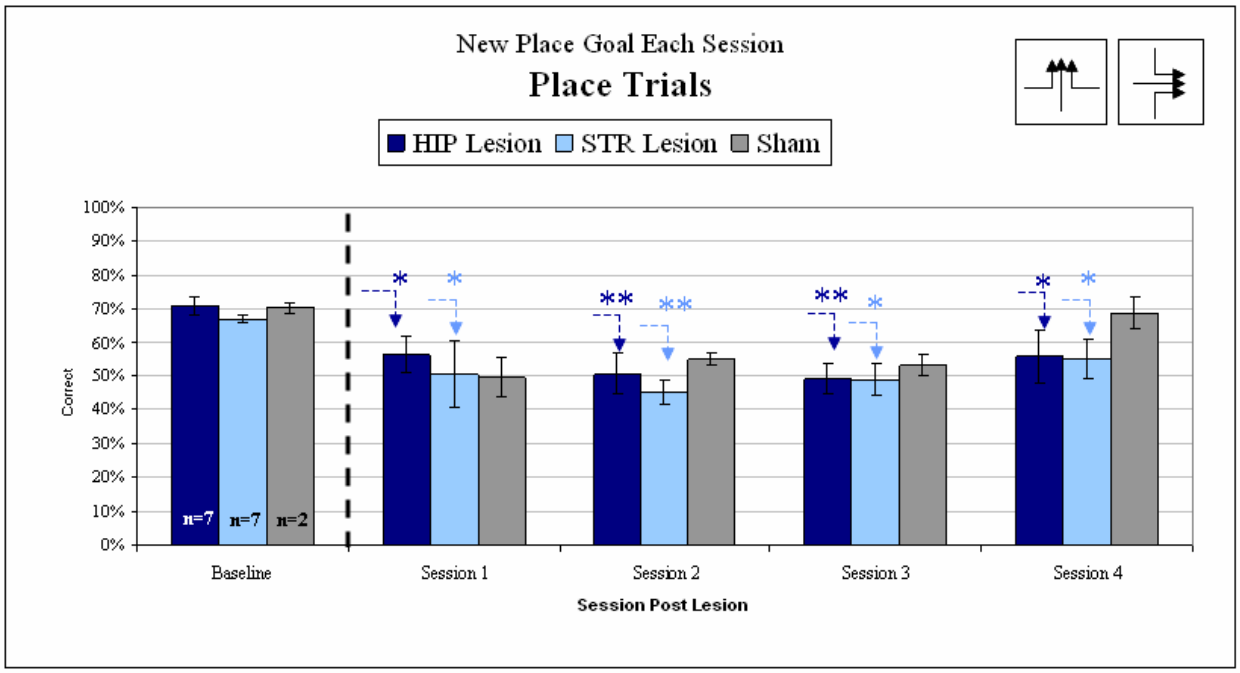

Fig. 1. Percent correct made on *place* trials, before and after surgery in a novel response task. Rats with either hippocampal or striatal lesions were consistently impaired post lesion. All comparisons are within animal to pre surgery baseline. Baseline was defined as the average percent correct at days of criteria during training. * $p \leq 0.05$, ** $p \leq 0.01$.

For the response trials on Stage 4 post-surgery, the sham group showed no significant change in performance. Rats that had a lesion to their hippocampus showed a change in the percent of correct response trials compared to baseline on session 1 only (one-tailed paired t-test session 1 $t_{(6)}= 5.01$; $p< 0.01$). Rats that had a lesion to their striatum showed a change in the percent of correct response trials compared to baseline on all but session 3 of testing post surgery (one-tailed paired t-test session 1 $t_{(6)} = 3.79$; $p< 0.01$, session 2 $t_{(6)} = 2.71$; $p< 0.05$ session 4 $t_{(6)} = 3.81$; $p< 0.01$). As illustrated in Figure 2, rats with striatal lesions were impaired for several days while rats with hippocampal lesions recovered more quickly on response trials for Stage 4.

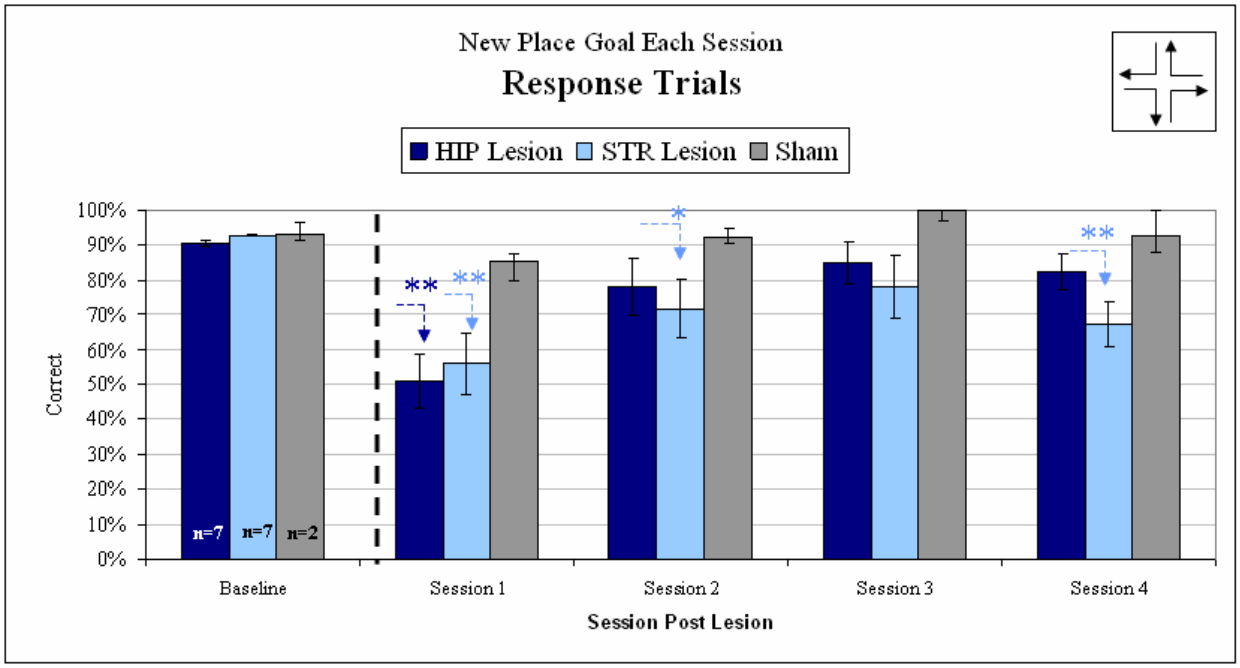

Fig. 2. Percent correct made on *response* trials, before and after surgery in a novel response task. Rats with striatal lesions were impaired for several days while rats with hippocampal lesions recovered more quickly. All comparisons are within animal to pre surgery baseline. Baseline was defined as the average percent correct at days of criteria during training. * $p \leq 0.05$, ** $p \leq 0.01$.

Prior to surgery, there was no significant difference in the number of trials committed on Stage 4 between groups. Following surgery, there was a difference in the number of trials committed on Stage 4 between groups (single factor ANOVA, $F_{(2,63)} = 4.59$ $p < 0.05$). There was no difference in the total number of trials committed by rats before and after surgery within the sham or hippocampal lesion group. However, there was a difference in the total number of trials committed by rats pre and post-surgery within the striatal lesion group (two-tailed t-test, $t_{(47)} = 2.01$ $p < 0.01$). As demonstrated in Figure 3, striatal-lesioned animals ran fewer trials post surgery.

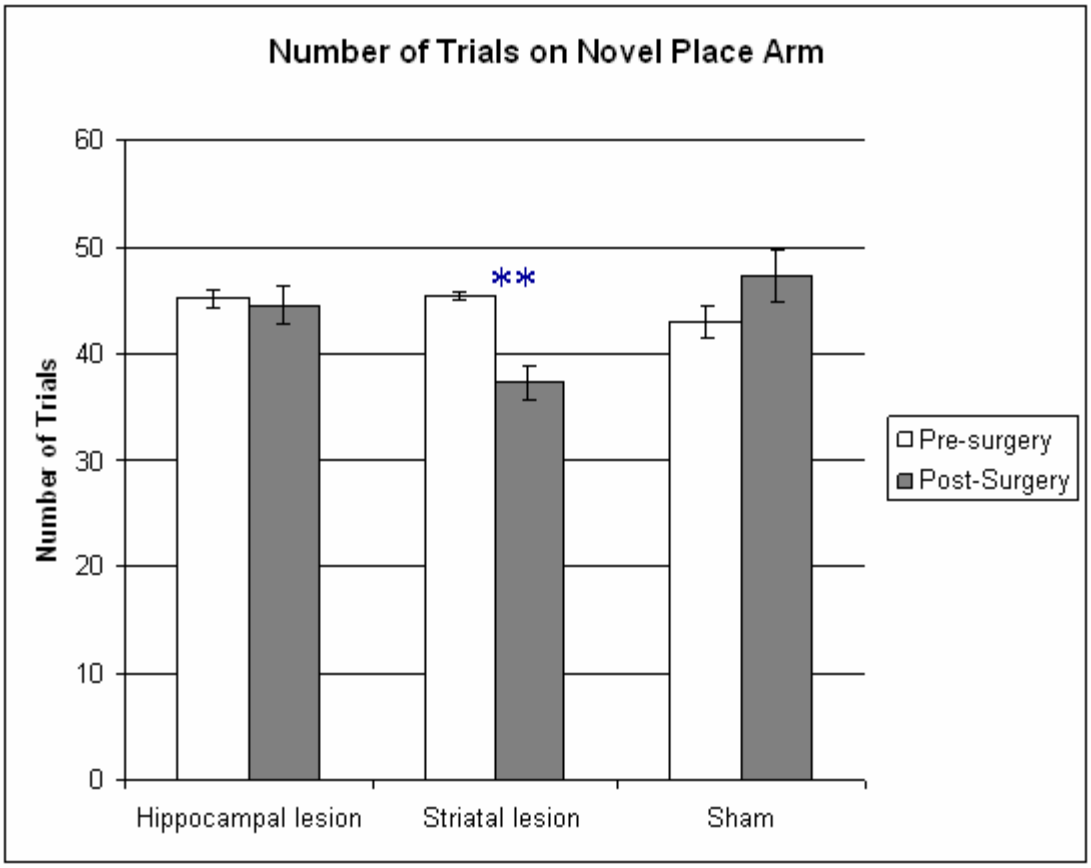

Fig. 3. Number of trials made before surgery and after surgery when given a novel place arm each day. There was a difference between groups. Striatal-lesioned animals ran fewer trials post surgery. * $p \leq 0.05$, ** $p \leq 0.01$.

Latency, or the time to complete each trial, was calculated by dividing the total time in seconds by the total number of trials. There was a difference in latency pre and post-surgery within the striatal lesion group (two-tailed t-test, $t_{(47)} = 2.01$ $p < 0.01$), hippocampal lesion group (two-tailed t-test, $t_{(47)} = 2.01$ $p < 0.01$), and sham group (two-tailed t-test, $t_{(47)} = 2.18$ $p < 0.05$). Prior to surgery, there was no significant difference in the latency for Stage 4 between groups. Following surgery, there was a difference in the time to complete each trial on Stage 4 between groups (single factor ANOVA, $F_{(2,63)} = 3.74$ $p < 0.05$). As demonstrated in Figure 4, striatal lesioned animals took more time to complete each trial post surgery.

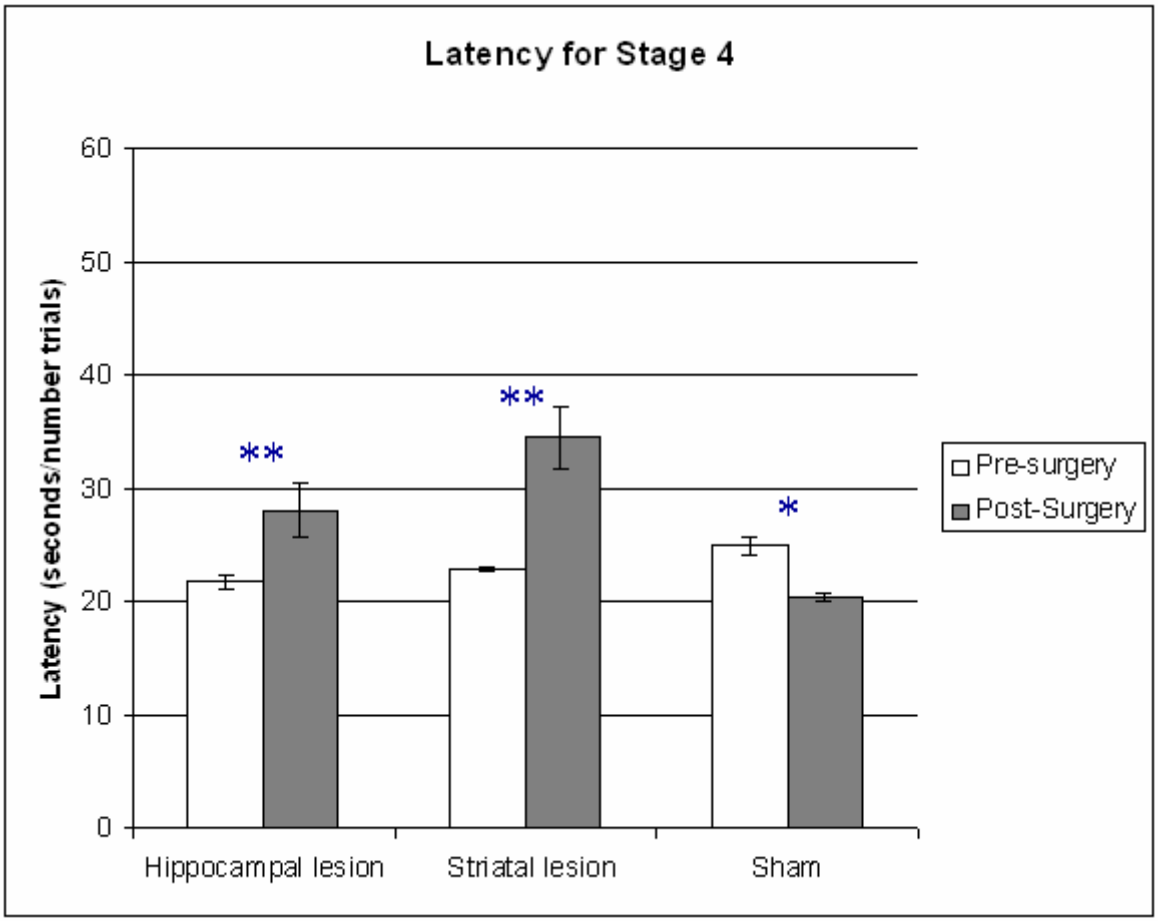

Fig. 4. Time to complete each trial before surgery and after surgery when given a novel place arm each day. There was a difference between groups post-surgery. Striatal lesioned animals took more time to complete each trial post surgery.* $p \leq 0.05$, ** $p \leq 0.01$.

For the place trials on Stage 3 (session 5 and 6) post-surgery, the sham group showed no significant change in performance. Rats that had a lesion to their striatum showed a change in the percent of correct place trials compared to baseline on all sessions of testing post surgery on Stage 3 (one-tailed paired t-test session 5 $t_{(6)} = 3.70$; $p< 0.01$, session 6 $t_{(6)} = 1.88$; $p= 0.05$). Rats that had a lesion to their hippocampus also showed a change in the percent of correct place trials compared to baseline on all sessions of testing post surgery on Stage 3 (one-tailed paired t-test session 5 $t_{(6)}= 3.27$; $p< 0.01$, session 6 $t_{(6)}= 2.11$; $p< 0.05$). As observed in Figure 5, rats with either hippocampal or striatal lesions showed deficits on Stage 3 post-surgery.

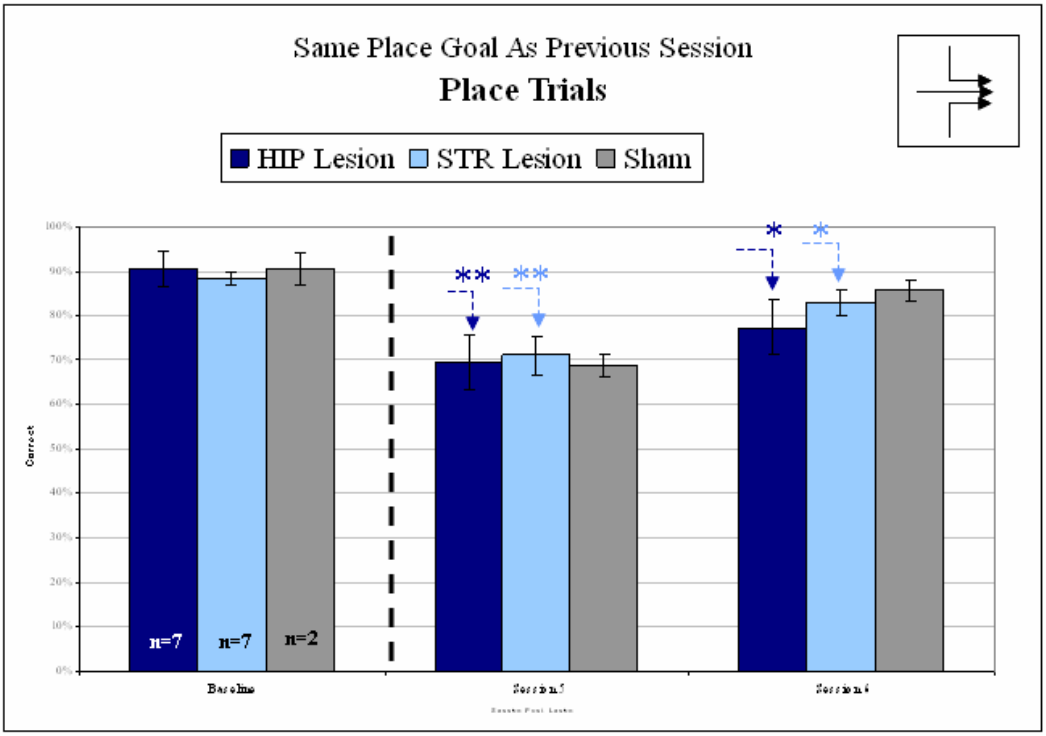

Fig. 5. Percent correct made on *place* trials, before and after surgery when given the same place arm each day. Rats with both lesion groups showed deficits. All comparisons are within animal to pre surgery baseline. Baseline was defined as the average percent correct at days of criteria during training. * $p \leq 0.05$, ** $p \leq 0.01$.

For the response trials on Stage 3 (session 5 and 6) post-surgery, the sham group showed no significant change in performance. Rats that had a lesion to their hippocampus also showed no significant change in performance. Rats that had a lesion to their striatum showed a change in the percent of correct response trials compared to baseline on all sessions of testing post surgery on Stage 3 (one-tailed paired t-test session 5 $t_{(6)} = 3.79$; $p < 0.01$, session 6 $t_{(6)} = 2.71$; $p < 0.05$). As illustrated in Figure 6, rats with striatal lesions remained impaired while rats with hippocampal lesions do not differ from pre lesion baseline.

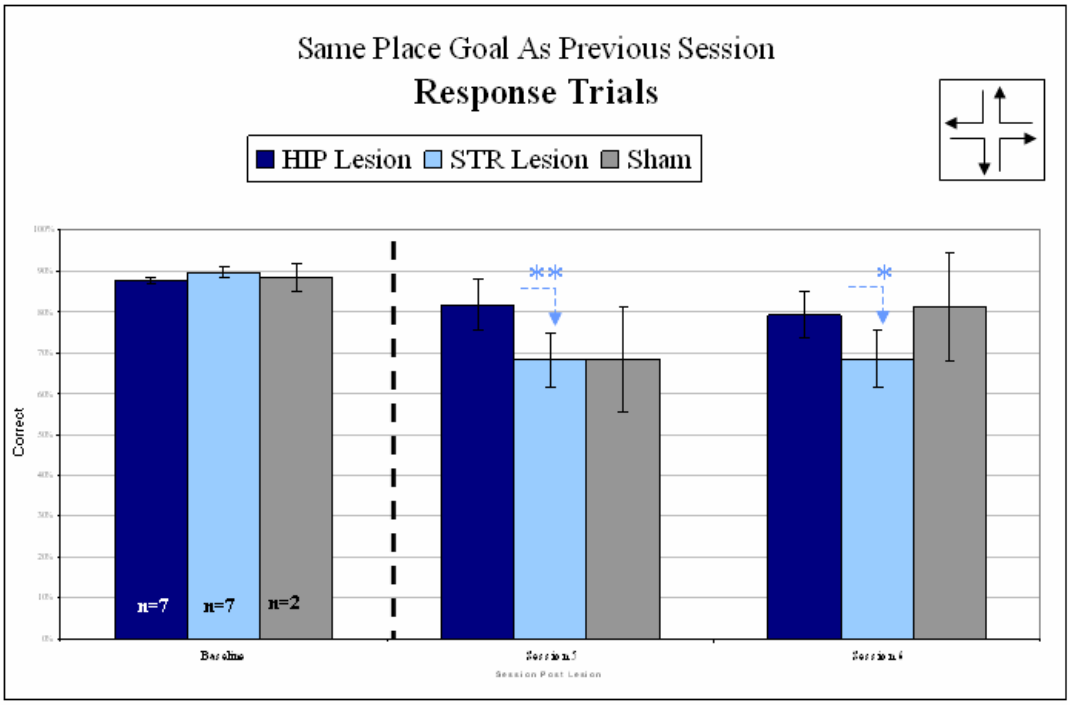

Fig. 6. Percent correct made on *response* trials, before and after surgery when given the same place arm each day. Rats with striatal lesions remained impaired while rats with hippocampal lesions do not differ from pre lesion baseline. All comparisons are within animal to pre surgery baseline. Baseline was defined as the average percent correct at days of criteria during training. * $p \leq 0.05$, ** $p \leq 0.01$.

Both pre and post surgery, there was no significant difference in the number of trials committed on Stage 3 between or within groups. As demonstrated in Figure 7, rats continue to run on the maze on trials post- surgery in which the place arm is in the same location each day.

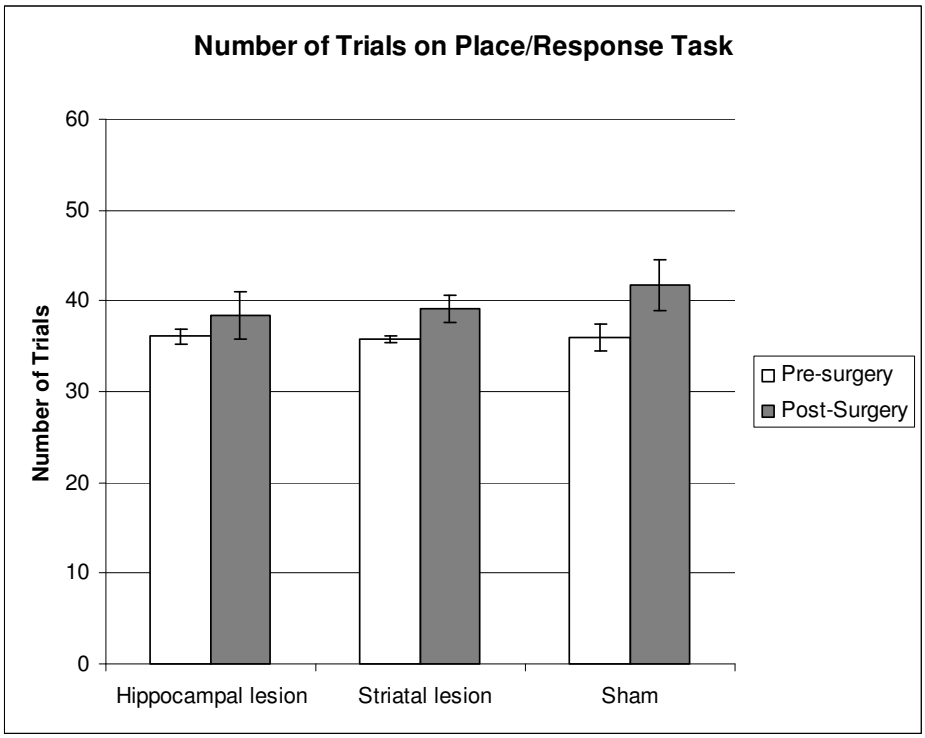

Fig. 7. Number of trials made before surgery and number of trials made after surgery using the same place arm each day. There was no difference between groups.

For the place trials on Stage 5 (sessions 7-13) post-surgery, there was no significant difference between groups in performance. Performance was tested relative to the chance level of choosing the correct arm (33%). As observed in Figure 8, all groups ran significantly better than chance.

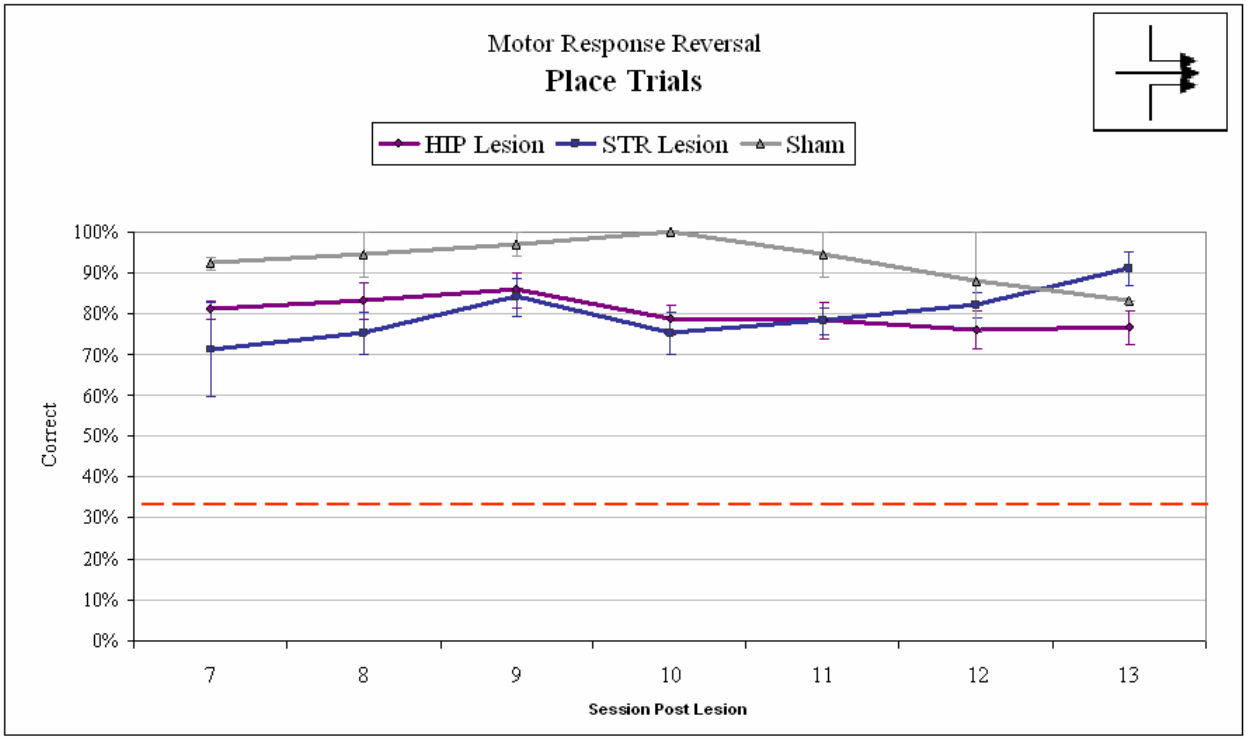

Fig. 8. Percent correct made on *place trials*, before and after surgery in a novel response task. There was no difference between groups and all groups were better than chance.

The response trials on Stage 5 (sessions 7-13) post-surgery was a novel task (new motor response), therefore no baseline performance could be taken for within animal comparison. Thus, performance was tested relative to change level of choosing the correct arm (33%) (Figure 9). Rats with hippocampal lesions performed significantly different from chance on sessions 8-13 (one-tailed student's t-test; session 8 $t_{(6)}= 2.74$; $p< 0.01$, session 9 $t_{(6)}= 3.99$; $p< 0.01$, session 10 $t_{(6)}= 7.43$; $p< 0.01$, session 11 $t_{(5)}= 6.07$; $p< 0.01$, session 12 $t_{(5)}= 4.64$; $p< 0.01$, session 13 $t_{(5)}= 6.81$; $p< 0.01$). The striatal lesioned animals improve significantly better than chance only starting at session 12 (one-tailed student's t-test; session 12 $t_{(6)}= 2.00$; $p< 0.05$, session 13 $t_{(6)}= 2.67$; $p< 0.05$). Thus, hippocampal lesioned animals performed significantly better than chance (33%) by session 8 of learning while striatal lesioned rats stayed near chance levels for the first 5 days of learning the novel task. The sham group showed no significant change from chance.

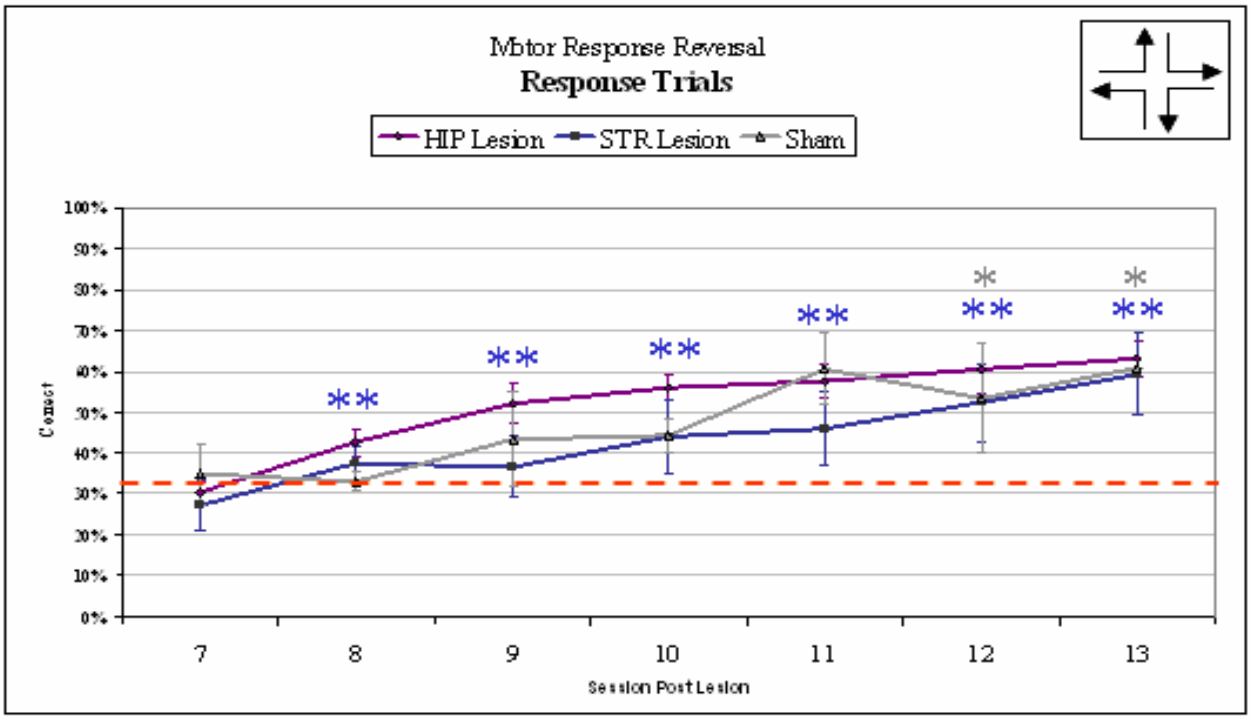

Fig. 9. Percent correct made on *response trials*, before and after surgery in a novel response task. Hippocampal lesioned animals performed significantly better than chance (33%) by session 2 of learning while striatal lesioned rats stayed near chance levels for the first 5 days of learning the novel task. The sham group showed no significant change from chance. * $p \leq 0.05$, ** $p \leq 0.01$

There was a difference in the number of trials committed on the 5th trial only of Stage 5 (session 11 overall post-surgery) between groups. Overall, as demonstrated in Figure 10, rats continue to run on the maze on trials post- surgery on the novel response task.

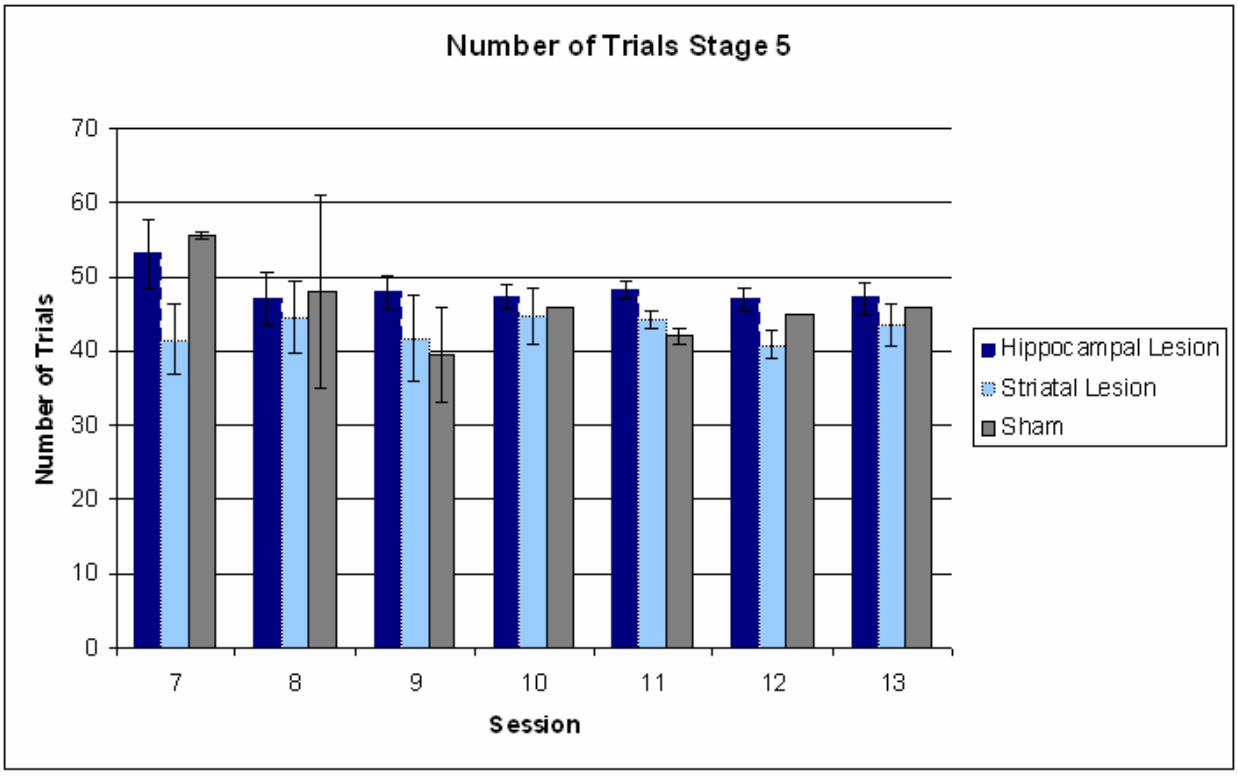

Fig. 10. Number of trials made after surgery on the novel response task. There was a difference in the number of trials committed on the 5th trial only of Stage 5 (session 11 overall post-surgery) between groups.

Discussion

The first 4 days of post surgery testing was the same task as just before the lesion surgery during training. During each session, the place goal was any one of the 4 arms of the plus maze and animals must remember within the session which arm is the place goal for that day (Stage 4). The motor response of a right turn has remained fixed throughout training and testing thus far. It was expected that rats with the hippocampal lesions would make more errors on the place trials during this task when compared to performance during criteria of training, however the amount of errors made on the response trials would be unaffected by the surgery compared to baseline. This hypothesis was supported by the results of the experiment. Rats with their hippocampus lesions made more errors on place trials during the first four days of post-surgery testing. Furthermore, it was expected that during the following two sessions, when the place goal was at a fixed location, that hippocampal lesioned rats would continue to make more errors on place

trials but would not make errors on response trials. This hypothesis was also supported by the results of this experiment as rats with hippocampal lesions continued to show deficits on place trials during the place trials with a fixed place goal, and did not differ from pre-lesion baseline on response trials. Thus, for both the moving place task and the fixed place task, animals with hippocampus lesions made more errors on place trials only. These results are consistent with previous findings that suggest that the hippocampus is specialized in the storage of spatial and contextual memory (O'Keefe & Nadel, 1978; Winocur and Olds, 1978; Wan et al., 1994; Jarrard, 1995; Eichenbaum, 1999; Li et al., 1999; Richmond and Colombo, 2002), and that damage to the hippocampus greatly impairs performance on spatial memory tasks (Meck et al., 1984; Aggleton et al., 1986; Raffaele and Olton, 1988; Schacter et al., 1989; Li 1993; Sziklas et al., 1998; Ward et al., 1999; Wrenn et al., 1999; He et al., 2002; Hasselmo et al., 2002; Sziklas and Petrides, 2002). Furthermore, apart from immediately following surgery (session 1), animals with hippocampal lesions did not show a difference in their performance on response trials. Our findings are important in that it indicates that under conditions of continuous competition between strategies the hippocampus continues to be needed even long after acquisition of the task.

In order to test the acquisition of a novel motor response task, the response was changed from a right turn, to a left turn for the following 7 days. As expected, hippocampal lesioned animals were faster at learning this novel response task than both the striatal lesion and sham group, performing above chance levels by the second day of the task. These results were consistent with previous studies that have suggested facilitated acquisition of a striatum-dependent task in animals with hippocampus inactivation (Chang & Gold, 2003; Compton, 2004).

It was further expected that during the novel place arm task (Stage 4) as well as the fixed place arm task (Stage 3) post-surgery, rats with the striatal lesions would make more errors on the response trials when compared to performance during criteria of training, whereas the amount of errors made on the place trials would be unaffected by the surgery. While the hippocampal lesion group showed selective impairment on place trials, there was no selectivity in the striatal lesioned group. Animals with striatal lesions showed deficits in performance on both the place and response trials during the first 6 sessions following surgery. Previous research has shown that the striatum is associated with motor responses and habitual behaviors (Packard and Knowlton, 2002; Christie & Dalrymple- Alford, 2004; Yin & Knowlton, 2006; Daberkow et al., 2007; Robertson, 2007; Graybiel, 2008), yet our study suggests that the striatum was involved in both spatial and response trials.

In addition, rat with striatal lesions had a harder time learning the new response task, as expected. Whereas hippocampal lesioned animals performed significantly better than chance (33%) by the second day of learning, striatal lesioned rats stayed near chance levels for the first 5 days of learning the novel task. The results are consistent with previous experiments on learning response tasks (Packard and Knowlton, 2002); the striatum is necessary for learning a new response, or response reversal task.

The impairments on the place trials during the first six days following lesions of the striatum may be due to a habituation of the spatial strategy. Past research has been shown that when learning a navigation task the hippocampus and striatum navigation systems compete and with training there is a shift from using a place to a motor-response strategy (Packard & McGaugh, 1996; Packard, 1999; Canal et al., 2005; Chang & Gold, 2003). Although the intent of the novel place arm task (Stage 4) was to avoid the place task from becoming habitual, rats

received months of training in order to hit criteria for surgery. Thus, perhaps even the spatial task may have become habitual.

In addition, the results from the striatal lesioned animals may have been due to the size of the lesion. Each of the striatal lesioned animals experienced lesions extending from the dorsolateral striatum into medial striatum. Previous studies have suggested that this area of the brain is more involved in spatial processing than the dorsolateral stiatum (Devan & White, 1999; Pistell et al., 2009).

Sham rats were expected not to differ in the amount of errors made in either place or response tasks compared to performance during criteria of training. The results show that the sham group did not change their performance on either the place or response trials during the first six sessions, post-surgery when the place goal arm was either moving or fixed. However, it was further expected that that the sham group would have slightly more difficultly in learning a new motor response task than the hippocampal lesioned animals, but would learn the new response task faster than rats with striatal lesions. This hypothesis was not fully supported by the results; the sham rats performed at chance level (33%) during all sessions when learning the new response task. A major limitation to the sham group, which may have caused discrepancies in the results, is the small sample size (n=2). To control for the variability in the results, it would be beneficial to use a larger number of rats in future experiments. The additional subjects would minimize the effects of outliers on the results.

Finally, it was expected that there would be no difference in the number of trials made pre and post-surgery on any of the tasks. This hypothesis was not fully supported by the results; interestingly, there was a difference between groups during the novel place arm task (Stage 4) following surgery. Animals with their striatum lesioned ran fewer trials post-surgery during this

task. The results may be due to the difficulties faced by rats with lesions of the stratum on both place and response trials, which may have increased stress and perhaps led to frustration or lack of motivation for the chocolate sprinkle reward (Kleen et al., 2006). Another possible explanation may be the result of impairments in motor ability due to the convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum (McFarland & Harber, 2000). There was a difference in latency between groups during the novel place arm task following surgery; animals with lesions to their striatum took more time to complete each trial on the plus maze. The results are consistent with previous research that suggests that damage to the striatum corresponds to the loss of motor functioning (Pisa & Schranz, 1988; Fricker et al., 1996; Nixon & Passingham, 1998; Eagle et al., 1999). The fewer number of trials completed post-surgery by the striatal lesioned animals correspond to the greater amount of time these animals took to complete each trial. The deficits in performance seen in this study by striatal lesioned animals suggest that the impairments in motor ability would most likely not account for their difficulty in choosing the correct arm on the place and response trials. However, more trials completed by these rats post-surgery would have helped minimize the effects of outliers and may have allowed for a greater illustration of the effects of the striatal lesions.

The study provides insight into the role of integration of hippocampal and striatal learning systems during an active navigational task. Rats with their hippocampus lesioned showed selective deficits on place trials post lesion and learned the novel motor response more quickly than striatal lesioned or sham rats. The results suggest that the hippocampus continues to be necessary for the ability to solve a maze task using a spatial strategy even after the task is well learned. Moreover, rats with their stratum lesioned showed deficits on both place and response

trials, even after the task was well learned, and had difficulties learning the novel motor response.

It would be interesting to further investigate the performance of rats with lesions to *both* the striatum and the hippocampus to examine if other strategies exist to solve the maze, or in order to further stress the importance of these two brain areas to solve the maze. Furthermore, it would have been beneficial to, following post-surgery testing, examine how damage to hippocampus or striatum would affected the acquisition of a more simple navigational task which would test spatial or response strategies separately. Possible future experiments could also more closely monitor electrophysiological activity of rats on the maze in order to further gain insight into how these structures compete or cooperate with each other. Understanding the integration of hippocampal and striatal navigational systems may help us better comprehend the brain dynamics underlying similar navigational processes in humans.

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