



Extensive training and hippocampus or striatum lesions: Effect on place and response strategies

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ABSTRACT

The hippocampus has been linked to spatial navigation and the striatum to response learning. The current study focuses on how these brain regions continue to interact when an animal is very familiar with the task and the environment and must continuously switch between navigation strategies.

Rats were trained to solve a plus maze using a place or a response strategy on different trials within a testing session. A room cue (illumination) was used to indicate which strategy should be used on a given trial. After extensive training, animals underwent dorsal hippocampus, dorsal lateral striatum or sham lesions. As expected hippocampal lesions predominantly caused impairment on place but not response trials. Striatal lesions increased errors on both place and response trials. Competition between systems was assessed by determining error type. Pre-lesion and sham animals primarily made errors to arms associated with the wrong (alternative) strategy, this was not found after lesions.

The data suggest a qualitative change in the relationship between hippocampal and striatal systems as a task is well learned. During acquisition the two systems work in parallel, competing with each other. After task acquisition, the two systems become more integrated and interdependent. The fact that with extensive training (as something becomes a “habit”), behaviors become dependent upon the dorsal lateral striatum has been previously shown. The current findings indicate that dorsal lateral striatum involvement occurs even when the behavior is spatial and continues to require hippocampal processing.

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1. Introduction

When moving through the environment (e.g. foraging for food, avoiding danger, looking for a mate, returning home) animals must be able to flexibly use multiple navigations strategies. Different brain systems process the same environmental information in multiple parallel ways allowing for a variety of behavioral strategies (see [1,2]). Two exemplar systems are the hippocampus system and the dorsal lateral striatum system. The hippocampus is necessary for processing spatial information. Rats with damage to either the hippocampus or inputs to the hippocampus are impaired in the spatial water maze [3,4], win-shift radial arm maze [5,6], and contextual fear conditioning [7,8]. The dorsal lateral striatum is thought to mediate associations between a stimulus and a reinforced response [9], or between actions and outcomes [10]. Damage to the dorsal striatum causes impairments on egocentric maze learning tasks [11], visual cued discrimination [12], and win-stay radial arm maze [6,13]. When initially learning to navigate through an environment, both rats [14] and humans [15,16] start out using spatial strategy (using landmarks as cues) associated with activity in the hippocampus;

though with increased training the strategy shifts to a motor response (using body turn or movement information) associated with activity in the striatum [17–19].

Two paradigms used to differentiate the strategy used by the hippocampus and striatum are the T-maze probe and the single strategy training task. The T-maze paradigm consists of training animals to find food at one end of a maze shaped like a “T”. Probe trials reveal whether the choice was based on spatial location (e.g. east arm) or motor response (e.g. right turn). Initially, rats use a spatial strategy, but after further training will switch to a motor response; this is true across days [14] or within a single training session [20]. T-mazes that probe animals for strategy use are based on a single trial where the animal has only two arms to choose from. However by giving the animal only two choices, any reduction in one strategy (e.g. place) would necessitate an increase in the choice of the other arm, indicating increased use of the alternative strategy.

The single strategy training paradigm examines how rapidly rats acquire either a place or response task in a plus maze. Inactivating a brain system makes it harder for animals to learn a task based on strategies linked to that system [3,11]. There is also evidence of competition between systems, such that inactivation of one system may facilitate learning of the other strategy [6,13,21–23].

In contrast to the above findings regarding acquisition, less is known regarding the continuous interplay between the hippocampus

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and the striatum. It is plausible that in a familiar environment under natural conditions animals should be able to use multiple strategies depending on the situation. Packard and McGaugh's [14] data suggest a continuous interaction between systems, since inactivation *even after task acquisition* can change behavioral strategy. The present study examined the effect of lesions on a task where over-trained rats continuously switched between a spatial (place) and a motor response strategy [24]. Using a 4 arm plus maze allowed the animal to choose a goal arm that could be associated with a place strategy, a motor response, or an arm associated with neither strategy (Fig. 1a). In addition, animals' ability was examined on a spatial reference, spatial working memory, fixed motor-response and learning a new motor response.

Of current interest was the degree to which 1) the hippocampus (HIP) and striatum (STR) are involved in place and response navigation after a task is well learned, 2) lesions to one system enhance the use of the other intact system, 3) how these lesions affect new learning/reversals.

2. Materials and methods

2.1. Subjects

Eighteen female F344 rats (approximately 7–11 months of age at the beginning of training) (Harlan, IN) were used in this experiment. Rats were singly housed in transparent polyethylene tubs, in a room with a 12:12-h light:dark cycle. All animals were weighed daily and extensively handled before any behavioral training. Given the age of the animals post surgery (11–13 months) and the 85% *ad lib* weight food restriction, presumably they were no longer cycling (see [25]). Furthermore, there are no sex or estrogen differences on this task once it is well learned [24]. All experimental procedures were conducted in accordance with the guidelines of the University of Connecticut Animal Care Committee.

2.2. Apparatus and pre-training

Prior to maze training, rats were acclimated to chocolate sprinkles in their home cage. During pre-training, rats were trained to run a triangular runway for chocolate sprinkle reward until they ran 5 trials in under 5 min. For training on the place/response task, a black Plexiglas plus maze was used (arms 112.4 cm long, 10.8 cm

wide, and raised 15.9 cm), with four black Plexiglas runways forming a perimeter around the maze. Selected perimeter runways were raised at the end of a trial to provide a path which the animals followed to the next start location (see Fig. 1b).

Rats ran one session per day in a dimly lit room. Trials started with a 10 second wait at the start location at the end of an arm, followed by a choice of three possible goal arms. Upon making a choice (4 limbs on an arm), the animal was blocked from returning to the maze and perimeter arms were raised to provide a path to the next start location. If the correct goal was chosen then the animal progressed to the next start arm (new trial); if an error was made, the arm choice was recorded and the rat returned to the same start arm until the correct choice was made. Each session lasted no longer than 20 min or until they ran 32 correct trials, whichever came first. Sessions were balanced to represent all start locations and trial types throughout, such that rats not correctly completing 32 trials still had roughly equal distribution of all trial types.

2.2.1. The response only task

Rats first learned the response task, and were trained to always make a right turn to receive the reward (Fig. 2a). Once the rat completed 80% of the total number of trials correctly for 2 consecutive days, the place strategy was introduced.

2.2.2. Spatial reference memory vs. response task

Response trials occurred in a dimly lit room. Place trials were cued by a flashing light in a fixed location at the corner of the north and west walls about 1.5 m above the floor. Because the overhead lighting in the room was dim, the flashing light was apparent regardless of the animals' location on the maze or orientation. On place trials the flashing light began during the 10 second wait period and continued until the animal made a correct choice. Initially each session incorporated large blocks of place or response trials (Fig. 2b). The size of the block was between 10 and 16 consecutive trials (either place or response) before switching to the other strategy. This meant no more than 2 strategy switches per session. Sessions were counterbalanced such that animals switched from response to place, and from place to response equally. Upon reaching 80% of the total number of correct place and 80% correct of the total number of response trials for 2 consecutive days, place and response trials were interleaved in a pseudorandom fashion. Each session had approximately an equal

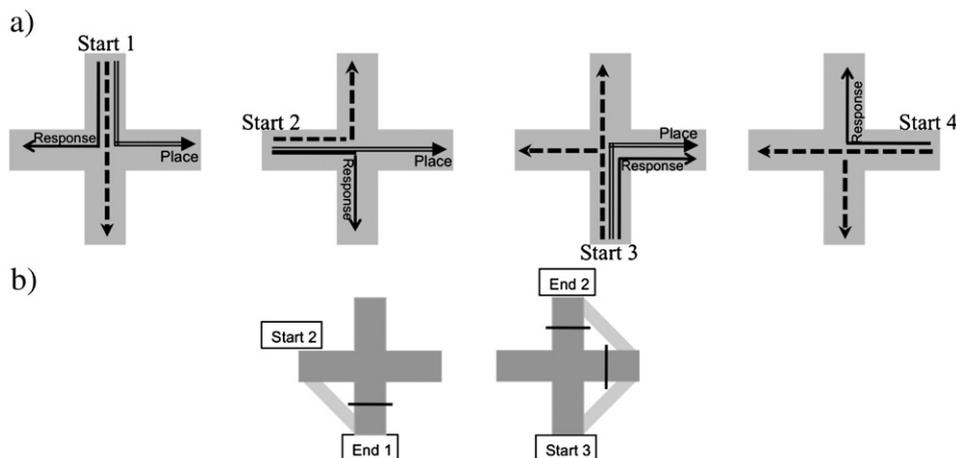
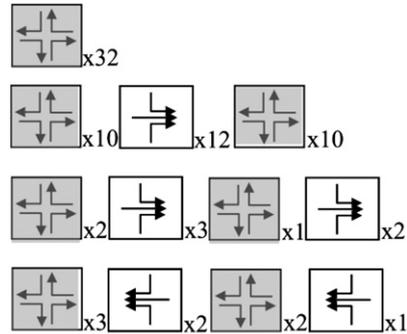


Fig. 1. Trial situation and arm choice. a) Each trial was designated as a response or place trial as indicated by the flashing light cue (not shown). Starting from the north or west arm gave competing choices, since the place (double line) and response (solid line) strategies indicated different goals; starting from the south both strategies indicated the same goal; starting from the west (*i.e.* on the place goal) eliminated the place option, leaving the animal with a single strategy (response). Using the place strategy on a response trial or the response strategy on a place trial was recorded as a wrong strategy error and was differentiated from errors made to the "other" (neither strategy, dashed line) arms. b) Upon reaching the end of the chosen arm, the animal was blocked from re-entering the maze and the perimeter runways leading to the next starting location were raised, providing a path to the next start location.

Training

- a:** Response trials only
Left turn
- b:** Large sets of place and response trials
Place goal remained at east arm
Left turn motor response
- c:** Pseudorandom mixed place and response trials
Place goal remained at east arm
Left turn motor response
- d:** Pseudorandom mixed place and response trials
New place goal each session
Left turn motor response



Surgery

- e:** Sessions 1-4: Pseudorandom mixed trials
New place goal each session
Left turn motor response
- f:** Sessions 5-6: Pseudorandom mixed trials
Place goal remained at east arm
Left turn motor response
- g:** Sessions 7-13: Pseudorandom mixed trials
Place goal remained at east arm
Right turn motor response

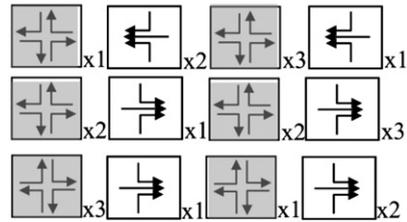


Fig. 2. Arrows within the boxes indicate correct trajectory of the rat from all possible starting locations. Shaded boxes indicate a dim room (motor response strategy) while non-shaded boxes indicate the flashing light condition (place strategy). Each session consisted of a maximum of 32 trials. a: Training started with only response trials, once this was learned animals progressed to both strategies. b: The session was divided into blocks of response and place (spatial reference memory) trials, the least number of consecutive trials before a switch was 10, while the most was 16. After learning to switch 1 or 2 times per session animals progressed to c: Pseudorandom continuous switching between place and response trials. The maximal consecutive trials before a switch was 3. d: Spatial working memory task, introduced a new place goal at the beginning of each session, the response task remained unchanged. Post surgery, animals were tested on e: Spatial working memory (4 sessions), then f: Spatial reference memory (2 sessions) with the place goal in the east arm. g: Combined spatial reference memory and response reversal training (7 sessions), the place location fixed in the east and the motor response a left rather than a right turn.

representation of both trial types and start arms, with no more than 3 successive trials of one strategy (Fig. 2c).

2.2.3. Spatial working memory vs. response task

Once performing at 80% correct on both trial types for 2 consecutive days, a working memory task was introduced. For this task, the place goal location was changed daily, all other cues (e.g. room cues, maze orientation, and flashing light) remained unchanged (Fig. 2d). To indicate the correct goal location for the day, the rat was placed on the goal arm containing food reward for 20 s as the light flashed before the first trial. Once performing at 60% correct on place trials and 80% correct of response trials for 3 consecutive days, rats underwent surgery.

2.3. Surgery

After reaching criterion, 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 28.67 mg/kg ketamine, 0.2 mg/kg acepromazine, and 2.89 mg/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 4 mm posterior, 2.5 mm lateral from bregma) or the dorsal striatum (0.3 mm anterior and 0.3 mm posterior, 4 mm lateral from bregma). Ibotenic acid (MP Biomedicals; Aurora, OH) was dissolved in 0.1 M PBS for a concentration of 10 mg/ml. Infusion cannula (Plastics one; Roanoke, VA) securely attached to the stereotaxic device were lowered into the brain for infusion (3–3.5 mm ventral for dorsal hippocampus, 5–6 mm ventral for dorsal striatum). At each site, 0.5 μ l was infused using a dual infusion pump (KD Scientific; Holliston, MA) and microsyringe (Hamilton; Reno, NV) at a rate of 0.15 μ l/min. For

sham surgeries, holes were drilled either above hippocampus or lateral striatum and infusion cannula were inserted 2 mm into the cortex and removed, however no drug was infused.

2.4. Histology

Following behavioral training, animals were anesthetized with CO₂ and perfused intracardially with saline followed by 3.7% formaldehyde solution. Brains were stored in formaldehyde and then cryoprotected in 30% sucrose for 3 days. Brains were sliced in 50 μ m slices and mounted on a glass microscope slide. Tissue was stained with 0.25% Thionin, coverslipped, cleaned, and examined for the extent of damage.

2.5. Post lesion testing

Post lesion testing began 5–10 days (8.1 ± 1.6 days) after surgery and lasted 13 sessions (one session per day). Testing sessions still consisted of both place and response trials, and performance was assessed on all trial types. Testing sessions 1–4 were the spatial working memory task (the same task as prior to surgery), with the place goal at a new arm each session (Fig. 2e). On sessions 4–6 the place goal remained fixed at the same location as during the initial spatial reference memory training (Fig. 2f). Response trials on sessions 1–6 continued to be the same right turn learned prior to lesions. Sessions 7–13 introduced a reversal of the motor response, rats now had to turn left (rather than right) to receive the response trial reward while the place goal remained fixed (Fig. 2g). One rat (STR lesion) ran only 5 trials on session 1 and therefore repeated the same session the following day; its “session 1” data were pooled across the 2 sessions. Another rat (HIP lesion) did not complete 32 trials on the last 3 sessions of the response reversal task (sessions 11–13), its data were not included in analysis of these sessions.

3. Results

3.1. Training

Training incrementally incorporated both place and response strategies (Fig. 2). The average number training days to reach criterion for surgery was 53 days. The response only task was learned (reached criteria) in 12 ± 0.86 (mean \pm SEM) sessions, introducing the place strategy took an additional 16.7 ± 1.73 sessions. Once animals mastered one or two switches between the two tasks, the spatial reference task (intermixed trials with a fixed goal location) took 4.8 ± 0.65 sessions. After learning that the goal was the east arm, switching to the spatial working memory task (with a daily change of the place goal location) took another 19.3 ± 2.32 sessions. Prior to lesions, there was no difference between groups in the number of sessions to reach criteria on each of these tasks (One-way ANOVA for each stage of training, all $p > 0.1$). After lesions, presumably all groups were equally motivated to complete the task since there was no difference in total number of trials completed per session between groups (mean \pm SEM during spatial working memory test: HIP 44.57 ± 3.15 , STR 35.9 ± 5.28 , Sham 47.25 ± 1.0 . During spatial reference test: HIP 38.36 ± 1.86 , STR 37.80 ± 3.23 , Sham 41.75 ± 1.25 . During response reversal: 48.66 ± 1.32 , STR 41.66 ± 3.30 , 46.0 ± 2.71 ; ANOVA all $p > 0.1$).

3.2. Verification of lesions

The extent of lesions was verified for all animals. Damage was assessed by cell loss and the presence of gliosis. Lesion size was mapped out on stereotaxic coordinates [26] and is depicted in Fig. 3. Hippocampal damage was restricted to the dorsal hippocampus and included areas of CA1–CA3 and the dentate gyrus. Striatum lesions were restricted to the dorsal region and mostly contained within the lateral region.

3.3. Analysis of type of trial

Each session encompassed trials of both strategies, therefore we investigated the effect of lesion type on place and response trials. A within animal design was used comparing the correct performance before and after surgery for each different type of trial: spatial working memory, spatial reference memory, and response trials (Fig. 4). Repeated measures ANOVA (surgery \times lesion-type \times trial type) showed an effect of surgery ($F_{(1,45)} = 72.25$, $p < 0.001$), a surgery by lesion-type interaction ($F_{(2,45)} = 4.5$, $p < 0.05$), and a trial type by lesion-

type interaction ($F_{(2,45)} = 4.5$, $p < 0.05$). Thus while there was an overall deficit in performance after surgery, the type of lesion affected performance on each trial type differently. To examine how lesion-type affected performance, the data were broken down by post surgery session.

Analysis of performance on place trials shows that compared to performance before surgery, after surgery both the HIP lesion and the STR lesion groups were impaired on spatial working memory trials (Fig. 5A). Hippocampal lesioned animals showed a consistent impairment in performance on spatial trials, showing a significant deficit on place trial performance in almost all sessions post surgery (two-tailed paired t -test session 1 $t_7 = 2.5$, $p < 0.05$; session 2 $t_7 = 3.9$, $p < 0.01$; session 3 $t_7 = 4.8$, $p < 0.01$). On sessions 5 and 6 (Fig. 5B), despite the place goal location remaining fixed, the HIP lesion group was still impaired (two-tailed paired t -test session 5 $t_7 = 3.8$, $p < 0.01$; session 6 $t_7 = 2.6$, $p < 0.05$). Striatum lesioned animals were also impaired on both the spatial working memory (two-tailed paired t -test session 2 $t_6 = 5.3$, $p < 0.01$; session 3 $t_6 = 2.9$, $p < 0.05$) (Fig. 5A) and reference memory place trials (two-tailed paired t -test $t_6 = 3.7$, $p < 0.05$) (Fig. 5B).

Analysis of performance on response trials (Fig. 5C) shows the HIP lesion group with an impairment only on session 1 (two-tailed paired t -test $t_7 = 5.6$, $p < 0.01$). The STR lesion group showed a pronounced and consistent decline from pre-lesion performance on almost all sessions post surgery (two-tailed paired t -test session 1 $t_6 = 3.8$, $p < 0.01$; session 2 $t_6 = 2.7$, $p < 0.05$; session 4 $t_6 = 3.8$, $p < 0.01$; session 5 $t_6 = 3.1$, $p < 0.05$; session 6 $t_6 = 3.0$, $p < 0.05$). The sham group showed no impairment relative to their pre-surgery performance on any trial type.

3.4. Analysis of type of error

The animals were very well trained and tended to make very few errors. Table 1 shows the number of each error type before and after lesions. Therefore, in order to examine for changes in pattern of errors independent of differences in overall performance (*i.e.* total errors) the proportion of the different error types was calculated at criterion (pre-surgery) and on the last two testing days (sessions 5 and 6). A Wilcoxon signed-ranks test was used to compare each group's performance pre- and post-surgery (Fig. 6).

Pre-surgery, the overall distribution of errors on place and response trials was not different between groups (Kruskal–Wallis test, all $p > 0.1$) and animals tended to make the same number of errors on place and response trials (Fig. 6). Post surgery, sham animals

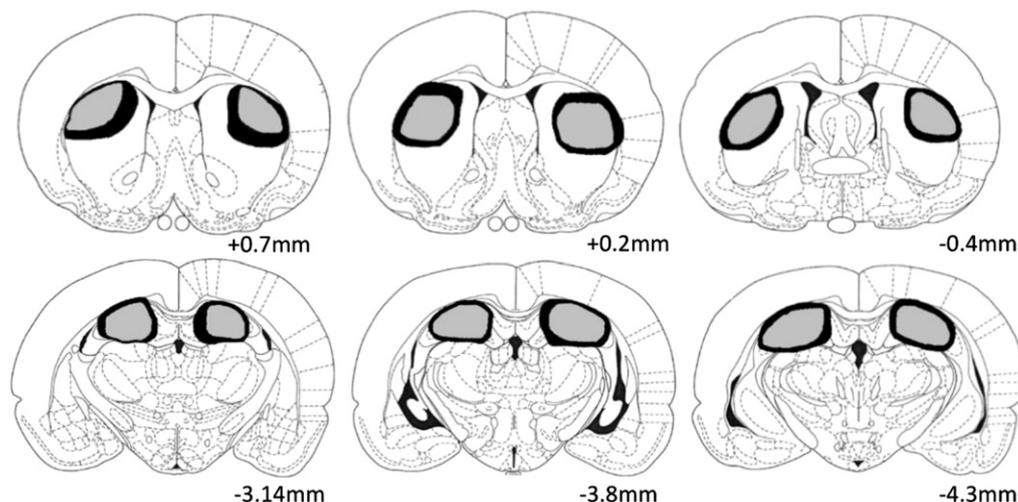


Fig. 3. Size of lesions in both the striatum (top) and hippocampus (bottom). The lesions are superimposed on coronal sections at +0.70, +0.20, and -0.40 from bregma for striatum lesions and -3.14 , -3.80 , and -4.30 from bregma for hippocampus lesions [26]. Smallest lesion is represented in lighter shaded area while the largest lesion is depicted in darker shaded area.

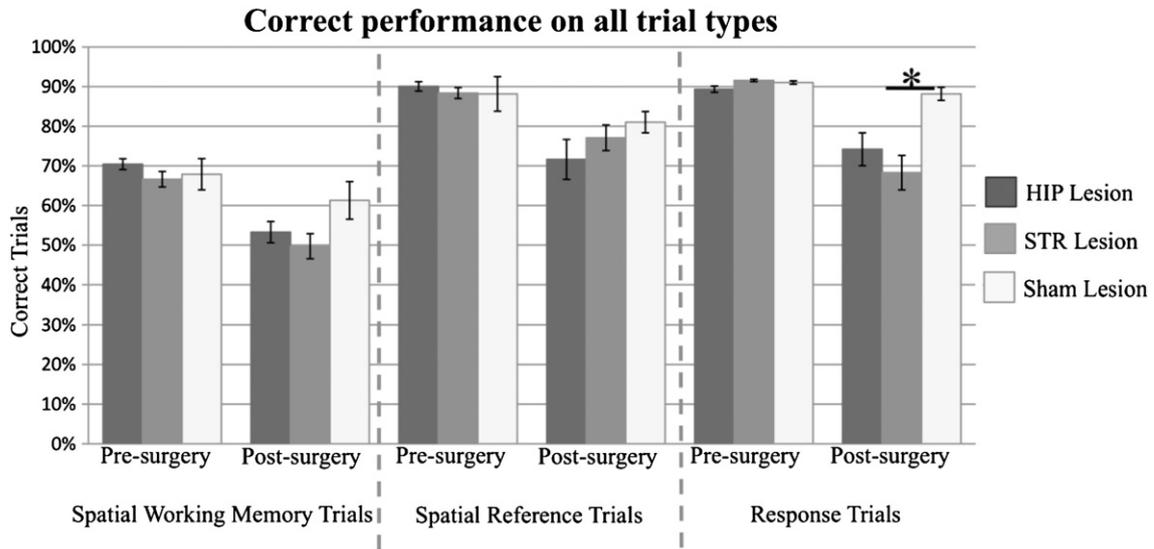


Fig. 4. Comparison of correct performance on different trials before and after lesion. Trials were either from the spatial working memory task (place goal was learned at the beginning of each session) or the spatial reference memory (place goal was held constant on east arm), and all response trials. Mean percentage correct while at criteria performance (pre-surgery), was compared to post-surgery performance (across all testing days). Overall performance decreased post surgery ($p < 0.001$) with interactions with lesion type ($p < 0.05$) and lesion type by trial type ($p < 0.05$). (**post hoc* $p < 0.05$).

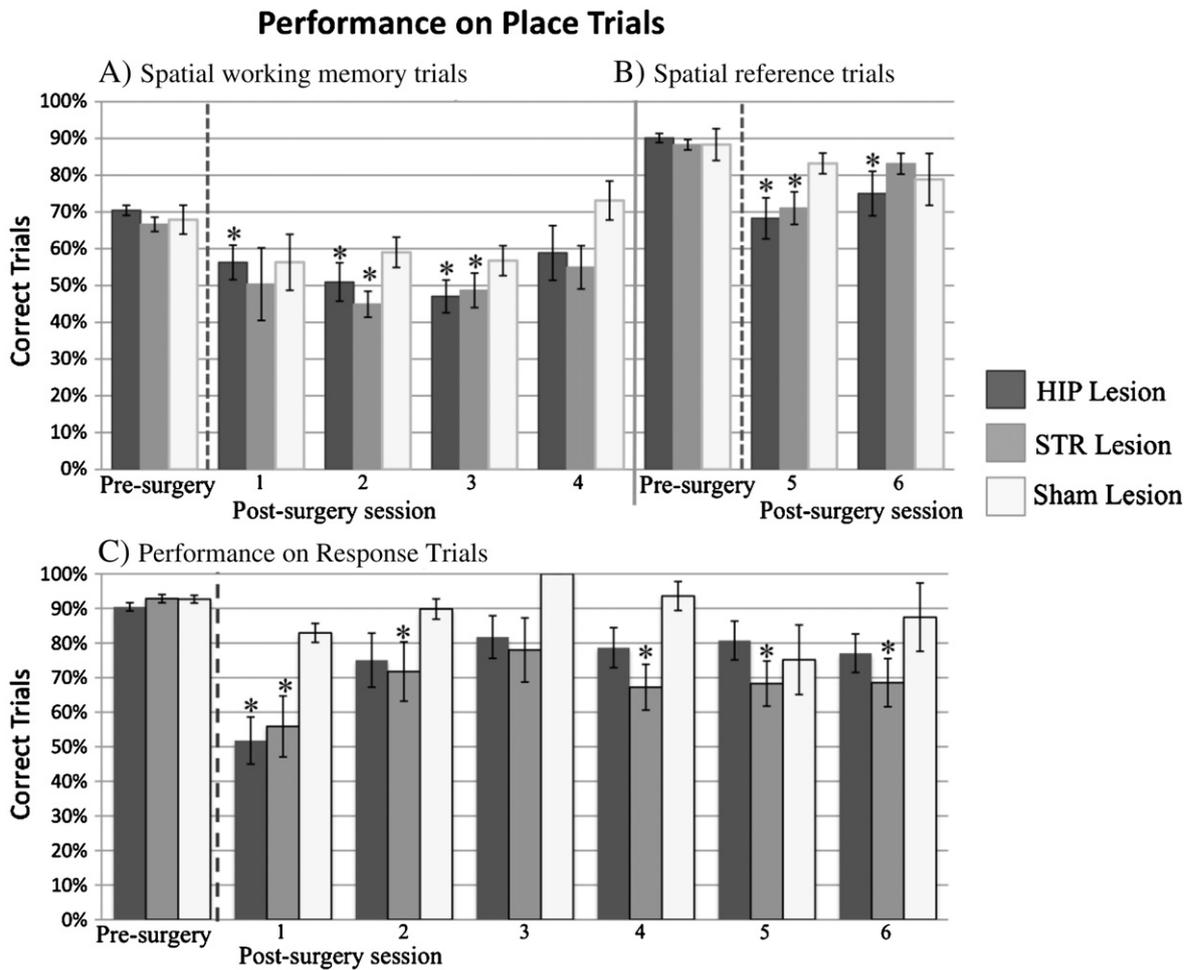


Fig. 5. Comparison of pre-surgery performance to each session post surgery. A) Spatial working memory task (Fig. 2e): Both hippocampus (HIP) and striatum (STR) lesions impaired performance, the Sham lesioned group showed no significant change from pre-surgery performance on any testing session. B) Spatial reference memory task (Fig. 2f): HIP lesioned animals showed continued impairment even after the place goal remained in a constant location, STR lesioned group was impaired on only some sessions. C) All response trials (Fig. 2e+f): HIP lesioned animals showed a transient impairment immediately post surgery, while STR lesioned animals showed continued deficits in response trial performance. (*paired *t*-test to pre-surgery $p < 0.05$).

Table 1

Number of errors (mean \pm SEM) for each trial type pre- and post-surgery. Errors stemming from choosing the wrong strategy are differentiated from choices to the other arms associated with neither strategy.

		Type of error			
		Place trials		Response trials	
		Wrong strategy	Other strategy	Wrong strategy	Other strategy
HIP lesion	Pre	1.44 \pm 0.29	0.31 \pm 0.15	2.06 \pm 0.28	0.25 \pm 0.14
	Post	2.69 \pm 0.78	3.81 \pm 0.68	2.63 \pm 0.63	1.38 \pm 0.30
STR lesion	Pre	1.79 \pm 0.21	0.21 \pm 0.11	2.00 \pm 0.31	0.00 \pm 0.00
	Post	2.21 \pm 0.55	1.57 \pm 0.36	5.00 \pm 1.02	2.07 \pm 0.54
Sham lesion	Pre	2.17 \pm 0.60	0.00 \pm 0.00	1.67 \pm 0.33	0.50 \pm 0.22
	Post	2.00 \pm 0.77	2.17 \pm 0.70	3.17 \pm 1.17	1.00 \pm 0.63

showed a similar pattern of errors (Wilcoxon signed-rank test, $p > 0.1$). Conversely, the HIP and STR lesion groups showed a shift in the relationship between place and response errors post surgery. STR lesions showed a relative decrease in place trial errors while HIP rats showed a relative increase in place trial errors (Wilcoxon signed-rank, both $p < 0.05$).

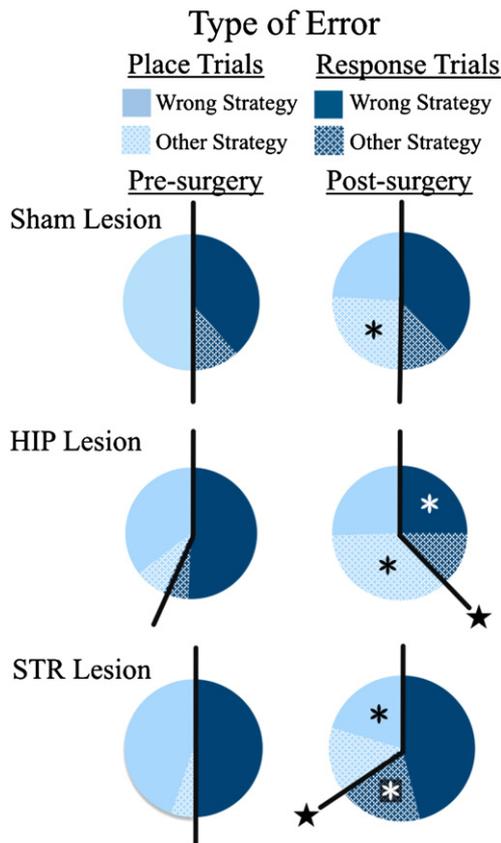


Fig. 6. Analysis of type of error during sessions 5 and 6. Prior to surgery, animals predominantly made errors choosing the wrong strategy on both place and response trials. After surgery, HIP lesions caused an overall reduction of using the place strategy; the overall proportion of errors on place trials shifted, and erroneously choosing place on response trials decreased. Errors on place trials shifted from predominantly wrong strategy to choosing the “other” arm. STR lesions led to reduced expression of the response strategy, shifting the overall proportion of errors, and erroneously choosing response on place trials decreased. Errors choosing the “other” arm on response trials increased. Sham lesions didn’t change the distribution of errors on place or response trials, but did increase the proportion of other strategy choices on place trials. (*_{outside} indicates shift in overall proportions of place/response trial errors, $p < 0.05$). (*_{inside} indicates shifts in proportions of wrong strategy or other strategy choices on place and response trials, $p < 0.05$).

The configuration of the plus maze allowed for multiple start locations differing in their relationship to the goal. Based on the choices available to the animal at the start of each trial, errors were broken down by whether they used the wrong strategy (*i.e.* went to the place goal on a response trial or made a response turn on a place trial) or whether they chose an arm not associated with either strategy (see Fig. 1).

Pre-surgery, most errors indicated the use of the wrong strategy (solid vs. stippled filling in Fig. 6). Within animal comparisons pre and post surgery for each lesion-type showed the sham lesioned group increased the proportion of other strategy errors on place trials (Wilcoxon signed rank test, $p < 0.05$). HIP lesions led to an increase in other strategy errors on place trials and fewer wrong strategy (*i.e.* place) errors on response trials (Wilcoxon signed rank test, both $p < 0.05$), while STR lesions caused an increase in other strategy errors on response trials and fewer wrong strategy (*i.e.* response) errors on place trials (Wilcoxon signed rank test, both $p < 0.05$). Thus the post surgery shift in error patterns was not related to an increased use of the alternative strategy but increases in other (neither) strategy errors, indicative of possible disorientation rather than simply competition between systems.

3.5. Analysis of performance on response reversal task

On sessions 7–13, the place goal remained fixed in the east, but the response goal was reversed (from right to left turn). On place trials, there was a main effect of lesion-type (RMANOVA $F_{(2,10)} = 5.39$, $p < 0.05$). A *post hoc* analysis showed the HIP lesion group was significantly different from the sham animals (Scheffe $p < 0.05$). A within animal comparison to pre-lesion performance showed that both HIP and STR lesioned groups continued to be impaired ($t_7 = 4.0$, $p < 0.01$; $t_6 = 3.8$, $p < 0.01$ respectively), while sham animals were not different ($p > 0.1$) (Fig. 7A). On response trials, there was a main effect of session (RMANOVA $F_{(6,84)} = 17.52$, $p < 0.001$) (Fig. 7B). Since this was a novel task and no pre-lesion performance data was available for a within animal comparison, the rate of learning was evaluated for each group by comparison to chance performance (33%). The HIP lesion group was better than chance on sessions 8–13 (one-tailed Student’s *t*-test session 8 $t_6 = 2.7$, $p < 0.05$; session 9 $t_6 = 3.9$, $p < 0.01$; session 10 $t_6 = 6.3$, $p < 0.01$; session 11 $t_6 = 6.0$, $p < 0.01$; session 12 $t_6 = 4.7$, $p < 0.01$; session 13 $t_6 = 7.8$, $p < 0.01$). Sham animals showed better than chance performance on sessions 11 through 13 (one-tailed Student’s *t*-test session 11 $t_2 = 5.4$, $p < 0.05$; session 12 $t_2 = 2.7$, $p < 0.05$; session 13 $t_2 = 7.1$, $p < 0.01$). STR lesion group performed better than chance only on sessions 12 and 13 (one-tailed Student’s *t*-test session 12 $t_6 = 2.0$, $p < 0.05$; session 13 $t_6 = 2.7$, $p < 0.05$).

4. Discussion

The current study focused on the role of the hippocampus and striatum while well trained animals switched between two highly familiar strategies. Performance was assessed a few days after surgery and all animals were affected by the surgery. The benefit of animals using both a place and response strategy allowed a within animal comparison of the effect of lesions on multiple strategies. Notably the extent of the deficits, recovery to baseline performance, and the types of errors seen, differed among the three groups.

4.1. Effect of hippocampus lesions

Animals that received lesions of the hippocampus made more errors on place trials, with little prolonged effect on response trials. This was seen for both the working and reference memory versions of the task, as well as in the place trials during the response reversal task (Fig. 7). Therefore under conditions of continuous competition between systems, the hippocampus was needed for spatial tasks even

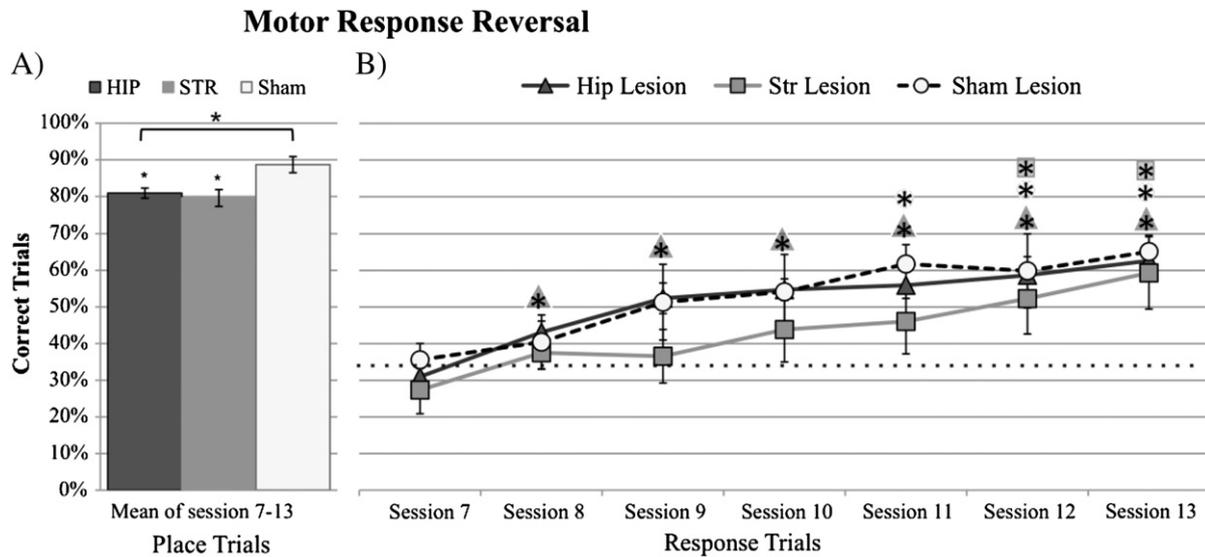


Fig. 7. Performance during response reversal. A) Performance on place trials (mean ± SEM of sessions 7–13). HIP lesioned group is impaired relative to sham animals (*RMANOVA post hoc $p < 0.05$). Both the HIP and STR lesioned group are still impaired relative to pre-lesion performance (* $p < 0.01$). B) Performance on response trials. Since the reversal was a novel task, all comparisons were made to chance performance (33%). Hippocampus lesioned animals started performing better than chance on the second learning day (session 8). Sham animals performed better than chance starting on session 11, while the striatum lesioned animals performed better than chance only on sessions 12 and 13 (* $p < 0.05$).

after acquisition and prolonged training (see [27]). Interestingly the number of hippocampal cells recruited on this maze does not differ if it is a spatial or response trial, however different ensembles of cells are activated when the task is switched [28,29].

Analysis of error pattern during the spatial reference memory task showed that before lesions, errors were predominantly due to the animals choosing the wrong (alternative) strategy on both place and response trials. After hippocampus lesions, as expected, errors on response trials were no longer caused by an incorrect choice of the place strategy. Unexpectedly, errors on place trials were not caused by an incorrect choice of the response strategy; rather there was an increase in the choice of the “other” arm. Notably, post acquisition hippocampal inactivation also seemed to cause random choices rather than choosing the alternative strategy [14]. Thus given multiple goal locations the hippocampal lesioned do not simply revert to the response strategy. Interestingly, the degree of place trial difficulty (i.e. working or spatial reference memory goal) had little impact on the extent of lesion induced performance deficit.

Animals with hippocampal lesions learned the response reversal faster than both the sham and the striatum groups, performing better than chance by the second training session. This is in agreement with previous literature that has shown that animals with hippocampal lesions acquire motor-response tasks more quickly [6,13,21].

4.2. Effect of striatum lesions

While the hippocampal lesioned animals showed selective impairments on place trials, animals with lesions of the striatum showed increased errors on both place and response trials. While the striatal animals were impaired on the spatial trials the deficits were more pronounced on the response trials. The degree of response impairment was larger, it was more consistent across days, and there was a shift to more response than place trial errors.

After striatal lesions, there were fewer wrong strategy (response) errors on place trials, and errors on response trials shifted from predominantly wrong strategy (place) to more errors to the other choice. Therefore while there are impairments on both place and response trial types, when the striatum is damaged, errors stemming from choosing a response strategy decrease.

Striatum lesioned animals also showed slower acquisition of a response reversal relative to both sham and HIP lesioned rats, in

agreement with previous experiments that demonstrate the striatum is necessary for learning a new motor response [9].

While hippocampus lesioned animals showed selective impairment on place trials, in the striatum lesioned group the impairment was less selective including both place and response trials. It is possible that this was due to our dorsal lateral lesions including some damage to medial regions of the striatum, since the medial region is involved in spatial processing [30,31]. A second possibility is that in a well learned task (i.e. after extended training), even a spatial task (affected by hippocampal lesions) incorporates dorsal lateral striatal processing. To examine these possibilities, the extent of damage in the lateral striatum and medial dorsal striatum was determined by an experimenter blind to the animal's behavioral performance. All STR animals had extensive damage to the dorsal lateral striatum (Fig. 3). Increasing the size of the lesion was related to poorer performance (a lower % of correct trials) on the place trials (Table 2); the effect was significant and stronger in the lateral striatum than in the medial striatum. No such correlation was seen with regard to response trials. In total, these findings suggest dorsal lateral striatum involvement in spatial navigation after extensive training.

4.3. Conclusions

In the current study competition between systems could manifest in two different manners. First, lesion of one system would allow faster acquisition of a task based on the alternative system. In fact this was found when the animals learned the response reversal

Table 2

Correlation between the extent of damage in the medial striatum and the lateral striatum to correct performance on place and response trials. Extent of damage was assessed to regions of the dorsal lateral and dorsal medial subregions separately; low scores indicated minimal damage while high scores indicated severe damage. There was no correlation to performance on response trials; more extensive damage did not further decrease the percentage correct on response trials. Poorer performance on place trials was significantly correlated to more damage in the lateral, but not medial, striatum (* $p < 0.05$).

Correlation between striatal damage and performance		
	Place trials	Response trials
Medial damage	−0.675	−0.112
Lateral damage	−0.891*	−0.087

(hippocampus lesioned animals learned fastest). These data are similar to previous reports indicating a competition between hippocampus and striatum during acquisition (e.g. [14,20,21]). The second form of competition would be an increase in the use of the alternative strategy beyond acquisition. This was not found. Lesioned animals showed an increase choice of the “other” arm, rather than dominance by the preserved system. A simple competition between strategies should have resulted in an inverse relationship between response strategies with little change in the proportion of “other” responses. The error analysis indicated that indeed pre-lesion and post-lesion control animals showed a dichotomous competition between alternative strategies (errors were almost always choosing the wrong strategy) [24].

Taken together the data suggest a qualitative change in the relationship between hippocampal and striatal systems as a hippocampal task is well learned. During acquisition the two systems work in parallel, competing with each other. Beyond task acquisition, once both strategies are familiar and have resulted in reinforcement, the two systems become more integrated and interdependent. The fact that with extensive training (as something becomes a “habit”), behaviors become dependent upon the dorsal lateral striatum has been previously shown [32]. The current findings indicate that dorsal lateral striatum involvement occurs even when the behavior is spatial and continues to require hippocampal processing.

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