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The Effect of Striatal Lesions on Place and Response Learning

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### Abstract

In the current study, contribution of sub-regions of the striatum (a part of the basal ganglia in the rat brain) to place and response learning were examined in regards to their contribution to place and response learning. A T-maze was used to test the hypothesis that dorsolateral striatal lesions reduce response learning, and that dorsomedial striatal lesions impair place learning. Rats were trained using a consistent South start arm with a consistent food reward at the end of the West arm of the maze. Rats were then tested using a North arm start position to determine if they were place or response learners. In Experiment 1, pre-training lesions of the dorsolateral striatum disrupted response learning, but not place learning, relative to sham-operated controls. Lesions of the dorsomedial striatum did not affect place or response learning. In Experiment 2, selective lesions of the dorsomedial striatum were done in order to dissociate the anterior and posterior regions. Lesions of the posterior dorsomedial striatum disrupted place learning, whereas lesions of the anterior dorsomedial striatum did not. Thus, in agreement with previous research, our results show that response learning is mediated by the dorsolateral striatum. More importantly, we identified the posterior dorsomedial striatum as a contributing locus of place learning in the basal ganglia of the rat brain.

## The Effect of Striatal Lesions on Place and Response Learning

People acquire knowledge by making associations between stimuli encountered in their environment on a daily basis. There are several operating principles that distinguish multiple memory systems underlying learning and memory. One of these learning and memory principles involves two types of memory attributed to distinct brain structures: explicit (declarative) memory and implicit (non-declarative) memory. Explicit memory deals with facts and recollection of episodes. Areas of the brain implicated in explicit memory are the hippocampus and medial temporal lobe (Yin, Knowlton & Balleine, 2002). The specific region of the basal ganglia called the striatum contributes to the formation of implicit (non-declarative) memory. Implicit memory accounts for performance of procedural tasks. Dialing a telephone number is a procedural task exemplifying implicit memory. The task is performed as a consequence of remembering where the digits on a telephone are located relative to others, not the telephone number itself. No thought is required when dialing a telephone number because it is based on a learned response, a type of implicit memory. Previous research by Packard and Knowlton (2002), found that lesions to the dorsolateral striatum might inhibit the formation of response learning. The present study seeks to clarify these results. Furthermore, the study seeks to find out if place learning, determined by expected outcomes or goals, can be inhibited by lesions to the dorsomedial striatum.

There are two learning systems, place and response learning, that can account for deliberate cognitive functions and habit formation, respectively. The principles that

account for place versus response learning are part of the cognitive view proposed by Tolman (1948) and the Stimulus-Response (S-R) view proposed by Thorndike (1933) and Hull (1943). The cognitive view states that behavior is guided by expected outcomes or goals. A relationship between two or more stimuli is learned. This learned relationship accounts for purposeful behavior. An example of purposeful behavior based on expected outcomes is place learning, by which an animal learns to associate a place (stimulus 1) with food (stimulus 2). The association will break, and the animal will cease to visit, when food is no longer found at that location. The animal will only perform an action if it provides a desired outcome. In contrast to the Cognitive view, the S-R view accounts for habit formation based on antecedent stimuli (i.e., past experiences). An animal may perform an action because it previously received a consistent food reward, not because it is currently receiving the reward. In other words, the animal does not re-analyze the scenario. Instead, behavior is based on habits formed from previously experienced stimuli. The formation of habits based on antecedent stimuli is termed response learning. In essence, response learning reflects habit formation whereas place learning, more deliberate and based on conscious associations, is based on outcome.

In the past, it has been suggested that lesioning one brain region will inhibit the corresponding memory system and will result in the preferential use of the alternative learning system (Packard, 1999). Packard (1999) hypothesized that post-training glutamate enhancement of the hippocampus or caudate-putamen biases an animal to use a specific memory system. Injecting an agonist such as glutamate in the hippocampus should increase cognitive behavior. Rats receiving glutamate injections in the caudate putamen should exhibit more response learning. To test this hypothesis, a cross maze was

used. The rats were trained to turn left to go west, starting at a South<sub>arm</sub>, on days 1-7 and 9-15. On days 4-6 of training, the rats received an injection of glutamate or saline in either the hippocampus or caudate. On days 8 and 16<sub>2</sub>, the rats were tested from a novel North<sub>start</sub> arm. Rats that turned west were designated place learners. Conceivably, these rats formed a cognitive map designating the spatial location of the food reward. Rats that learned to make the left turn were designated response learners because they appeared to have learned a response tendency to turn left. Extended training caused a shift in control of learned behavior for rats receiving the saline injection. On day eight, saline injected rats were place learners<sub>2</sub>; however<sub>2</sub> on day 16 they exemplified response learning. Rats that received the glutamate injection into the hippocampus never showed a shift in behavior control. Instead<sub>2</sub> they were place learners on both day 8 and 16. Rats that received the injection of glutamate into the caudate were response learners on days 8 and 16, which suggests a quickened shift to response learning. Packard's results suggest that post<sub>training</sub> glutamic injections to the hippocampus and caudate-putamen can bias the use of memory systems (place vs. response, respectively) to control learned behavior in a time<sub>dependent</sub> manner. Furthermore, the results are consistent with the hypothesis that two systems are selectively mediating cognitive learning and S-R formation (Packard, 1999).

Research establishing the competing systems hypothesis in entire brain structures such as the hippocampus and striatum<sub>2</sub> set the premise for future research which sought to understand the possibility of dissociation of function within a single brain structure (i.e. the basal ganglia).

Further research by Yin et al. (2002) showed that the dorsolateral striatum, not the entire basal ganglia, is necessary for habit formation. This research aimed to investigate the role of the dorsolateral striatum in habit learning by devaluing the outcome (i.e., reward) after training. Outcome devaluation was used to dissociate actions and habits. Devaluation was incurred through the pairing of sucrose with lithium chloride, which resulted in taste aversion. The rats were trained before devaluating the outcome. Training involved requiring rats to press a lever on an interval schedule in order to form habitual behavior. Once trained to press the lever to obtain an outcome (sucrose), the outcome was devalued by pairing it with lithium chloride. During devaluation, a rat with a dorsolateral lesion will press the lever less frequently. The lesioned rat is able to analyze the new situation, realize that pressing the lever is harmful, and thereby avoid the outcome by not performing the action. Lesioned rats are sensitive to outcome devaluation because they cannot form habits. However, normal rats, those with an intact dorsolateral striatum, are not as sensitive to outcome devaluation. The pairing of lithium chloride and sucrose does not cause complete taste aversion because the rat continues to perform the habitual response. The behavior for these subjects is not dependent on outcome. Instead, it is elicited by external stimuli supplied by the consistent lever in the box. Habits are fixed, gradually acquired, and independent of the outcome. In contrast, actions are flexible, quickly learned and controlled by the expected outcome (e.g., food reward).

In the experiment by Yin et al. (2002), outcome devaluation helped determine whether the dorsolateral striatum influenced actions based on outcome expectancy or habits. The results indicate that rats lesioned in the dorsolateral striatum were sensitive to devaluation; therefore, their behavior is controlled by expectancy of the outcome. To

determine the effects of inhibition on learning, lesioned rats were compared to a control called the sham group. The sham and lesioned groups underwent virtually all the same surgical procedures with the exception of the neurotoxic drug injection. The sham group did not receive the injection. As a result, the sham group was not sensitive to devaluation. Their behavior was autonomous of the goal and controlled by surrounding stimuli. The data suggests that the dorsolateral striatum may be necessary for learning of S-R habits. When the dorsolateral striatum is lesioned, behavior is controlled by goal-directed behavior.

Previous research provides evidence for the competing systems hypothesis and the influence of the dorsomedial striatum in S-R learning. Packard's paper (1999) attributes the competing systems to entire brain structures (i.e., the hippocampus and striatum) (Packard, 1999). Specifically, place learning is attributed to the hippocampus. The striatum is implicated in response learning. Further research by Yin et al. (2002), shows that competing systems of function can potentially exist within the basal ganglia itself. When the dorsolateral striatum is lesioned, rats exhibited more place learning than response learning. However, the competing region of the striatum, that which could possibly increase response learning when lesioned, had not been located.

To support the hypothesis of a competing system within the basal ganglia, a region within the striatum must influence place learning. The present study postulates that the dorsomedial striatum influences place learning. In contrast, the dorsolateral striatum is believed to participate in response learning. Heterogeneity of function within the striatum is determined by lesioning distinct spatial locations in rats. It is hypothesized that if the dorsolateral striatum is lesioned, rats will become place learners

(i.e. deliberately use cognition). If the dorsomedial striatum is lesioned, rats will become response learners (i.e., form habits).

## Methods

### *Subjects*

Subjects were 44 adult male Long-Evans rats (350-500g), maintained at 85% of their free-feeding weight. Each rat cohabited with another rat of the same breed and gender in cages with a temperature controlled environment, and a 12-hour light-dark cycle.

### *Procedure*

Apparatus. The T-maze, outlined by Packard (1999), was used to test for the dissociation of function in the dorsomedial and dorsolateral striatum.

The T-maze was made of wood painted white and the arms were lined with Plexiglas to make alleyways. A black curtain that surrounded the maze served to keep the environment constant, with a white light in the southeast corner to serve as an extra-maze cue. Red lighting was directly above the maze to control for brightness.

Surgery. Animals were anesthetized with sodium pentobarbital before brain lesions were performed. During surgery four groups of rats were created: Rats with lesions in the dorsal lateral striatum, the anterior dorsal medial striatum, the posterior dorsomedial striatum or no lesion at all. The control group consisted of shams (i.e. rats that were not lesioned). An injected neurotoxic drug, NMDA, was used to induce the lesions. Surgery was performed prior to T maze training and testing.

Histology. Animals were anesthetized with sodium pentobarbital and perfused. The rats were perfused transcardially with .9% saline followed by 10% formaldehyde solution. The brains were stored in 10% formalin solution. They were then transferred to 25 % sucrose fomalin solution before 50um coronal sections were sliced.

Staining. The slides were then stained with thionin. The slides were examined to verify that the lesions were performed in the correct region of the striatum.

Behavioral procedure. Before maze training, rats were deprived of food. A T-maze was used to test if rats were response learners or place learners. The experiment consisted of three phases. During the preconditioning phase on day one, rats were introduced to the T-maze. Each rat was individually taken from its cage and placed in an opaque box. The box was turned in different directions, around a vertical axis, to disorient the rat. The rat was then taken from the box and placed in the south end of the T-maze. The rats were allowed to explore the maze for five minutes (300 seconds). Training, which occurred in phase two, consisted of 14 sessions, each of which consisted of four trials. The sessions took place on days 2 through 7 and 9 through 15. In each trial, the rats were placed in the South arm of the T-maze. From the south start box the rats were trained to obtain a food reward each time they arrived at the end of the consistent west arm.

The food reward was a Fruit Loop pellet. The time rats took to complete each trial (go from the south arm of the maze to the west arm) was measured and recorded in seconds. The maximum time permitted for each trial was 300 seconds. The arm the rat chose on

each trial (west or east) was also recorded for each trial. After each trial, the rats were taken out of the maze and placed in a box that was turned in different directions to disorient the rat. After each training session, the rats were given three food pellets. Before training a new subject, the maze was cleaned with alcohol so that odor would not be a confounding variable. The rats were trained using a fixed ratio schedule of continuous reinforcement. The goal arm had a reward (food pellet) that served as the motivator for the rats to choose the west arm.

During the third phase, rats were given a probe trial to cause response extinction on the 8<sup>th</sup> and 16<sup>th</sup> days. During the test, no food reward was placed in the west goal arm. In this phase, the rats were placed in the north arm of the T-maze and tested to see what type of learning had occurred. Rats that turned left (towards the east arm) were classified as response learners; rats that turned right (towards the west arm) were classified as place learners. The data for each rat was then compared with the type of brain manipulation done during profusions. The brains were sliced in a histology lab and stained to ensure the brain was manipulated correctly.

## Results

Similar to the sham group, rats with anterior dorsomedial lesions did not show a preference for either response or place learning. In the sham group, approximately half the rats were response learners, while the other half were place learners. Rats with posterior dorsomedial lesions showed significant results ( $p < .05$ ) when tested. The posterior dorsomedial lesion resulted in a bias for response learning. Results for the dorsolateral lesions were not significant ( $p > .05$ ). However, complementary to research

by Yin et al. (2002) implicating the dorsolateral striatum in response learning, the current data indicates that the posterior dorsomedial striatum is involved in place learning.

Furthermore, it provides support for the competing systems hypothesis. Inhibiting one region biases rats to use the learning system controlled by the competing region.

As shown in Figure 1, the sham group showed no preference for either place or response learning. There were five place learners and six response learners in the sham group. The anterior dorsomedial group show a significant preference: 9 place learners and 5 response learners. The posterior dorsomedial group showed significant results when compared to the sham group ( $\chi^2(1,26) = 5.38, p < .05$ ). There was 1 place learner and 14 response learners in the posterior dorsomedial group. The dorsolateral group did not show significant results  $\chi^2(1, 20) = 2.15, p > .05$ . There were seven place learners and two response learners in the dorsolateral group. Figure 2 shows the location of NMDA lesions (Paxinos and Watson, 1998). Histology was performed to ensure the accuracy of NMDA lesions. Stained tissue slices did not show apparent damage in areas outside the striatum for the lesioned groups.

### Discussion

From the data, it can be concluded that the sham group and the anterior dorsomedial groups did not demonstrate a preference for either response or place learning. Rats with posterior dorsomedial lesions tend to show response learning more often. Rats with dorsolateral lesions were not predominantly place learners. However the current data on PDMS groups, combined with Yin's previous work (2002), suggests the possibility of dissociation of function within the striatum. In essence, lesioning one region within the striatum could disrupt one memory system and allow the competing

memory system to take over. The results support the involvement of the PDMS in place learning. Future studies supporting the involvement of the DMS in response learning are required to strongly support a competing systems hypothesis and dissociation of function within the dorsal striatum.

Previous research (Packard and Knowlton, 2002) supports heterogeneity of function between different brain structures. The hippocampus is indicated in place learning, and the basal ganglia is implicated in response learning. Future studies sought to show heterogeneity within dorsal striatal region of the basal ganglia. A study by Yin et al. (2002) suggests that the dorsal striatum is involved in response learning; however, it failed to show that the PDMS is involved in place learning.

To demonstrate heterogeneity within the dorsal striatum, it is first necessary to demonstrate that region-selective lesions result in preferential usage of response or place learning. In this experiment, the anterior and posterior regions of the dorsomedial striatum were lesioned in rats. Results indicate that rats with posterior dorsomedial lesions tend to show a bias for response learning when compared to the control group. This preference for response learning suggests that lesioning the posterior dorsomedial striatum inhibits place learning. The results suggest that the posterior dorsomedial striatum is involved in place learning. When the current study is looked at independently, it does not support the dissociation of function within the striatum. However, the data clearly shows that the PDMS is involved in place learning. This brain region has never been shown to play an important role in place learning. Furthermore, when the current data is combined with Yin's work, suggesting the role of DMS in response learning, the dissociation of function within the striatum is highly probable. Prior to this study,

heterogeneity within the basal ganglia could not be suggested because the role of the striatum in place learning had not been established. By identifying the posterior dorsomedial striatum's involvement in place learning, this study provides support for heterogeneity and the competing systems within the basal ganglia.

It is important to consider the importance of the basal ganglia in Parkinson's diseases (PD) and Obsessive-Compulsive disorder (OCD). PD patients have difficulties forming habits (response learning). This may explain why they have a hard time responding to external stimuli and initiating actions such as walking; therefore, increasing habit formation by inhibiting the dorsomedial region of the striatum may serve as a treatment for Parkinsonian behavior. Inhibiting the posterior dorsomedial striatum to increase habit formation can be attempted hence, a competing system has been identified in the striatum. However, this research experiment does not specify the degree to which the dorsomedial striatum must be inhibited. Although inhibiting the dorsomedial striatum may facilitate normal behavior, too much inhibition may decrease place learning to abnormal levels thereby causing diseases such as OCD

In obsessive-compulsive disorder (OCD) patients it appears that the goal-directed system (place learning) is impaired. Therefore, OCD patients may form habits more quickly than persons without a diagnosis of OCD. According to the competing systems hypothesis suggested by recent studies, inhibiting the dorsolateral system should increase place learning while decreasing response learning. Again inhibiting the hyperactive system should increase activity of the hypoactive system. However, the current findings are limited to the former statement, as they do not specify the level of inhibition required to obtain normal functioning in an individual with either PD or OCD. Future research

should aim at finding what drugs, and in what quantities, can be used to inhibit pathways causing a bias for one system over another. When the proper level of inhibition can be achieved the neural systems underlying place and response learning will function in parallel thereby restoring normal behavior.

The data, combined with previous research (Yin et al., 2002) suggests striatal heterogeneity underlying place and response learning. In turn, heterogeneity permits a competing system to operate within the basal ganglia. Under normal circumstances the systems underlying learning (the posterior dorsomedial and the dorsolateral striatum) seem to operate in parallel and compete with each other in controlling behavior. Damage to one system can bias the use of the other system. Lesioning a striatal region (e.g. PDMS) will bias the use of the learning system (e.g. response learning) controlled by an intact striatal region (e.g. DMS). In conclusion, identification of the striatum in both place and response learning provides support for heterogeneity and competing systems within the dorsal striatum.

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