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Memory for Objects and Places Following Lesions of the Hippocampus or Perirhinal Cortex in Rats

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A Thesis

in

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ABSTRACT

Memory for Objects and Places Following Lesions of the Hippocampus or Perirhinal Cortex in Rats

Lee H. Francis

Retrograde memory for object discrimination problems and spatial information was assessed in rats that had received either bilateral aspiration lesions of the perirhinal cortex or bilateral NMDA lesions of the hippocampus. Rats learned three different object discrimination problems. They learned one problem approximately 72 hours prior to surgery, another problem approximately 24 hours prior to surgery, and a third problem approximately 1 hour prior to surgery. The rats also learned a place-memory problem, in which they were required to learn the location of a submerged platform in a pool of water, either 72 or 3 hours prior to surgery. Following recovery from surgery, rats were tested for 1) their ability to remember the presurgery object discrimination and place-memory problems, as well as 2) their ability to acquire new object discrimination problems. Neither lesion caused significant retention deficits for the object discrimination problems. Rats with perirhinal cortex lesions were impaired at acquiring the first postsurgery object discrimination problem but unimpaired at acquiring a second postsurgery object discrimination. Rats with hippocampal lesions were unimpaired at acquiring either postsurgery object discrimination problem. Rats with hippocampal lesions, but not those with perirhinal cortex lesions were impaired on the place-memory task that had been learned prior to surgery. These findings suggest that: 1) the hippocampus, but not the

perirhinal cortex, plays an essential role in spatial memory, and 2) neither the hippocampus, nor the perirhinal cortex play an essential role in long-term memory for object discrimination problems.

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Clinical patients that have sustained large lesions of the medial temporal lobe exhibit memory loss for events that occurred both prior to the lesion (retrograde amnesia) and subsequent to the lesion (anterograde amnesia) (Scoville & Milner, 1957). Further, some patients exhibit a form of retrograde amnesia that is temporally graded such that recent memories are forgotten whereas remote memories remain intact. The lesions sustained by these patients typically involve a number of medial temporal lobe structures including the hippocampal formation (hippocampus proper, dentate gyrus and subiculum), rhinal cortex (including the entorhinal and perirhinal cortices) and the parahippocampal gyrus. Despite decades of research into these phenomena, the precise mnemonic roles of individual structures within the medial temporal lobe remain unclear.

Animal models have been used in attempts to both replicate this disorder and determine the precise roles of individual medial temporal lobe structures in memory processes. This research has resulted in numerous, disparate models concerning the mnemonic roles of medial temporal lobe structures. One set of models maintains that the hippocampal formation and the parahippocampal region (including the entorhinal and perirhinal cortices as well as the parahippocampal gyrus) comprise a unitary memory system (Eichenbaum, Otto & Cohen, 1994) that is responsible for the consolidation of long-term memory (McClelland, McNaughton & O'Reilly, 1995; Squire & Zola-Morgan, 1991). Further, these models maintain that the role of medial temporal lobe structures in memory is quite general with respect to the information content of what is being remembered. For example, this temporal lobe memory system is thought to be

responsible for the consolidation of both spatial and nonspatial information. This contradicts models that propose that the mnemonic functions of specific structures within the medial temporal lobe are divisible in terms of information type. For example, it has been proposed that the hippocampus and perirhinal cortex are components of functionally dissociable memory systems responsible for information about places and objects, respectively (Mumby & Pinel, 1994; Murray, 1996).

The majority of experiments that have examined the role of medial temporal lobe structures in memory have focused on anterograde memory. Relatively few have examined the effects of selective lesions of medial temporal lobe structures on retrograde memory. Of the many questions that remain concerning the mnemonic roles of individual medial temporal lobe structures, the experiments and literature review presented in this thesis will attempt to address the following: 1) Do selective lesions of the hippocampal formation or rhinal cortex cause retrograde amnesia?, 2) If deficits exist following these lesions, are the mnemonic roles of these structures dissociable in terms of the type of information involved?, and 3) Is there evidence of a deficit in memory consolidation? That is, do selective lesions of the hippocampal formation or perirhinal cortex cause temporally-graded retrograde amnesia?

The relevant literature is reviewed in the following pages. The first section will examine the characteristics of medial temporal lobe amnesia in humans and the neurological damage that is necessary to produce the amnesic syndrome. The second section will review some of the animal models of medial temporal lobe function. The

third section will examine the roles of the hippocampal formation and perirhinal cortex in memory for object-discriminations. The fourth section will examine the roles of these structures in memory for spatial information. Finally, the fifth section will provide a brief outline of the experimental design and hypotheses for the experiments presented in this thesis.

Characteristics of medial temporal lobe amnesia in humans.

An often cited example of medial temporal lobe amnesia is the clinical case of H.M.. At the age of 27, H.M. received a bilateral resection of the medial temporal lobes in the hopes of removing the epileptic focus of his severe and persistent seizures (Scoville & Milner, 1957). A recent MRI analysis of H.M.'s brain revealed a bilaterally symmetrical lesion including approximately half of the hippocampal formation (including the hippocampus proper, dentate gyrus and subiculum), most of the amygdala, virtually all of the entorhinal cortex, and the dorsal half of the perirhinal cortex (ie. superior to the collateral sulcus) (Corkin, Amaral, Gonzalez, Johnson & Hyman, 1997).

Since his surgery, H.M. has suffered from a severe anterograde memory deficit, such that he is unable to form certain types of long term memories (Sidman, Stoddard & Mohr, 1968). His short term memory (Wickelgren 1968), as well as the ability to learn various motor skill tasks (Corkin, 1968), however, remain intact. In addition, H.M.exhibits temporally-graded retrograde amnesia for events that occurred up to three years prior to his surgery (Scoville & Milner, 1957; Milner, Corkin & Teuber, 1968).

This particular deficit is thought to reflect a disruption in the consolidation of long-term memory (McClelland et al., 1995; Squire & Alvarez, 1995). According to this hypothesis, memories for specific events are consolidated over time. During this time, neurological changes are thought to occur such that memory becomes more resistant to disruption. Relatively recent memories, that have not been thoroughly consolidated, are, therefore, thought to be more susceptible to disruption than are remote memories. The presence of temporally-graded retrograde amnesia in H.M. led researchers to suspect that the medial temporal lobe plays an important role in this consolidation process. Unfortunately, due to the large number of medial temporal lobe structures damaged in H.M., researchers were unable to ascertain exactly which structure played a necessary role in memory consolidation.

Two patients, L.M. and W.H. have bilateral damage to the hippocampal formation and neighbouring entorhinal cortex. Unlike H.M., the damage was not caused by surgery. L.M.'s lesions appear to be the result of seizures brought on by years of alcohol abuse, while the cause of W.H.'s lesion is thought to result from an ischemic episode. Like H.M., however, both of these patients suffer from anterograde amnesia and retrograde amnesia, although their deficits are not as severe as those seen in H.M. (Rempel-Clower, Zola, Squire & Amaral, 1996). These findings fit with the idea that the medial temporal lobe plays an essential role in the consolidation of long-term memory. However, in both of these cases, the neural damage extended beyond the medial temporal lobe so researchers were unable to rule out the possibility that these damaged structures

participated in memory consolidation.

Clinical evidence suggests that damage to the hippocampal formation is not sufficient to cause retrograde amnesia in humans. Two patients, R.B. (Zola-Morgan, Squire & Amaral, 1996) and G.D. (Rempel-Clower et al., 1996), sustained bilateral lesions of the CA1 field of the hippocampus, as well as other brain areas, as a result of a transient ischemic episode. Both patients displayed difficulty forming new long-term memories for events that occurred following their ischemic episodes but their memory for events that occurred prior to the ischemic episodes was intact.

Overall, the clinical evidence suggests that damage to the hippocampal formation and surrounding cortex may be sufficient to cause both anterograde and retrograde amnesia. Hippocampal damage, in the absence of obvious cortical damage can cause anterograde amnesia with no evidence of retrograde impairment. It is important to note, however, that the clinical evidence does not rule out the possibility that complete lesions of the hippocampal formation would result in retrograde amnesia. It may be that the severity of retrograde amnesia is related to the extent of the damage to the hippocampal formation.

Animal models of medial temporal lobe function.

An animal model was developed that resembled human amnesia in several key respects. Monkeys with aspiration lesions of the hippocampal formation and surrounding cortical areas displayed a pattern of spared and impaired memory abilities

similar to H.M., including the preservation of certain kinds of long-term memory abilities (Zola-Morgan & Squire, 1984) and intact short-term memory (Alvarez, Zola-Morgan & Squire, 1994), along with an inability to remember specific episodes or events (Mahut, Moss & Zola-Morgan, 1981). In addition, lesioned monkeys exhibit temporally-graded retrograde amnesia (Zola-Morgan & Squire, 1990). This memory deficit was initially attributed to the hippocampal damage and not the damage to surrounding cortical areas. One resulting theory was that the hippocampus plays a necessary, but time-limited role in long-term memory formation either by temporarily storing memory for events, or by playing an active role in guiding subsequent storage in neocortical areas (McClelland, McNaughton & O'Reilly, 1995; Squire & Zola-Morgan, 1991). Support for this idea comes from the findings that rats with selective lesions of the hippocampal formation display temporally-graded retrograde amnesia for trace eyeblink conditioning (Kim, Clark & Thompson, 1995), contextual fear conditioning (Kim & Fanselow, 1992), and socially transmitted food preference (Winocur, 1990).

A related model of medial temporal lobe function maintains that the hippocampal formation and the parahippocampal region (including the entorhinal and perirhinal cortices as well as the parahippocampal gyrus) comprise a single, unitary memory system (Eichenbaum, Otto & Cohen, 1994). According to this model, information is initially processed within the parahippocampal region and then by the hippocampal formation. In this manner, all of these anatomical structures play a time-limited role in long-term memory formation.

The model put forth by Eichenbaum et al. (1994) also maintains that the role of the hippocampal and parahippocampal region is quite general with respect to the information content of what is being remembered. For example, memory for both spatial and non-spatial information should be affected by lesions of the medial temporal lobe. Other models propose that the mnemonic roles of certain medial temporal lobe structures are dissociable in terms of information type. For example, it has been suggested that the hippocampal formation is important for memory of only certain kinds of information, such as places (Jarrard, 1993; Morris, Garrud, Rawlins & O'Keefe, 1982; O'Keefe & Nadel, 1978). Similarly, the perirhinal cortex is thought to play a preferential role in memory for objects (Mumby & Pinel, 1994; Murray, 1996). Some recent findings have lent support to these models. In two separate experiments, lesions of the hippocampal formation caused deficits on spatial memory tasks but not those involving object recognition (Ennaceur, Neave & Aggleton, 1996; Glenn & Mumby, 1996). In the same experiments, lesions of the perirhinal cortex caused deficits in object recognition but not on certain spatial memory tasks (Ennaceur, Neave & Aggleton, 1996; Glenn & Mumby, 1996).

Retrograde Memory for Object-Discrimination Problems

Numerous researchers have employed the object-discrimination task in their attempts to assess memory abilities in lesioned animals. Animals are trained to discriminate between two objects, one of which is associated with food. The ability to

learn and retain the problem are used as indices of memory ability.

Salmon, Zola-Morgan and Squire (1987) tested monkeys with large lesions of the medial temporal lobe and found that they displayed severe and long-lasting retrograde amnesia for object discrimination problems. These monkeys were first trained on several object discrimination problems between eight months and two weeks prior to surgery. They then received bilateral aspiration lesions of the hippocampal formation, amygdala, and overlying cortical areas (including the entorhinal and perirhinal cortices as well as the parahippocampal gyrus). When tested for their retention of the preoperatively learned problems, the lesioned monkeys displayed no retention of these problems. Their performance did not differ significantly from chance and the deficits remained despite repeated retesting. Although this experiment suggested that lesions of the medial temporal lobe can cause retrograde amnesia, it did not lend support to the theory that these structures play a time-limited role in memory formation because the memory loss exhibited by the lesioned monkeys was not temporally graded.

Lesioned monkeys did display temporally-graded retrograde amnesia in an experiment performed by Zola-Morgan and Squire (1990). The monkeys in this experiment were trained on several object-discrimination problems at various time points between sixteen and two weeks prior to surgery. They then received lesions that included the hippocampal formation, entorhinal cortex, perirhinal cortex and parahippocampal gyrus. When tested for their retention of the pre-operatively acquired problems, the lesioned monkeys performed worse than controls on the problems acquired two and four

weeks prior to surgery but not at any other times. In addition, the lesioned monkeys displayed significantly better retention for the problems acquired twelve weeks prior to surgery compared to those acquired either two or four weeks prior to surgery. This pattern of spared remote memory and impaired recent memory is thought to be indicative of a disruption in the process of memory consolidation. Recent memories, that have not been thoroughly consolidated are lost, whereas remote memories, that have been thoroughly consolidated, are retained. The authors interpreted the results of this experiment as indicative of a time-limited role of the hippocampal formation in memory formation.

Selective lesions of the hippocampal formation, however, do not cause retrograde amnesia for object discrimination problems in rats (Astur, Mumby, Weisand & Sutherland, 1994; Wible, Shiber & Olton, 1992). This is true for both complete lesions of the hippocampal formation and ischemic lesions of the CA1 field of the hippocampus (Wood, Mumby, Pinel & Phillips, 1993). Similarly, neurotoxic lesions of the CA1 field do not cause retrograde amnesia for object discriminations in monkeys (Ridley, Timothy, Maclean & Baker, 1995).

If the retrograde amnesia demonstrated by lesioned monkeys in both the Salmon et al. (1987) and the Zola-Morgan and Squire (1990) experiments was not due to the hippocampal damage, then it may have been due to the damage sustained by adjacent rhinal cortex. Some researchers have hypothesized that one of these cortical areas, the perirhinal cortex, is part of a neural system responsible for memory concerning objects

(Mumby & Pinel, 1995; Murray, 1996). Relatively few experiments have examined the effect of rhinal cortex lesions on retrograde memory for object discrimination problems. In one such experiment, Thornton and Murray (1996) found that monkeys with combined lesions of the entorhinal and perirhinal cortex displayed retrograde amnesia for object discrimination problems learned at sixteen weeks and one week prior to surgery. The memory loss was not temporally-graded. Astur, Mumby and Sutherland (1995), however, found that rats with perirhinal cortex lesions were unimpaired in their retention of preoperatively learned object discrimination problems.

There are at least two potential explanations for the discrepancy in the results found by Thornton and Murray (1996) and Astur et al. (1995). The first potential explanation is the difference in lesion sizes. Thornton and Murray lesioned both the perirhinal and entorhinal cortices but Astur et al. lesioned only the perirhinal cortex. The results of these experiments, therefore, suggest that the entorhinal cortex plays an essential role in memory consolidation.

A second potential explanation for the discrepancy in the results is the fact that rats and monkeys are trained somewhat differently on object discrimination problems. Monkeys typically learn the task very quickly (within one to two sessions) and are often taught sets of object discrimination problems instead of a single problem (e.g. Thornton & Murray, 1996; Zola-Morgan & Squire, 1990). Rats, on the other hand, are typically trained across several days on a single object discrimination problem (e.g. Astur et al., 1994 & 1995, Wible et al. 1992). Zola-Morgan and Squire (1984) have suggested that the

use of massed versus distributed training can result in differences in the nature of the information that is learned. It is, therefore, possible that the discrepancy between the results of the Thornton and Murray (1996) and the Astur et al. (1995) experiments may be due to a difference in training procedures.

Although large medial temporal lobe lesions result in extended retrograde amnesia, selective lesions of either the hippocampal formation (Astur et al., 1994) or perirhinal cortex (Astur et al., 1995) do not result in any retrograde amnesia for object discrimination problems learned one week or more prior to surgery (the shortest learning-to-lesion interval used in the above mentioned experiments). It is therefore unclear what role, if any, these individual medial temporal lobe structures play in the consolidation of long term memory for object discrimination problems. The possibility remains, however, that these structures play a role in memory consolidation for object discriminations, but that this role lasts for a shorter time period than one week.

Retrograde Memory for Places

Selective lesions of the hippocampal formation in rats cause both anterograde (see review by Barnes, 1988) and retrograde (e.g. Bolhuis, Stewart & Forrest, 1994) deficits on tests of spatial memory. It is not yet clear what role, if any, the perirhinal cortex plays in spatial memory abilities. Perirhinal cortex lesions have been reported to cause no impairment (Astur, Mumby, & Sutherland, 1995; Ennaceur, Neave & Aggleton, 1996; Wiig & Bilkey, 1994a), mild impairment (Wiig & Bilkey, 1994b), and severe impairment

(Nagahara, Otto & Gallagher, 1995; Rothblat, Vnek, Gleason & Kromer, 1993) on tests of anterograde memory. Perirhinal cortex lesions have been reported to have no effect on tests of retrograde memory for spatial information in rats (Astur, et al., 1995).

Two separate experiments have shown that rats with ibotenic acid lesions of the hippocampal formation display ungraded retrograde amnesia for place-memory problems in a water maze (Astur et al., 1994; Bolhuis et al., 1994). In both experiments rats learned the location of a fixed, hidden platform in a water maze across several days. Bolhuis et al. (1994) used a between-subjects design in which groups of rats learned the task at either three days or fourteen weeks prior to receiving lesions of the hippocampal formation. Both lesioned groups were equally impaired on the task relative to rats that had received sham surgery. Astur et al. (1994) employed a within-subjects design such that all of the rats learned two different place-problems. The problems were learned in separate rooms, thereby providing the rats with two different sets of spatial information. The first problem was learned fourteen weeks prior to surgery and the second problem was learned two weeks prior to surgery. As in the Bolhuis et al. (1994) experiment, the rats received either sham surgery or hippocampal lesions. The lesioned rats were impaired on both place-memory problems regardless of when it had been originally learned. Similarly, lesions of the hippocampal formation were found to cause ungraded retrograde amnesia for spatial two-choice discrimination problems, in which rats were required to learn which of two arms in a radial arm maze was rewarded (Cho, Kesner & Brodale, 1995). The rats could learn the location of the rewarded arm relative to the extramaze cues provided by

the experimenters. Rats learned two, successive discrimination problems, prior to receiving electrolytic lesions of the hippocampal formation or sham lesions. Lesioned rats were impaired on this task regardless of when the task had originally been acquired. These results suggest that the hippocampal formation is important for some aspect of spatial information processing but that it is not necessarily involved in the consolidation of this memory.

Sutherland, Arnold and Rodriguez (1987) found that lesions restricted to the dentate gyrus of the hippocampal formation caused temporally-graded retrograde amnesia for spatial information. Rats learned the location of a hidden, fixed platform in a water maze. They then received neurotoxic lesions of the dentate gyrus or sham surgery at various time points between one and twelve weeks following task acquisition. Lesioned rats were impaired but those that had learned the task twelve weeks prior to surgery performed better than those that had learned the task between one and four weeks prior to surgery. This result suggests that the hippocampal formation does play a role in the consolidation of long-term memory for spatial information.

Another experiment found that although rats with hippocampal lesions were impaired on a water maze spatial task, the deficits exhibited by these rats did not suggest an impairment in long-term memory for the task (Morris, Schenk, Tweedie & Jarrard, 1990). Rats that had previously received extensive training on a hidden platform task in a water maze received lesions of the hippocampal formation or sham lesions. When tested for their retention of the task, rats with hippocampal lesions exhibited abnormal swim

patterns that interfered with their ability to navigate to the platform. This resulted in lesioned rats requiring more time than controls to locate the platform. During a probe trial, in which the platform was removed and the swim paths of the rats were recorded, lesioned rats crossed over the previous location of the platform as often as did sham rats. The authors interpreted this finding as reflecting a deficit in navigational ability and not memory ability. That is, the lesioned rats remembered where the platform was located but had difficulty navigating toward it in an organized fashion (Morris et al., 1990).

To assess the effects of perirhinal cortex lesions on retrograde memory for spatial information, Astur, Mumby & Sutherland (1995) trained rats on three place-memory problems in a water maze. The problems were learned at various time points between two and fourteen weeks prior to surgery. Rats with bilateral aspiration lesions of the perirhinal cortex were unimpaired in their retention of the previously learned problems.

Overall, the results of the present experiments confirm that lesions of the hippocampal formation impair performance on spatial memory tasks in rats. It is not clear, however, whether these deficits reflect an impairment in spatial memory so much as an impairment in spatial navigation ability. The role of the perirhinal cortex in spatial memory processing is not yet known and will become clearer with further experimentation. Based on the results of the Astur et al. (1995) experiment, it does not appear that this structure plays a role in the consolidation of long-term memory for such information. The possibility remains, however, that the perirhinal cortex plays a role in memory consolidation, but that this role lasts for a shorter time period than two weeks,

which was the shortest learning-to-lesion interval used in the Astur et al. (1995) experiment.

Experimental Design and Hypotheses

The purpose of the present set of experiments was to assess the effects of selective lesions of the hippocampal formation and perirhinal cortex on retrograde memory for object discrimination problems and spatial information in rats. Specifically, rats learned three object-discrimination problems prior to receiving lesions of the hippocampal formation or perirhinal cortex. They learned one problem approximately 72 hours prior to surgery, another problem approximately 24 hours prior to surgery, and a third problem approximately 1 hour prior to surgery. They also learned a place-memory task, in which they were required to learn the location of a submerged platform in a pool of water. Each rat learned this task either 3 days or approximately 3 hours prior to surgery. The effects of selective lesions of the hippocampal formation and perirhinal cortex were assessed in experiments 1 and 2, respectively. It was hypothesized that the hippocampus and perirhinal cortex are components of dissociable memory systems responsible for the consolidation of spatial and object information, respectively. It was, therefore, predicted that; 1) hippocampal, but not perirhinal cortex lesions would cause retrograde amnesia for the place-navigation task, and 2) perirhinal cortex, but not hippocampal lesions would cause retrograde amnesia for the object-discrimination problems. In addition, these experiments were designed to investigate the possibility that

these structures play a time-limited role in the formation of long-term memory (Eichenbaum, et al. 1994; Squire & Zola-Morgan, 1991). Evidence that rats remembered the remotely acquired problems better than those acquired more recently would be seen as supporting this hypothesis.

EXPERIMENT 1A

The hippocampus is considered an essential component of a temporal lobe memory system (Eichenbaum, Otto & Cohen, 1994; Squire & Zola-Morgan, 1991). In addition, this structure is thought to play an essential, yet time-limited role in the formation of long-term memory (McClelland, McNaughton & O'Reilly, 1995).

Previous experiments have found that rats with hippocampal lesions exhibit temporally-graded retrograde amnesia for trace eyeblink conditioning (Kim, Clark & Thompson, 1995), contextual fear conditioning (Kim & Fanselow, 1992) and socially transmitted food preference (Winocur, 1990). These findings support the hypothesis that the hippocampal formation plays an essential role in the consolidation of long-term memory.

Some researchers have proposed that the mnemonic role of the hippocampal formation is restricted in terms of the type of information to be remembered (e.g. O'Keefe & Nadel, 1978). Numerous experiments have shown that hippocampal lesions cause deficits on spatial memory tasks (see review by Barnes, 1988), however, the effect of hippocampal lesions on memory for other types of information is still unclear. For example, one experiment found that lesions of this structure do not cause anterograde or retrograde amnesia for object discrimination problems (Astur, Mumby, Weisand & Sutherland, 1994). This finding contradicts the hypothesis that the hippocampal formation plays an essential role in memory consolidation. Rather, it suggests that the mnemonic role of this structure may be restricted in terms of the type of information to

be remembered.

The purpose of this experiment was to assess the effects of selective lesions of the hippocampal formation on retrograde memory for object discrimination problems and spatial information. In addition, this experiment was designed to test the hypothesis that the hippocampal formation is involved in the consolidation of memory but that this role lasts for a shorter time period than was previously thought. Rats were trained on three object discrimination problems. They learned one problem approximately 72 hours prior to surgery, another problem approximately 24 hours prior to surgery, and a third problem approximately 1 hour prior to surgery. They also learned a place-memory task, in which they were required to learn the location of a submerged platform in a pool of water. Each rat learned this task either 3 days or approximately 3 hours prior to surgery. These particular learning-to-lesion intervals were chosen because they were shorter than those used in previous experiments (eg. Astur et al., 1994). It was predicted that hippocampal lesions would cause retrograde amnesia for the place-memory problem but not for the object discrimination problems.

Method

Subjects

The subjects were 24 experimentally naive, adult male, Long-Evans rats (Charles River, Quebec) that weighed between 300 and 350 grams at the start of the experiment. The rats were housed individually in standard laboratory cages on a 12:12 light-dark

schedule with lights on at 9:00am. All behavioral testing was conducted during the light phase of the cycle. The rats were allowed free access to water for the duration of the experiment and free access to food for two to five days prior to the start of the food restriction regimen. For the remainder of the experiment, the rats were fed an average of 25 grams of rat chow per day. The amount fed to any individual rat varied, between 20 and 30 grams, according to its performance in the object-discrimination testing apparatus. Rats that were performing too slowly were fed less so that they would be more motivated to work for food in the apparatus. The opposite was true for rats that were running too quickly.

Surgery

All rats were anaesthetized with sodium pentobarbitol (Somnotol, 65 mg/kg) 45 minutes after reaching criterion on the last presurgery object discrimination problem.

One rat from each of the matched-pairs of rats received a bilateral lesion of the hippocampal formation (group HPC; n=12). Lesions were made with bilateral, intrahippocampal injections of a 5.1M solution of N-methyl D-aspartate (NMDA) dissolved in 0.1M phosphate buffered saline. The rats were positioned in a stereotaxic apparatus (David Kopf Instruments), their scalp was incised and retracted to reveal the skull, and 8 small holes were drilled in the skull (see Appendix A for coordinates). NMDA-solution was injected into 10 sites bilaterally (see Appendix A). Injections were made using 10 ul Hamilton syringes that were mounted in an infusion pump (KD

Scientific) and connected to 30 gauge cannulae by polyethylene tubing. NMDA-solution was infused at a flow rate of .15 microlitres per minute until a total of 4 microlitres had been injected at each site. The solution was allowed to diffuse for 2 minutes following each injection prior to the canulae being removed. In order to prevent seizures, lesioned rats were injected with diazepam (maximum dose = 3.5mg) upon awakening from the anesthetic. Sham surgery was performed on the remaining 12 animals (group SHAM). For these animals, the skull was exposed and the injection holes were drilled. The injection canulae were lowered so that they pierced the dura and parietal cortex that overlie the hippocampal formation. The injection canulae were then removed and no NMDA solution was injected. All rats received antibiotic following surgery (Ayercillin, 15,000 units, i.m.).

Object-Discrimination Problems: Apparatus & Procedures

Apparatus. Figure 1 shows the object-discrimination testing apparatus. It was constructed of sheet aluminum (thickness = 0.127 cm). It consisted of a straight runway that was 61cm long and 17cm wide, with side walls (39cm high) and two wooden guillotine doors (33cm x 17cm) that led to goal areas located at either end of the runway. Each goal area (38cm x 15cm) contained two recessed food wells 3cm in diameter and 2cm deep. The food wells were separated by a dividing wall (9cm high and 9cm wide) which protruded from the end wall (39cm high and 38cm wide). The food wells were centred

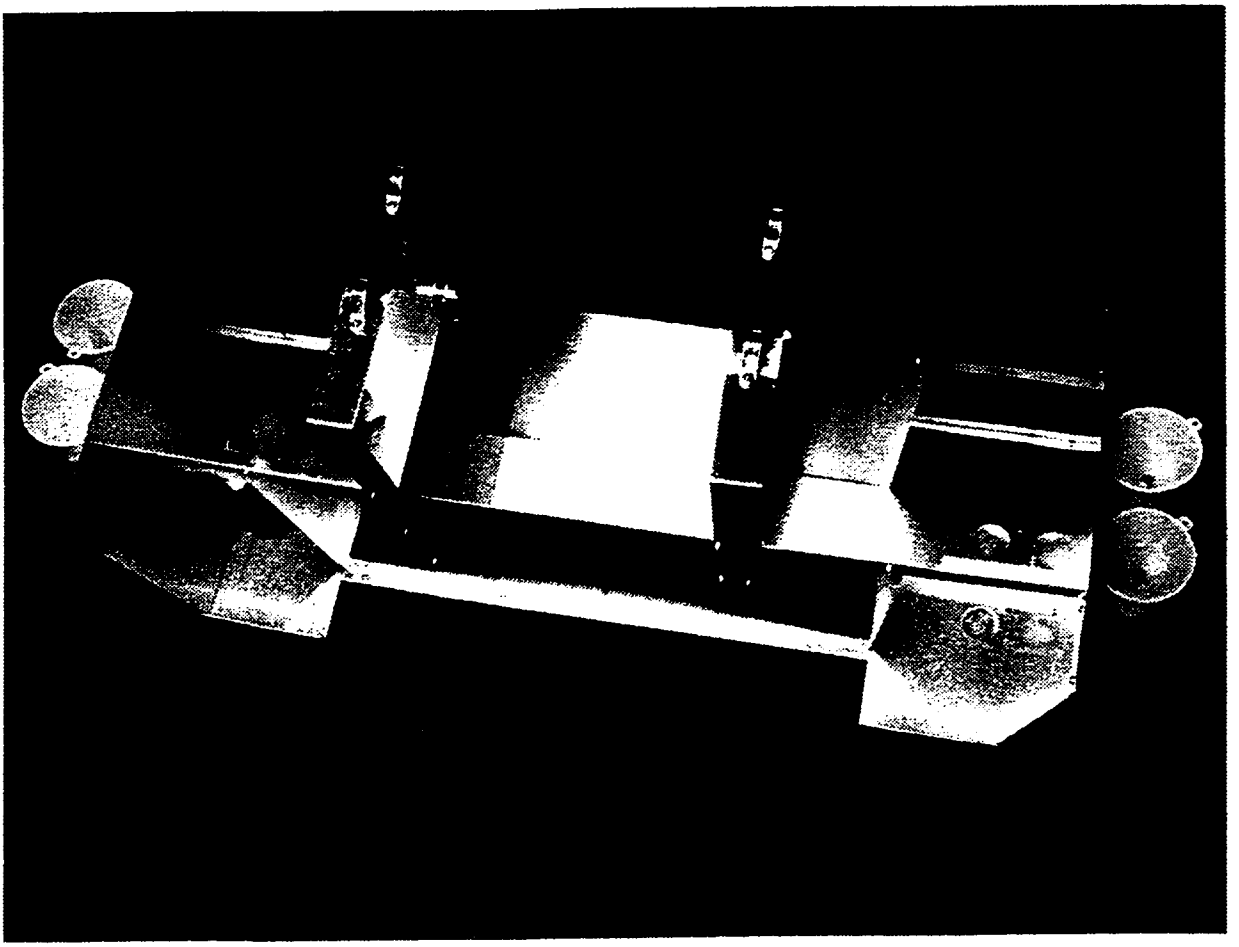


Figure 1. The object discrimination testing apparatus

3cm from the dividing wall and 2cm from the end wall. The sides of the goal areas were open to allow the experimenter to position objects over the food wells. Food pellets were delivered to the food wells via funnels that were mounted on the outside of the apparatus and connected to the food wells with vinyl tubing.

The object discriminanda consisted of five pairs of objects, selected so that they differed in a number of visible attributes, including size, shape and colour. All of the objects were large enough to cover the food wells but small enough and light enough to be easily displaced by the rats.

Preliminary Training. The rats were all tested individually. They were first habituated to the testing apparatus by training them to retrieve food pellets from the four wells. Each of the wells was baited with a few pellets and the rats were allowed to explore the apparatus and retrieve the pellets. Every time a well was emptied, the food was replaced once the rat had left the well area. Rats received one 20 minute session of habituation training per day until they were readily eating from all four food wells.

The rats were then trained to move back and forth between goal areas to retrieve food pellets. A food pellet was placed in one food well in one goal area and the rats were required to empty the baited well before a food well in the opposite goal area was baited. The location of the baited well alternated between left and right in a predetermined pseudo-random order so that food generally appeared equally often in each of the four food wells. The rats received one 20-minute training session per day, and this stage of

training continued until the rats were moving back and forth between goal areas at a relatively consistent speed, and could retrieve approximately 25 pellets in ten minutes. On average, rats required 5 training sessions to reach these criteria (*Mdn*=5, range = 2-9 sessions).

During the third stage of presurgery training, the rats were habituated to the sound and movement of the guillotine doors. Every time a rat retrieved a pellet from one of the goal areas, the door at the opposite goal area, was closed. When the rat approached the door, it was raised, and the rat was allowed to proceed to the baited goal area on the other side. This stage of training continued until the rats were moving from end to end at a consistent speed and could retrieve approximately 25 pellets in ten minutes. On average, rats required 2 training sessions to reach these criteria (*Mdn*=2, range = 2-6 sessions). The rats were assigned to matched pairs on the basis of their performance up to this stage of training.

Each pair of rats was then trained on an object discrimination problem. This was done to familiarize the animals with the procedural elements of the task. The same pair of objects was used for each rat. One object in the pair was correct (S+) and the other incorrect (S-) on all trials. The S+/S- designation was identical for rats within each matched-pair and counterbalanced between matched-pairs of rats so that object A was S+ for half of the rats and object B was S+ for the other half. At the beginning of each trial, the experimenter raised the guillotine door, thus allowing the rat access to the objects. The rat then displaced one of the objects from its food well; a food pellet was delivered to

that well if the rat displaced S+, but not if it displaced S-. The experimenter then removed both of the objects and lowered the guillotine door at the opposite end of the testing apparatus. The procedure was then repeated at the opposite end of the testing apparatus.

Each rat received 25 trials per day with an average delay of 15 seconds between trials. On the first day of training a food pellet was placed beneath S+ prior to the guillotine door being raised. This allowed the rats to use olfactory cues to guide their initial choices. In addition, the rats were allowed to correct their errors; if the rat initially displaced S-, it was allowed to displace S+ and retrieve the food pellet. On the second day of training, the rats were still allowed to correct their errors but the food pellet was not delivered until S+ was displaced. Thus, the rats could no longer use the smell of the food to guide their choices. On the third day of training the rats were allowed to displace only one of the two objects and were not rewarded unless S+ was displaced. Both objects were removed after the rat displaced one of them. Training continued until the rats displaced S+ on 22 out of 25 consecutive trials and could complete 25 trials in approximately 15 minutes. Rats typically required 3 training sessions to reach these criteria (*Mdn*= 3, range = 3-8 sessions).

Presurgery Training: Acquisition of Presurgery Object-Discriminations.

Following completion of preliminary training, each rat then began the principal phase of the experiment. Each of the rats learned three different object discrimination problems.

They learned one problem approximately 72 hours before they received surgery, another problem approximately 24 hours prior to surgery, and the third problem approximately 1 hour before surgery. Thus, there were three presurgery object-discrimination problems, hereafter referred to as the "-72 hour problem", the "-24 hour problem", and the "-1 hour problem". A different pair of objects was used for each discrimination problem. The S+/S- designation was identical for rats within each matched-pair and counterbalanced across matched-pairs of rats so that for each pair of objects, object A was S+ for half of the rats and object B was S+ for half of the rats.

The rats received only one training session for each of the three object discrimination problems. The rats were required to complete a minimum of 30 trials and training continued until the rat displaced S+ on ten consecutive trials. For the first 15 trials of each training session, a food pellet was placed beneath S+ prior to the guillotine door being raised. In addition, if the rat initially displaced S-, it was allowed to displace S+ and retrieve the food pellet. For all remaining trials the rats were allowed to displace only one of the two objects and were not rewarded unless S+ was displaced.

Postsurgery Testing: Acquisition of Postsurgery Object-Discriminations. Postsurgery testing commenced two weeks after surgery and continued for four days. On the first day of testing the rats were tested for their ability to acquire a new object discrimination problem, using the same single session procedure and learning criterion of ten consecutive correct trials that had been used for the presurgery problems. The rats

were tested until they had either reached criterion or had completed a maximum of 200 trials. They were then returned to their home cage for a period of approximately 15 minutes before beginning retention testing for the presurgery object-discrimination problems. In addition, five rats from each group learned a second new object-discrimination problem four days later, following retention testing for the presurgery object discrimination problems.

Postsurgery Testing: Retention of Presurgery Object-Discriminations. Retention testing commenced on the first day of postsurgery testing approximately 15 minutes after learning the first postsurgery object-discrimination problem. The rats were tested for their retention of the object-discrimination problems they had learned at 72, 24, and 1 hour prior to surgery. Rats received one testing session per day for three days. Each testing session consisted of ten trials for each of the three presurgery object-discriminations. The problems were presented in 6 blocks of 5 trials each per day with each block of 5 trials consisting of a particular pair of objects. The order in which the first three blocks were presented was counterbalanced and repeated for the second set of three blocks. For example, if the first block consisted of 5 trials of the -1 hour object discrimination problem, the next block could be of the -24 hour problem, and the third block would be of the -72 hour problem. The second set of three blocks was in the same order as the first. The rats were rewarded with a food pellet if they displaced S+ but not S-.

Retention testing continued on the second and third days of postsurgery testing. Prior to the start of these testing sessions, the rats were retested on the postsurgery object discrimination problem they had learned on the first day of testing. This was done in an effort to reduce or eliminate any nonmnemonic effects of the lesion, such as hyperactivity, that could interfere with the rats' performance on the retention trials (Shull & Holloway, 1985). This retesting continued until the rats either reached a criterion of eight correct out of ten consecutive trials or reached a maximum of 50 trials. They were then tested for their retention of the presurgery object discrimination problems. The order in which the blocks of problems were presented was shifted on each day. For example, a rat tested using the order -1 hour, -24 hour, -72 hour on the first day would be tested in the order -24 hour, -72 hour, -1 hour on the second day and -72 hour, -1 hour, -24 hour on the third day.

Place-Memory Problem: Apparatus and Procedures

Apparatus. The place-memory testing was conducted in a water-maze, which was a circular pool (137 cm in diameter x 46cm high) that was filled with water (23-25•C) to a depth of approximately 30cm. The water was made opaque by the addition of skim milk powder. A movable Plexiglas platform (28cm high and 10cm x 10cm wide), which was translucent at one end and had black tape on the other end, was used as the escape platform during testing. When placed below the surface of the water, with the clear end

up, the platform was invisible to the rats. When placed with the black end up, extending above the surface of the water, the platform was visible to the rats.

A VP118 Super Tracker with HVSWater software (HVS Image Ltd., Hampton, UK) was used to record both the rats' swim path and the length of time the rats required to locate the escape platform. These raw data were stored on a computer (IBM compatible, 486 DX).

The testing room, in which both the water maze and the tracking system were located, contained visual (eg. posters) and auditory (eg. radio) cues. These were provided so that the rats could learn the location of the hidden escape platform relative to these extramaze cues.

Preliminary training: Visible platform training. To lessen the potentially confounding effect of stress on the rats' learning of the place-memory problem (Conrad, Galea, Kuroda & McEwen, 1996), half of the rats in this experiment received habituation training in the water maze prior to learning the actual place-memory problem. These rats were habituated to the water maze by training them on a visible platform version of the task in which the escape platform was placed in the centre of the maze approximately 2 cm above the surface of the water with the black end up. The rats were tested individually. To begin each trial, the rat was lowered into the maze while facing the wall of the pool. The rat was then released into the pool. The release point varied among the four compass points (N,S,E,W) in a pre-determined pseudo-random order across trials so

that each release point was used once in each block of four trials and the order in which the release points were used varied between blocks of four trials. The escape latency was measured as the time from release until the rat touched the top of the escape platform with both front paws. Rats remained on the platform for 10 seconds between trials and received a rest period, in a cage located in the testing room, for approximately five minutes between each trial. If an animal was unable to locate the platform within 60 seconds it was placed on the platform for 10 seconds. Each rat completed 10 trials on the first day of testing and five trials on the subsequent day.

Presurgery Training: Acquisition of Place-Memory Problem. All rats were trained on a place-memory version of the task either approximately 72 or 3 hours prior to surgery. The platform was positioned in the centre of the north-west quadrant of the pool with the clear end up, resting approximately 2 cm below the surface of the water and. The rats could not see the platform but they could learn its location relative to the visual and auditory extramaze cues. Each rat completed a total of 16 trials in a single training session.

The final trial was a probe trial, hereafter referred to as the "presurgery probe", during which the platform was removed from the maze and the rats were allowed to swim in the pool for 20 seconds. This was done to assess how well the rats had learned the position of the hidden platform. The proportion of time the rats spent in the correct maze quadrant and the number of times they passed over the platform location was

recorded during the probe trial.

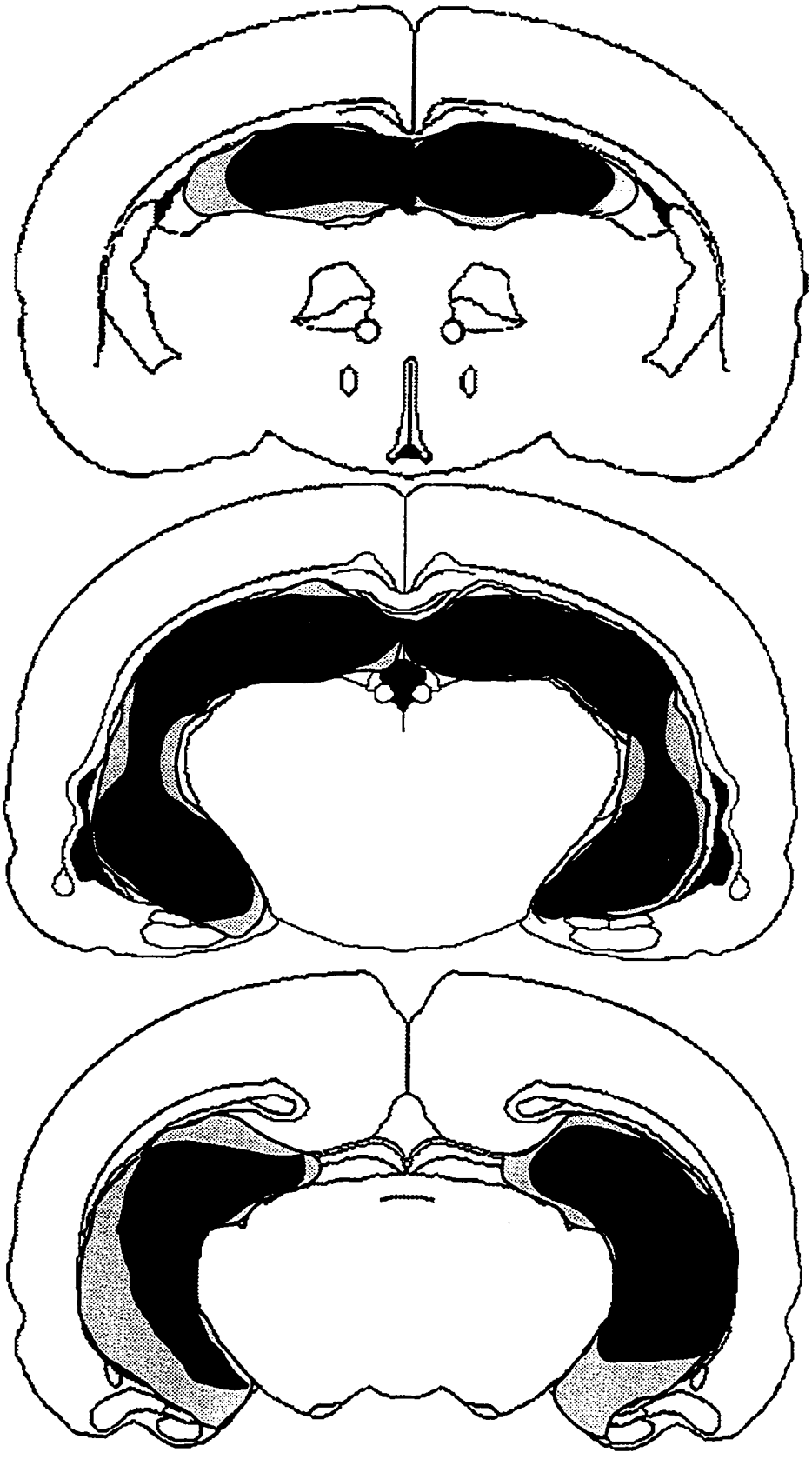
Postsurgery Testing: Retention and Reacquisition of Place-Memory Problem. Rats were tested for their retention and reacquisition of the place-memory problem that had been learned prior to surgery. Testing commenced after the rats had completed the postsurgery object discrimination testing. The testing procedure was identical to that used in presurgery training except that both the second and sixteenth trials were probe trials. The second trial probe, hereafter referred to as the "early postsurgery probe", assessed the rats' retention of the previously learned platform location and was used as an index of retrograde amnesia. The sixteenth trial probe, hereafter referred to as the "late postsurgery probe", assessed how well the rats relearned the location of the hidden platform and was, therefore, used to index a combination of retrograde and anterograde memory.

Results

Histology

Figure 2 shows the location and extent of the largest and smallest of the hippocampal lesions. The NMDA injections caused extensive cell loss in all principle subfields of the hippocampus and dentate gyrus. This loss was most pronounced in the dorsal hippocampus. There was some variability among rats in the extent of damage to

Figure 2. The location and extent of the hippocampal lesions is illustrated in coronal sections. The top section is located 2.8 millimetres (mm) posterior to Bregma, the middle section is 4.3 mm posterior to Bregma and the bottom section is 5.8 mm posterior to Bregma. In all three sections, the lightly shaded area indicates the largest lesion and the darkly shaded area indicates the smallest lesion.



Bregma -2.8

Bregma -4.3

Bregma -5.8

the ventral hippocampus as well as in the extent of extrahippocampal damage. Some rats sustained damage to one or more of the subiculum, alveus, and fimbria. In all cases, however, this damage was incomplete. In addition, the injection cannulae caused some parietal cortex and corpus callosum damage in all rats.

Object-Discrimination Problems

One rat in the HPC group displayed abnormal behaviour in the testing apparatus during postsurgery testing and did not complete the object discrimination testing. Specifically, this rat tended to remain in one goal end and did not to be appear motivated to complete the postsurgery testing. The data collected from this rat are not included in the object discrimination results.

Presurgery Results: Acquisition of Presurgery Object-Discriminations. The two groups of rats were well-matched in terms of their performance on the presurgery object-discrimination problems. Figure 3 shows the mean number of trials to criterion for the HPC and SHAM groups on the three presurgery object discrimination problems. A repeated measures ANOVA with lesion as a between-subjects factor and problem as a within-subjects factor revealed no significant difference between HPC and SHAM rats in the number of trials required to reach criterion, $F(1,21)<1$, no difference in acquisition rates among the three problems $F(2,42)<1$, and no significant interaction between these two factors, $F(2,42)<1$ (see Table 1 in Appendix B).

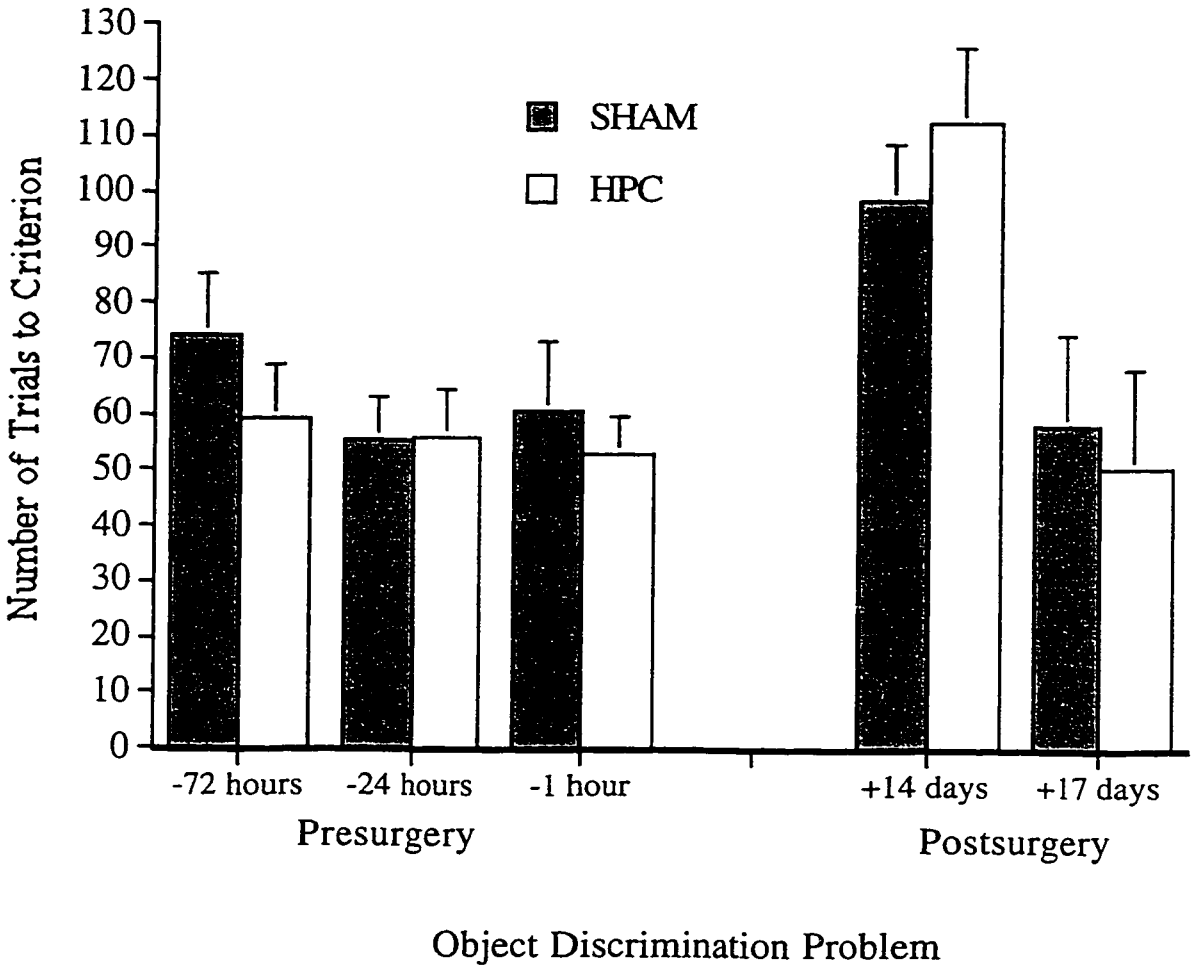


Figure 3. Mean number of trials (+*SE*) required by HPC and SHAM rats to reach criterion during original learning of all object discrimination problems.

Postsurgery Results: Acquisition of Postsurgery Object-Discrimination. Although the HPC and SHAM rats did not differ in their acquisition of the postsurgery problems, both groups required more trials to learn the first postsurgery problem than the second postsurgery problem. Figure 3 shows the mean number of trials to criterion for the HPC and SHAM groups on the two postsurgery object discrimination problems. HPC and SHAM rats did not differ in the number of trials required to reach criterion on the first postsurgery problem, $t(21)=.84$, $p>.05$. Acquisition of this first postsurgery problem was compared to acquisition of the presurgery problems. A repeated measures ANOVA with lesion as a between-subjects factor and problem as a within-subjects factor revealed a significant effect of problem, $F(3,63)=10.12$, $p<.05$, such that both groups required more trials to reach criterion on the first postsurgery problem compared to the -72 hour problem, $t(22)=3.6$, $p<.05$, the -24 hour problem, $t(22)=4.86$, $p<.05$, and the -1 hour problem, $t(22)=4.45$, $p<.05$ (see Table 2 in Appendix B).

Five rats from each group learned a second postsurgery problem. T-tests revealed that both groups required fewer trials to reach criterion on the second postsurgery problem than the first postsurgery problem, $t(9)=3.36$, $p<.05$, but that acquisition of this problem did not differ from acquisition of the -72 hour problem, $t(9)=1.89$, $p>.05$, the -24 hour problem, $t(9)=.17$, $p>.05$, or the -1 hour problem, $t(9)=.21$, $p>.05$. HPC and SHAM rats did not differ in the number of trials required to reach criterion on this second postsurgery problem, $t(9)=.33$, $p>.05$.

Postsurgery Results: Retention of Presurgery Object-Discriminations. Overall, HPC and SHAM rats did not differ in their retention of the presurgery object discriminations. Figure 4 shows the number of correct choices made by the HPC and SHAM groups on the three presurgery object discrimination problems summed across the three postsurgery retention test days. A repeated measures ANOVA with lesion as a between-subjects variable and with discrimination problem and test day as within-subjects variables revealed a significant effect of test day, $F(2, 42) = 9.21$, $p < .05$, indicating that the average number of correct choices increased significantly across test days. In addition, HPC rats tended to make fewer correct choices than did SHAM rats but this was not statistically significant, $F(1,21) = 2.97$, $p = .09$. There were no significant differences among the three problems, $F(2,42) = 1.0$, $p > .05$, and none of the interactions were statistically significant (see Table 3 in Appendix B).

The smallest unit used in the preceding analysis was the number of correct choices within a block of 10 trials. This number of trials may have allowed the lack of an anterograde deficit to overshadow the presence of a retention deficit. That is, 10 trials may have been sufficient for the rats to relearn the object discrimination problems thereby concealing any retention deficit they may have had. A possibly less confounded index of retention can be obtained by examining performance on only the first few postsurgery trials. Figure 5 shows the mean number of correct choices on the first block of 5 trials for each of the object discrimination problems. A repeated measures ANOVA with lesion as a between-subjects variable and problem as a within-subjects variable revealed no

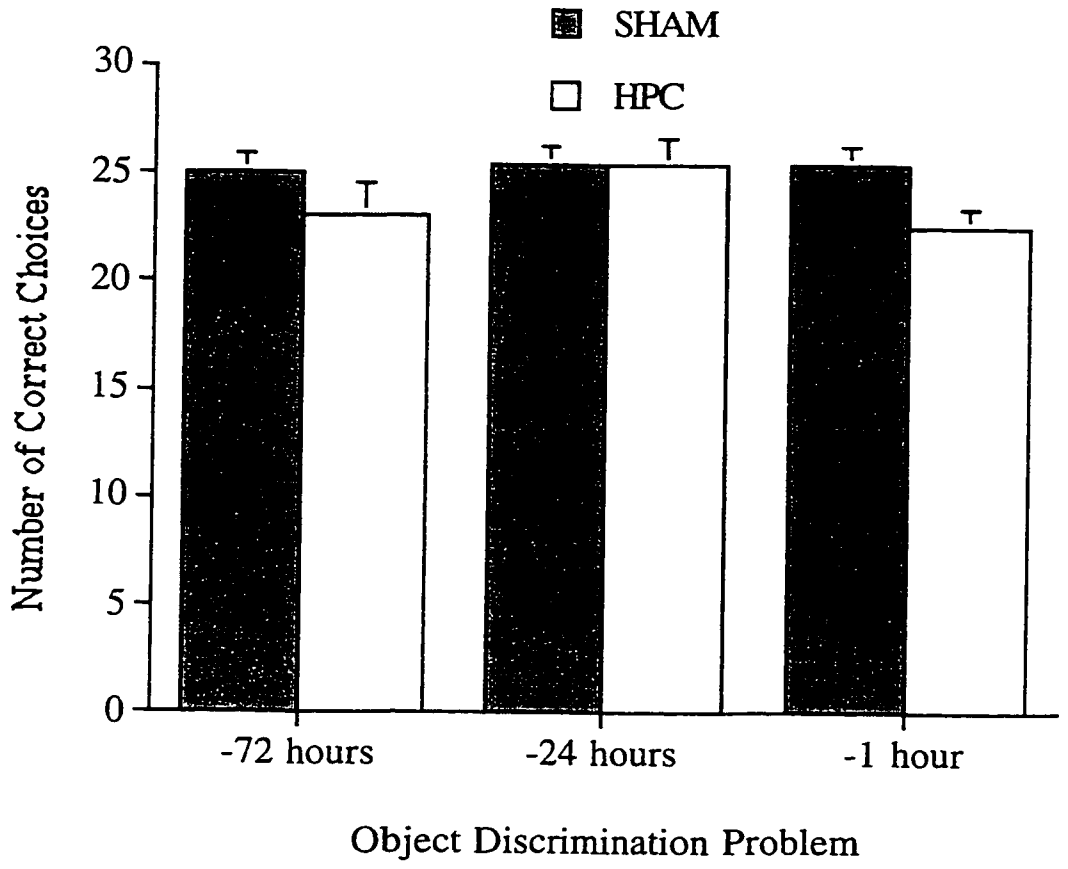


Figure 4. Mean number of correct choices (+*SE*) made by HPC and SHAM rats during retention testing for the presurgery object discrimination problems.

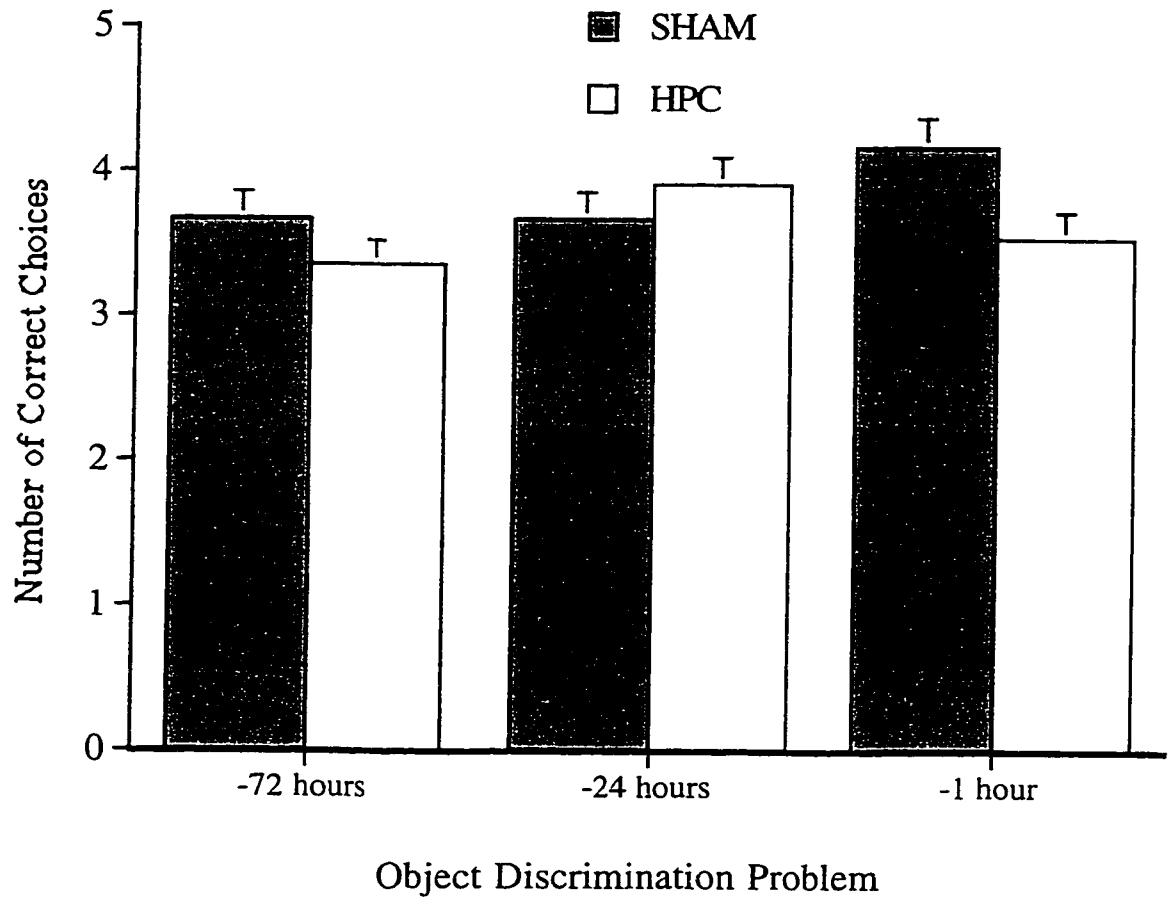


Figure 5. Mean number of correct choices (+*SE*) made by HPC and SHAM rats on the first 5 trials of retention testing.

significant main effects of lesion, $F(1,21)<1$, or problem, $F(2,42)<1$, and no significant interaction between these two variables, $F(2,42)<1$ (see Table 4 in Appendix B).

Place-memory Problem

Preliminary Training: Acquisition of the visible-platform task. The four groups were well-matched in terms of their performance on the visible-platform task in the water maze. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects variables and trial as a within-subjects variable revealed a significant effect of trial, $F(14,112)=16.84$, $p<.05$, indicating that the average escape latency (ie. the time required to locate the hidden platform) decreased across trials. None of the remaining main effects or interactions were statistically significant (see Table 5 in Appendix B).

Presurgery Results: Acquisition of Place-memory Problem. There were some groups differences in the ability to acquire the place-memory problem. Figure 6 shows the mean escape latencies on the presurgery place-memory problem for all four groups of rats. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects factors and trial as a within-subjects factor revealed a significant effect of trial, $F(14, 280) = 7.52$, $p <.05$, indicating that the average escape latency decreased across trials. In addition, there were marginally nonsignificant effects of lesion,

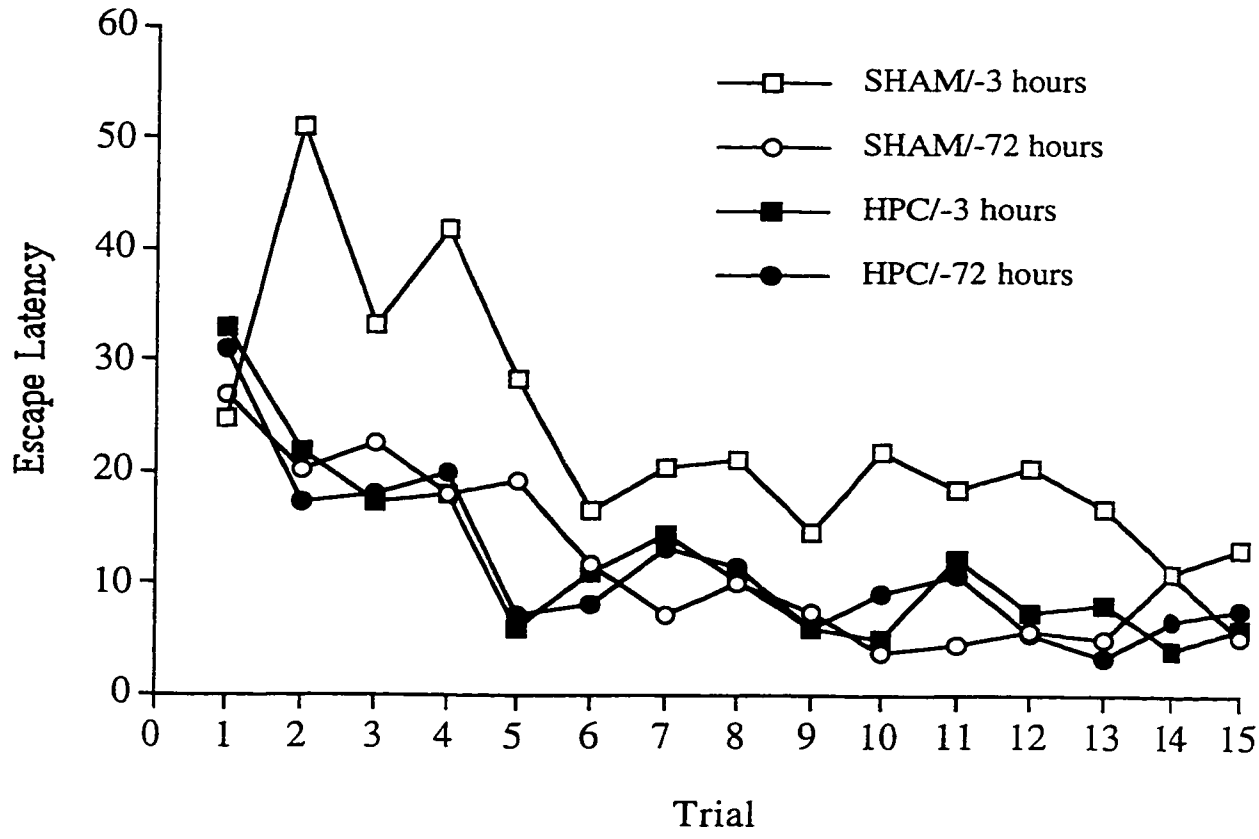


Figure 6. Mean latencies required to locate the hidden platform on each presurgery training trial. Results are shown for all four groups. *SE*'s (not shown) ranged from 0.6 to 10.9.

$F(1,20)=3.51$, $p=.08$, learning-to-lesion interval, $F(1,20)=3.7$, $p=.07$, and lesion x learning-to-lesion interval interaction, $F(1,20)=3.27$, $p=.09$ (see Table 6 in Appendix B). As shown in Figure 6, these marginally nonsignificant effects are due to the relatively poor performance of the SHAM/-3 hour group in comparison with the other three groups.

The relatively poor performance of the SHAM/-3 hour group continued on the presurgery probe trial. The rats' performance was compared to what would have been expected according to chance (ie. spending 25% of their time in the correct quadrant). Three of the groups, including the SHAM/-72 hour group, $t(5)=4.82$, $p<.05$, the HPC/-72 hour group, $t(5)=10$, $p<.05$, and the HPC/-3 hour group, $t(5)=5.84$, $p<.05$ demonstrated significantly above-chance performance. As shown in Figure 7, the performance of the SHAM/-3 hour group was near that of the other groups although it did not differ significantly from chance, $t(5)=2.46$, $p>.05$. An ANOVA with lesion and learning-to-lesion interval as between-subjects variables revealed no significant effect of lesion, $F(1,20)<1$, no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant interaction between these two variables, $F(1,20)<1$ (see Table 7 in Appendix B).

Postsurgery Results: Swim Latencies. HPC rats were impaired relative to SHAMS during postsurgery testing of the place-memory problem. Figure 8 shows the average postsurgery escape latencies for each of the four groups. A repeated measures ANOVA with lesion and learning-to-lesion as between-subjects factors and trial as a within-subjects factor revealed a significant effect of lesion, $F(1, 20) = 42.66$, $p < .05$, such

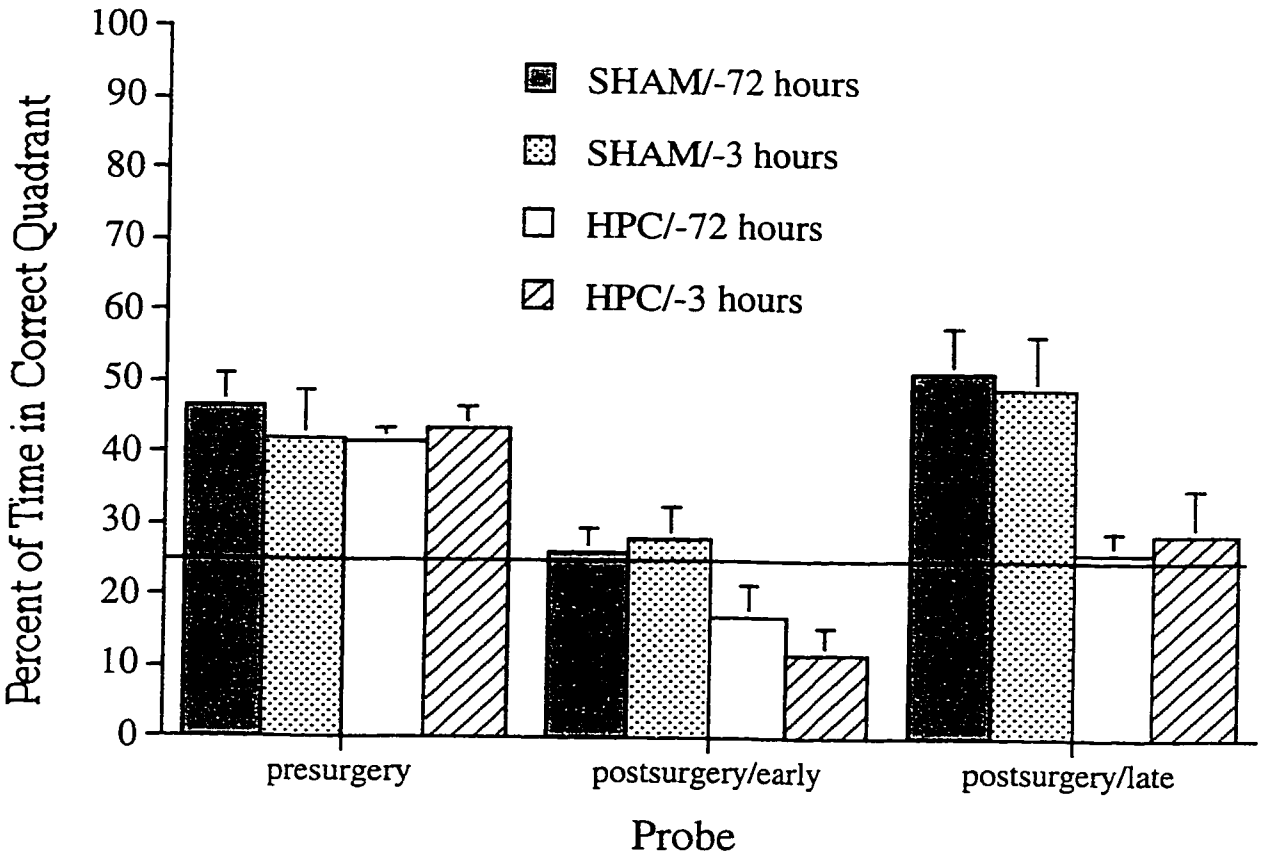


Figure 7. The percent of time (+*SE*) spent in the correct maze quadrant during the three probe trials. Results are shown for all four groups. The horizontal line represents chance performance.

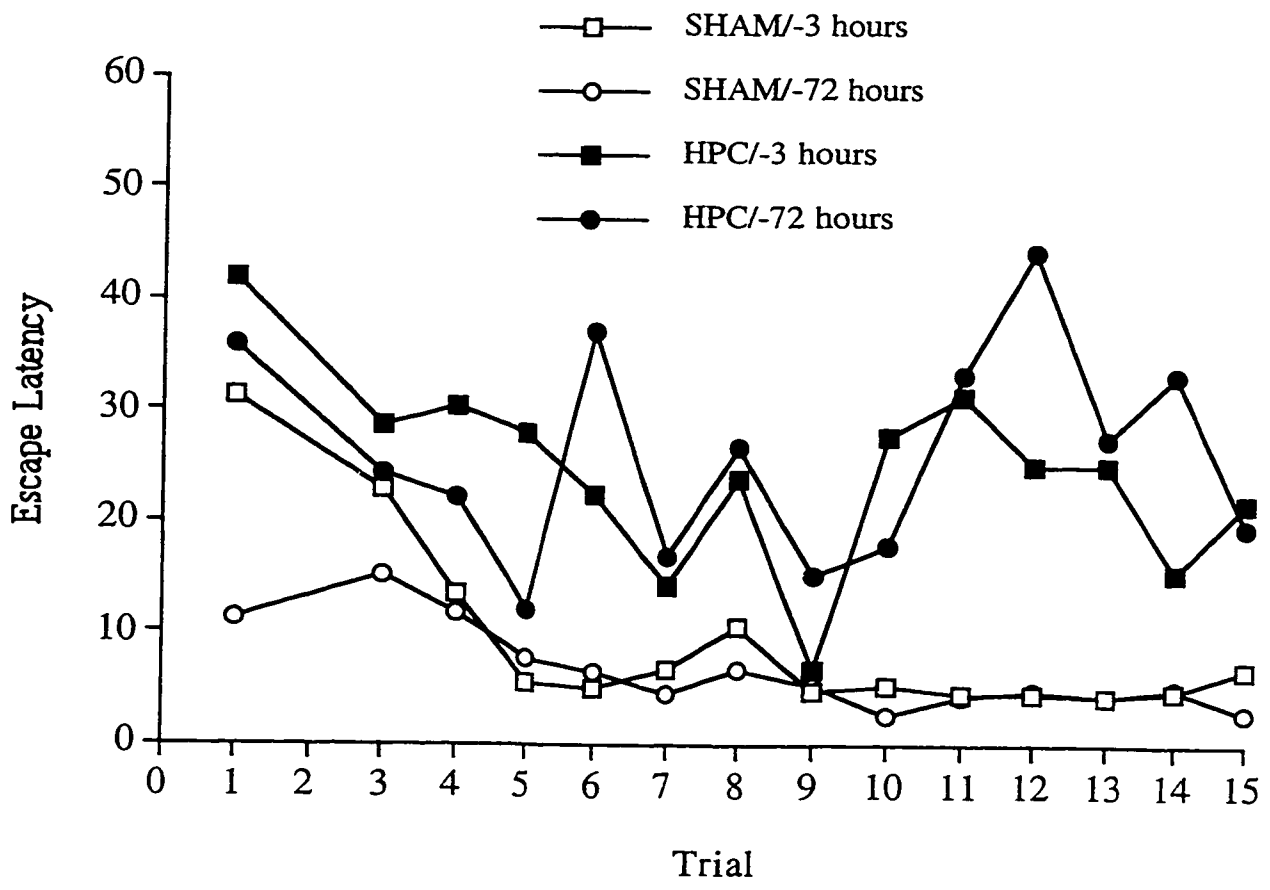


Figure 8. Mean latencies required to locate the hidden platform on each postsurgery testing trial. Results are shown for all four groups. *SE*'s (not shown) range from 4.1 to 12.2.

that HPC rats required longer latencies to locate the hidden platform compared to SHAM rats. There was also a significant effect of trial, $F(13, 260) = 3.05$, $p < .05$, indicating that the average escape latency decreased across trials. None of the remaining main effects or interactions were statistically significant (see Table 8 in Appendix B).

Postsurgery trial 1 escape latencies were compared to presurgery trial 1 escape latencies to assess how well the rats remembered the previously learned platform location. As shown in Figure 9, the SHAM/-72 hour group had a shorter average escape latency on postsurgery trial 1 than presurgery trial 1. This effect was not, however, statistically significant, $t(5)=1.5$, $p>.05$. The remaining three groups exhibited statistically nonsignificant increases in swim latencies, all p's $>.05$. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects factors and trial (pre- vs postsurgery) as a within-subjects factor revealed no significant main effects or interactions. The HPC rats tended to have longer escape latencies than did SHAM rats, but this difference did not reach the criterion of statistical significance (see Table 9 in Appendix B).

Postsurgery Results: Probe Trials. The HPC groups tended to spend less time in the correct maze quadrant during both of the postsurgery probe trials than did the SHAM groups. Figure 7 shows the percentage of time spent in the correct maze quadrant by each of the four groups during the probe trials.

The early postsurgery probe, which was conducted on the second trial, was

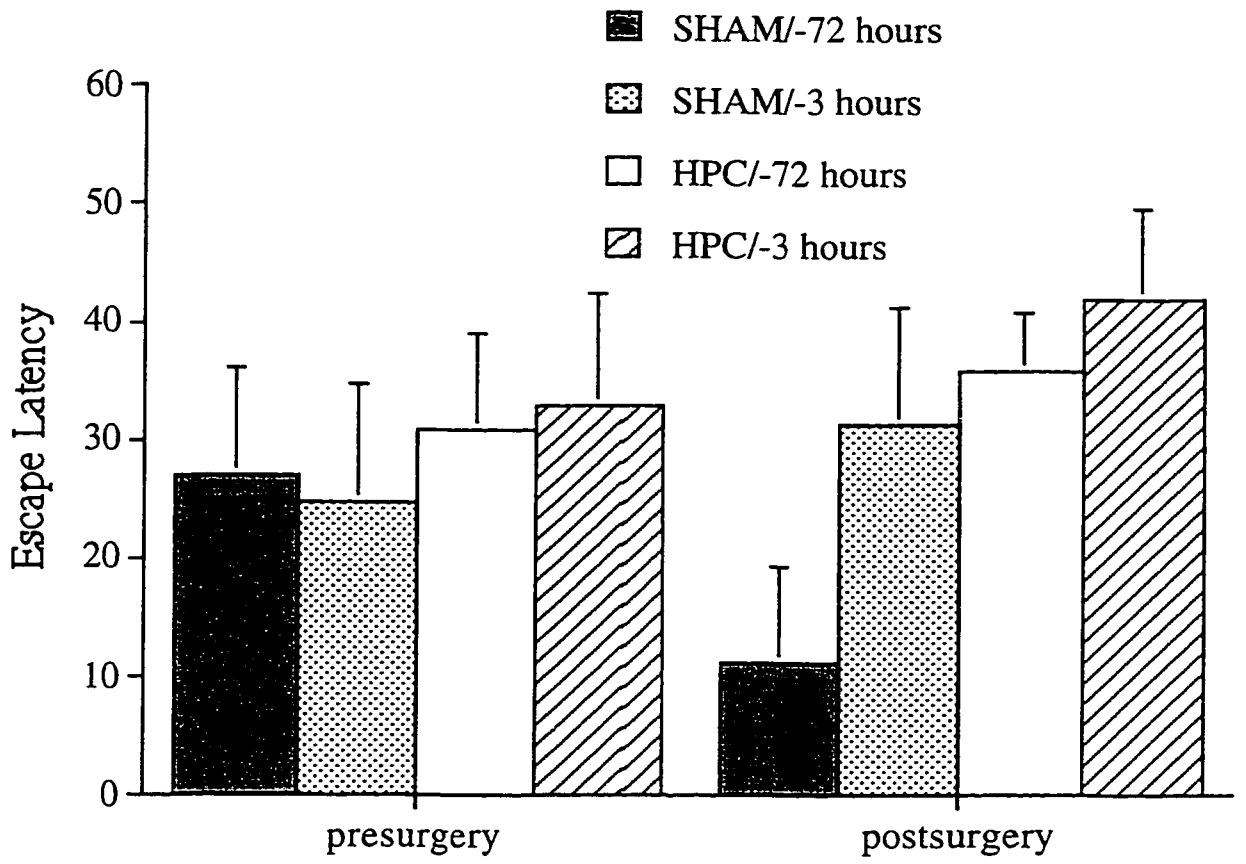


Figure 9. Mean latencies (+*SE*) required to locate the hidden platform on the first presurgery and the first postsurgery trials. Results are shown for all four groups.

designed to assess the rats' retention of the previously learned platform location. An ANOVA with lesion and learning-to-lesion interval as between-subjects factors revealed a significant effect of lesion, $F(1,20)=9.64$, $p<.05$, indicating that SHAM rats spent more time in the correct quadrant than did HPC rats. There was no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant lesion X learning-to-lesion interval interaction, $F(1,20)<1$ (see Table 10 in Appendix B). In addition, the performance of all four groups was compared to what would have been expected by chance (ie. 25% of their time in the correct quadrant). Three of the groups did not differ from chance performance, including the SHAM/-72 hour group, $t(5)=.37$, $p>.05$, the SHAM/-3 hour group, $t(5)=.64$, $p>.05$, and the HPC/-72 hour group, $t(5)=1.76$, $p>.05$. The HPC/-3 hour group spent significantly less time in the correct quadrant than would have been expected by chance, $t(5)=3.5$, $p<.05$.

The late postsurgery probe, which was conducted on the last trial, was designed to assess reacquisition of the platform location. An ANOVA with lesion and learning-to-lesion interval as between-subjects variables revealed a statistically significant effect of lesion, $F(1,20)=13.88$, $p<.05$, indicating that SHAM rats spent a greater percentage of their time in the correct quadrant than did HPC rats. There was no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant lesion X learning-to-lesion interval interaction, $F(1,20)<1$ (see Table 11 in Appendix B). The performance of all four groups was compared to what would have been expected by chance. Both the SHAM/-72 hour group, $t(5)=4.14$, $p<.05$, and the SHAM/-3 hour group, $t(5)=3.16$, $p<.05$,

demonstrated significantly above-chance performance. The performance of the HPC/-72 hour group, $t(5)=.32$, $p>.05$, and the HPC/-3 hour group, $t(5)=.59$, $p>.05$, did not differ from chance.

The rats' performance on the postsurgery probes was compared to that on the presurgery probe. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects variables and probe trial (presurgery vs early postsurgery vs late postsurgery) as a within-subjects variable revealed a significant effect of lesion, $F(1,20)=13.16$, $p<.05$, a significant effect of probe trial, $F(2,40)=29.36$, $p<.05$, and a significant lesion X probe trial interaction, $F(2,40)=5.73$, $p<.05$ (see Table 12 in Appendix B). Simple effects analysis of the lesion X probe trial interaction revealed significant differences between the HPC and SHAM groups on both the early postsurgery, $F(1,23)=10.14$, $p<.05$, and the late postsurgery probe trials, $F(1,23)=15.14$, $p<.05$, but no differences between the two groups on the presurgery probe, $F(1,23)<1$ (see Table 13 in Appendix B). Further analysis of the significant main effect of probe trial revealed that rats spent less time in the correct quadrant during the early postsurgery probe compared to both the presurgery probe, $t(23)=8.14$, $p<.05$, and the late postsurgery probe, $t(23)=5.54$, $p<.05$, but there was no difference between the presurgery and the late postsurgery probes, $t(23)=1.15$, $p>.05$.

Discussion

The main findings were that lesions of the hippocampal formation: 1)caused

deficits on a place-memory problem, although it is not clear whether this deficit reflects retrograde or anterograde amnesia, 2) did not cause anterograde amnesia for object discriminations, as demonstrated by the lack of difference between SHAM and HPC rats in acquiring the postsurgery object discrimination problems and 3) did not cause significant retrograde amnesia, as demonstrated by the lack of a significant difference between HPC and SHAM rats in the number of correct choices made during retention testing.

Interpretation of the results of the place-memory testing is complicated by the fact that SHAM rats did not display good retention of this problem. None of the groups demonstrated a preference for the correct maze quadrant on the early postsurgery probe, that was designed to assess how well the rats retained the place-memory problem they had learned prior to surgery. Also, none of the groups showed a significant decrease in escape latency from the first presurgery trial to the first postsurgery trial. In sum, neither the SHAM nor the HPC rats showed good retention of the place-memory problem they had learned prior to surgery. It is, therefore, impossible to determine whether the hippocampal lesions caused retrograde amnesia for spatial information.

Nevertheless, HPC rats were impaired on the place-memory problem. SHAM rats, but not HPC rats, reacquired the place-memory problem during postsurgery testing. This was particularly evident on the late postsurgery probe, that was conducted on the last trial of postsurgery testing. SHAM rats exhibited a preference for the correct quadrant and spent significantly more time in the correct quadrant than did HPC rats.

There was no significant difference between HPC and SHAM rats in the acquisition rates for the postsurgery object discriminations. Although both groups required more trials to acquire the first postsurgery problem than the second postsurgery problem, there was no significant difference between the groups on either one of these problems. It therefore appears that hippocampal lesions do not cause anterograde amnesia for object discrimination problems.

Overall, HPC rats showed good retention of the object discrimination problems they had learned prior to surgery. Although their scores were moderately lower than those obtained by SHAM rats, the mean retention scores obtained by HPC rats on each of the three presurgery problems were above chance, indicating that the HPC rats had not forgotten these problems. Moreover, there was no significant interaction between lesion and the time at which the problems were originally learned. That is, the retention scores of the HPC rats did not vary significantly according to the time at which the problems were originally learned. These results suggest that the hippocampus does not play a necessary role in the consolidation of long-term memory.

In sum, the main findings of Experiment 1A were that 1) hippocampal lesions did not cause anterograde amnesia for object discrimination problems, and 2) hippocampal lesions caused deficits on a spatial memory task. The results did not provide convincing evidence that the hippocampal formation is involved in consolidation of either spatial or nonspatial memory.

EXPERIMENT 1B

As shown in Figures 4 and 5, rats with hippocampal lesions showed good retention of the object discrimination problems they had acquired prior to surgery. Their scores, however, were moderately lower than those obtained by SHAM rats. Further, this modest difference between the two groups appears to be largely due to the HPC rats' relatively poor performance on the object discrimination learned 1 hour prior to surgery. Rats in group HPC, but not those in group SHAM received injections of diazepam, following surgery, in order to prevent seizures. The following experiment was designed to investigate the possibility that the small group difference in retention of the -1 hour problem was due to the amnestic effects of diazepam (Andrews, Grutzner & Stephens, 1996).

Method

Subjects

The subjects were 6 experimentally naive, adult male, Long-Evans rats (Charles River, Quebec) that weighed between 325 and 375 grams at the start of the experiment. The housing and feeding conditions were identical to those used in Experiment 1A.

Apparatus

The object-discrimination testing apparatus was identical to that used in Experiment 1A. The object discriminanda consisted of a pair of objects, selected so that

they differed in a number of visible attributes, including size, shape and colour. The objects were large enough to cover the food wells but small enough and light enough to be easily displaced by the rats.

Preliminary Training

The preliminary training procedure was identical to that used in Experiment 1A.

Pretreatment Training: Acquisition of Pretreatment Object-Discrimination

Following completion of preliminary training, each rat then began the principal phase of the experiment. The behavioral procedures used during pretreatment testing were very similar to those used in Experiment 1A. Rats learned one object discrimination problem within a single training session. The rats were required to complete a minimum of 30 trials and training continued until the rat displace S+ on ten consecutive trials. For the first 15 trials, a food pellet was placed beneath S+ prior to the guillotine door being raised. In addition, if the rat initially displaced S-, it was allowed to correct its error by displacing S+ and thereby retrieve the food pellet. For all remaining trials the rats were allowed to displace only one of the two objects and were not rewarded unless S+ was displaced. The same pair of objects was used for all rats. Object A was S+ for two rats in each group and object B was S+ for the remaining rat in each group.

Drug Treatment

All rats were anaesthetized with sodium pentobarbitol (Somnotol, 65 mg/kg) 45 minutes after reaching criterion on the pretreatment object-discrimination problem. Rats in group VAL (n=3) were injected with 1 mg of Diazepam (Hoffmann-La Roche, Mississauga, Ontario, Canada) upon awakening from the anesthetic. VAL rats received a second injection of Diazepam (1.5 mg) three hours later. These anaesthetic and diazepam administration procedures correspond with those used in Experiment 1A for the HPC rats and the dosage used was the largest dosage used in Experiment 1A. Saline control rats (group SAL, n=3) were injected with saline upon awakening from the anesthetic (2 cc) and again three hours later (3 cc).

Posttreatment Testing: Acquisition of Postsurgery Object-Discrimination

Testing commenced two weeks after drug treatment. The posttreatment testing procedures were very similar to those used in Experiment 1A. On the first day of testing the rats were tested for their ability to acquire a new object discrimination problem, using the same single session procedure and learning criterion of ten consecutive trials that had been used for the pretreatment object discrimination problem. Upon reaching criterion, the rats were then returned to their home cage for a period of approximately 15 minutes before beginning retention testing.

Posttreatment Testing: Retention of Pretreatment Object Discrimination

Retention testing commenced on the first day of posttreatment testing

approximately 15 minutes after learning the post-treatment object discrimination problem and continued for three days. Rats received one testing session per day, consisting of 10 trials of the problem they had learned prior to treatment. On the second and third day of retention testing, the rats were first re-tested on the post-treatment object discrimination problem they had learned on the first day of posttreatment testing. This retesting continued until the rats reached a criterion of eight correct out of ten consecutive trials. They were then tested for their retention of the pretreatment object discrimination problem. These procedures correspond with those used in Experiment 1A.

Results

Acquisition of Object-Discrimination Problems.

The treatment groups did not differ in their acquisition of either the pretreatment, $t(4)=.12$, $p>.05$, or the post-treatment, $t(4)=.19$, $p>.05$, object discrimination problems. A repeated measures ANOVA with groups as a between subjects factor and problem as a within subjects factor revealed no significant effects of group, $F(1,4)<1$, or problem, $F(1,4)<1$, and no significant group X problem interaction, $F(1,4)<1$ (see Table 14 in Appendix B).

Retention of Pretreatment Object-Discrimination Problem.

Diazepam did not interfere with the rats' ability to retain the pretreatment

problem. A repeated measures ANOVA with group as a between-subjects factor and test day as a within-subjects factor revealed no significant effect of group, $F(1,4)=0$, no significant effect of test day, $F(2,8)=1.4$, $p>.05$, and no significant group X test day interaction, $F(2,8)<1$ (see Table 15 in Appendix B).

Discussion

The main finding was that diazepam did not cause retrograde amnesia for an object discrimination problem learned 1 hour prior to drug treatment, as demonstrated by the lack of a significant difference between SAL and VAL rats in the number of correct choices made during retention testing. It therefore appears that the modest group difference between HPC and SHAM rats on the retention of object discrimination problems was not due to the fact that the HPC rats had received injections of diazepam following surgery.

EXPERIMENT 2

According to the model put forth by Eichenbaum et al. (1994), the perirhinal cortex is one of the anatomical structures included in the "parahippocampal region" (Eichenbaum et al., 1994). The parahippocampal region and the hippocampal formation are components of a temporal lobe memory system responsible for long- term memory formation. Information is initially processed within the parahippocampal region and then by the hippocampal formation. In this manner, the hippocampal formation relies on information it receives from the parahippocampal region and both of these regions play a role in long-term memory formation. Lesions directed at the perirhinal cortex should, therefore, disrupt long-term memory formation and cause retrograde amnesia.

Large lesions of the temporal lobe, including the hippocampal formation, parahippocampal gyrus, as well as the entorhinal and perirhinal cortices, cause temporally-graded retrograde amnesia for object discriminations in monkeys (Zola-Morgan & Squire, 1990). Selective lesions of the hippocampal formation, however, do not cause retrograde amnesia for object discriminations in either rats (Astur, et al., 1994; Wible, Shiber & Olton, 1992; Wood, Mumby, Pinel & Phillips, 1993; see also experiment 1A) or monkeys (Ridley, Timothy, Maclean & Baker, 1995). It is therefore possible that the retrograde amnesia exhibited by monkeys with large lesions of the medial temporal lobe was due to the damage sustained by the rhinal cortex and not the hippocampal formation. Thornton and Murray (1996) found that combined lesions of the entorhinal and perirhinal cortices caused retrograde amnesia for object discrimination problems in

monkeys. Astur, Mumby and Sutherland (1995), however, found that rats with perirhinal cortex lesions were unimpaired in their retention of preoperatively learned object discrimination problems.

Eichenbaum et al. (1994) also maintain that the mnemonic role of the temporal lobe memory system is quite general with respect to the information content of what is being remembered. For example, memory for both spatial and nonspatial information should be affected by lesions of the medial temporal lobe. This contradicts models in which the mnemonic roles of certain medial temporal lobe structures are dissociable in terms of information type. For example, it has been suggested that the perirhinal cortex plays a preferential role in memory for objects (Mumby & Pinel, 1994; Murray, 1996) and that the hippocampal formation plays a preferential role in memory for spatial location. Lesions of the perirhinal cortex cause impairments on object-recognition tasks in both rats (Ennaceur, Neave & Aggleton, 1996; Mumby & Pinel, 1994) and monkeys (Meunier, Bachevalier, Mishkin & Murray, 1993; Zola-Morgan, Squire, Amaral & Suzuki, 1989). Lesions of the hippocampal formation, however, do not cause impairments on this task in rats (Glenn & Mumby, 1996) or monkeys (O'Boyle, Murray & Mishkin, 1993). These findings contradict models in which the hippocampal formation and perirhinal cortex are considered to be serial components of a unitary memory system. Rather, these findings support the hypothesis that the mnemonic functions of the hippocampal formation and perirhinal cortex are dissociable in terms of the type of information to be remembered (Mumby & Pinel, 1994; Murray, 1996).

If the hippocampal formation relies on information it receives through its afferent connections from the rhinal cortex, then memory impairments that are observed following hippocampal lesions should also be observed following perirhinal cortex lesions (Eichenbaum et al., 1994). Numerous experiments have shown that lesions of the hippocampal formation cause deficits on place-memory tasks in rats (see review by Barnes, 1988). It is not clear what role, if any, the perirhinal cortex plays in spatial memory. Perirhinal cortex lesions have been reported to cause no impairment (Astur, Mumby & Sutherland, 1995; Ennaceur, Neave & Aggleton, 1996; Wiig & Bilkey, 1994a), mild impairment (Wiig & Bilkey, 1994b), and severe impairment (Nagahara, Otto & Gallagher, 1995; Rothblat, Vnek, Gleason & Kromer, 1993) on tests of anterograde memory and no impairment on tests of retrograde memory for spatial information in rats (Astur et al., 1995).

The purpose of this experiment was to assess the effects of perirhinal cortex lesions on retrograde memory for object discrimination problems and spatial information. The procedures used were very similar to those used in Experiments 1A and 1B. Rats were trained on three object discrimination problems. They learned one problem approximately 72 hours prior to surgery, another problem approximately 24 hours prior to surgery, and a third problem approximately 1 hour prior to surgery. They also learned a place-memory task, in which they were required to learn the location of a submerged platform in a pool of water. Each rat learned this task either 3 days or approximately 3 hours prior to surgery. These particular learning-to-lesion intervals were chosen because

they were shorter than those used in previous experiments (eg. Astur et al., 1995). It was predicted that perirhinal cortex lesions would cause retrograde amnesia for object discrimination problems but not for the place-memory problem.

Experiments 1A and 2 are presented as separate experiments for the following reasons: 1) Although the procedures used in Experiments 1A and 2 are very similar, they are not identical and it was expected that the procedural differences would result in differences on test scores obtained by rats in the two experiments, and 2) The object-discrimination testing procedures require the use of a nonautomated task. Rats' performance on the object-discrimination tasks may be susceptible to the consistency with which the experimenter administers the tests. Experiment 1A was the first time that the experimenter had used the testing apparatus. At the start of Experiment 2, however, the experimenter was considerably more experienced at using the object-discrimination testing apparatus and, therefore, was likely more consistent in the manner in which these tasks were administered.

Method

Subjects

The subjects were 24 experimentally naive, adult male, Long-Evans rats (Charles River, Quebec) that weighed between 300 and 350 grams at the start of the experiment. The housing and feeding conditions were identical to those used in Experiment 1A.

Surgery

All rats were anaesthetized with injections of sodium pentobarbitol (Somnotol, 65 mg/kg) 45 minutes after reaching criterion on the last presurgery object discrimination problem. One rat from each of the matched-pairs of rats received a bilateral lesion of the perirhinal cortex (group PRH; n=12). A coronal scalp incision was made and the skull overlying the perirhinal cortex was exposed. A hole was cut into the skull with a drill and the dura overlying the rhinal fissure was incised. The perirhinal cortex was then aspirated using a vacuum pump attached to a glass Pasteur pipette. The resulting cavity was then filled with Gelfoam (Upjohn Company, Don Mills, Ontario, Canada) and the skin was sutured. Sham surgeries were performed on the remaining half of the rats (group SHAM; n=12). These rats received coronal scalp incisions, thus exposing the skull. The skin was then sutured. All rats received antibiotic following surgery (Ayercillin, 15,000 units, i.m.).

Object-Discrimination Problems: Apparatus & Procedures

Apparatuses. The object-discrimination testing apparatus and place-memory testing apparatus were identical to those used in Experiment 1A. The object discriminanda used in this experiment were different from those used in Experiment 1A but they were selected in the same manner.

Procedures. Overall, the procedures used in this experiment are very similar to those used in Experiment 1A. The following procedures were identical to those used in Experiment 1A: 1) preliminary object discrimination training, 2) postsurgery retention testing of the presurgery object discriminations, 3) acquisition of the place-memory problem, as well as 4) retention and reacquisition testing of the place-memory problem. The procedures used for the following phases of testing were identical to those used in Experiment 1A with the following exceptions: 1) during acquisition of the presurgery object discriminations, the order in which pairs of objects were used as discriminanda was counterbalanced across matched pairs of rats. That is, the particular pair of objects used for each of the object discrimination problems varied in a predetermined manner. 2) During acquisition testing of the postsurgery object discriminations, all rats learned the first postsurgery problem. Eleven SHAM and nine PRH rats learned the second postsurgery problem. 3) All rats received habituation in the water maze prior to learning the place-memory problem.

Results

Histology

All of the rats in groups PRH sustained bilateral damage to the perirhinal cortex. Figure 10 shows the a lateral view of the largest and smallest bilateral lesions sustained by PRH rats. Figure 11 shows the largest and smallest PRH lesions in coronal sections. In addition to perirhinal cortex damage, all of the rats sustained some damage to the

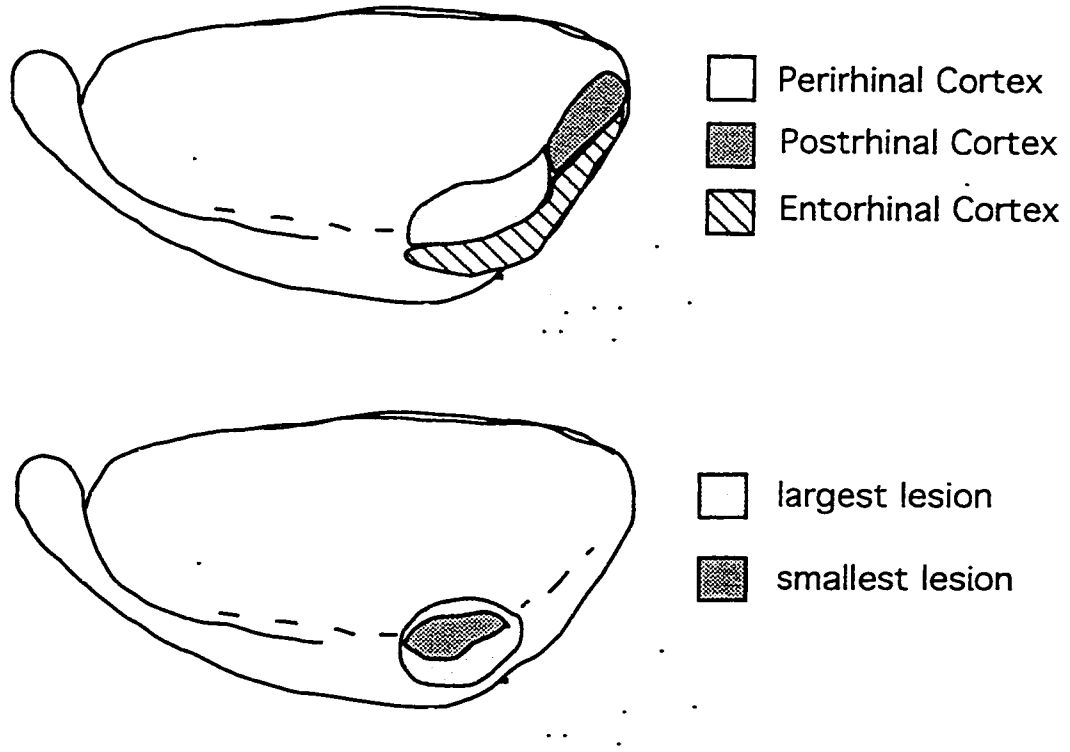
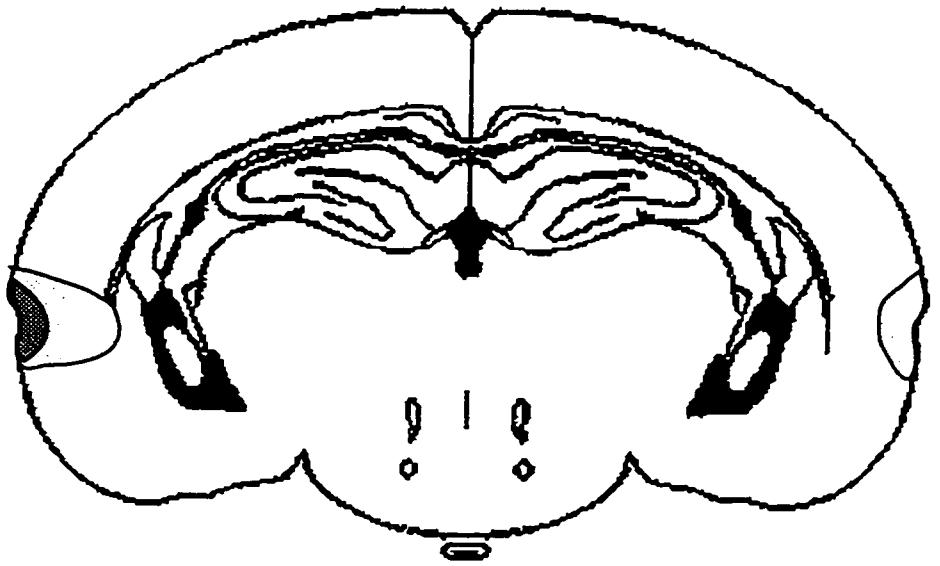
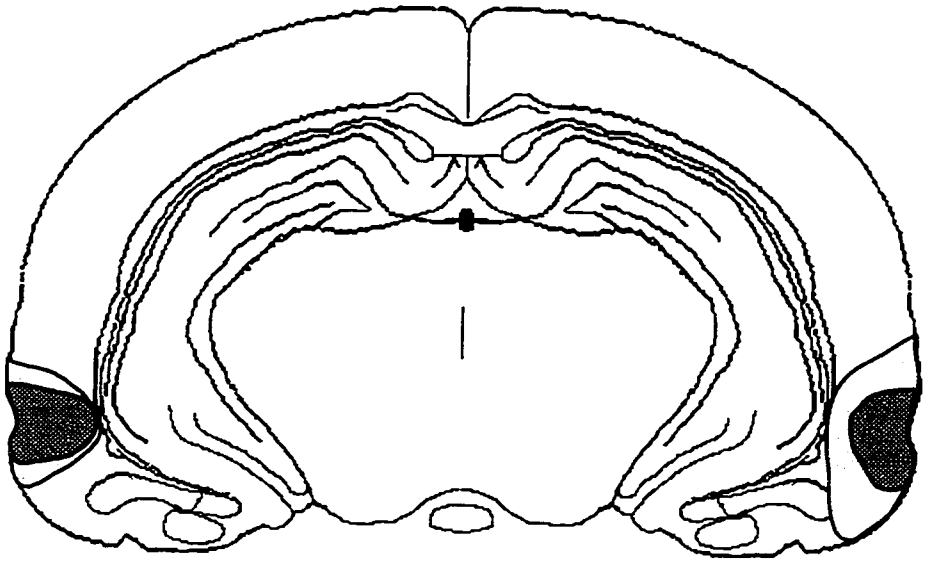


Figure 10. The top panel shows the estimated locations of the perirhinal, postrhinal and entorhinal cortices in the rat brain (Burwell, Witter & Amaral, 1995). The bottom panel shows a lateral view of the smallest and largest lesions sustained by PRH rats.

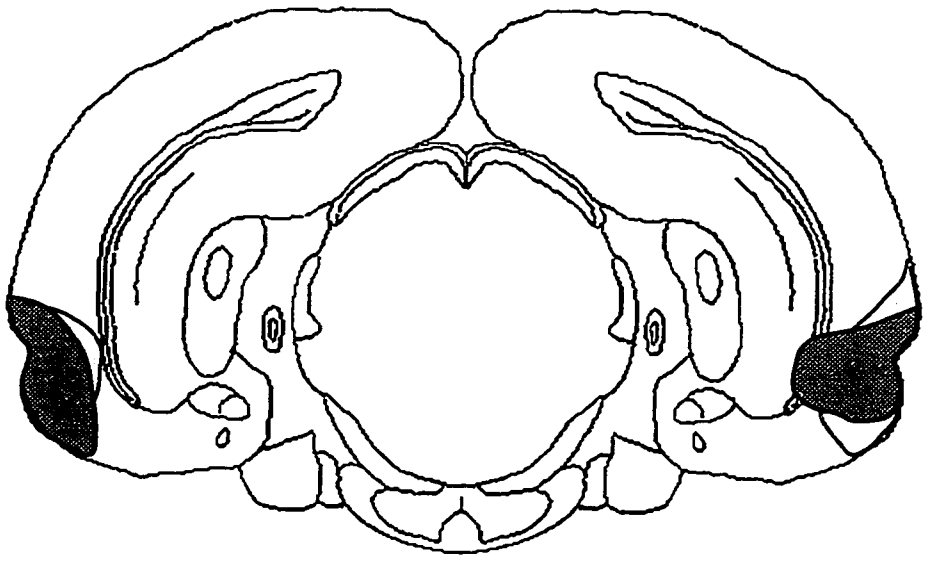
Figure 11. The location and extent of the perirhinal cortex lesions in coronal sections. The top section is located 3.8 mm posterior to Bregma, the middle section is 5.3 mm posterior to Bregma and the bottom section is 6.8 mm posterior to Bregma. In all three sections, the lightly shaded area indicates the largest lesion and the darkly shaded area indicates the smallest lesion.



Bregma -3.8



Bregma -5.3



Bregma -6.8

entorhinal cortex, although most of this region was spared. Some rats also sustained limited, unilateral damage to temporal association cortex areas Te2 and Te3. Seven rats sustained a small amount of unilateral damage to the ventral portion of the CA1 field of the hippocampus.

Object Discrimination Problems

Presurgery Results: Acquisition of Presurgery Object-Discriminations. The two groups of rats were well matched in terms of their performance on the presurgery object-discrimination problems. Figure 12 shows the mean number of trials to criterion for the PRH and SHAM groups on the three presurgery object discrimination problems. A repeated measures ANOVA with lesion as a between-subjects variable and problem as a within-subjects variable revealed no significant difference between PRH and SHAM rats in the number of trials required to reach criterion, $F(1,22)<1$, no difference in acquisition rates among the three problems, $F(2,44)<1$, and no significant interaction between these two variables, $F(2,44)<1$ (see Table 16 in Appendix B).

Postsurgery Results: Acquisition of Postsurgery Object-Discriminations. Figure 12 shows the mean number of trials to criterion for the PRH and SHAM groups on the two postsurgery object-discrimination problems. PRH rats required more trials to reach criterion on the first postsurgery problem than did SHAM rats, $t(22)=2.16$, $p<.05$.

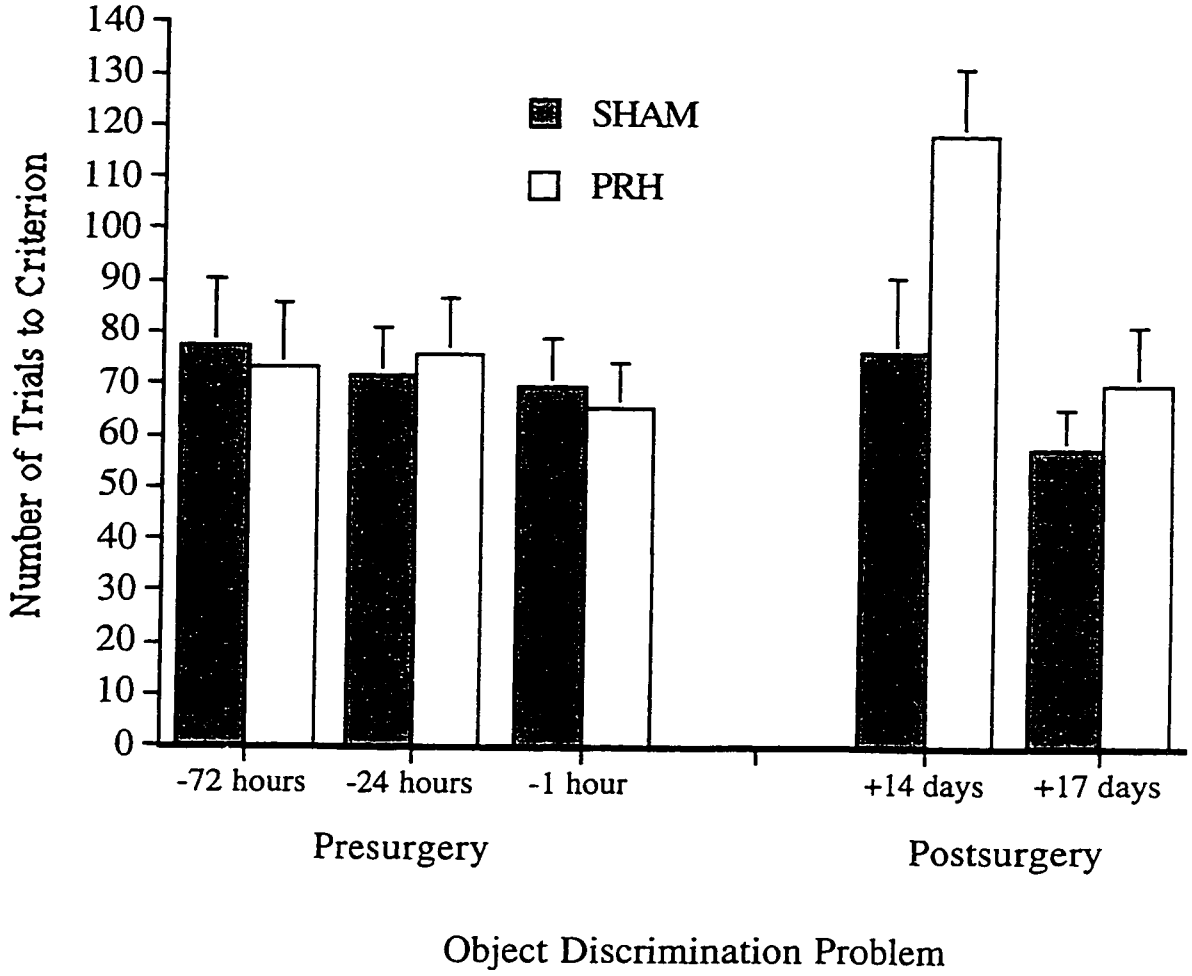


Figure 12. Mean number of trials (+*SE*) required by PRH and SHAM rats to reach criterion during original learning of all object discrimination problems.

Acquisition of this first postsurgery problem was compared to acquisition of the presurgery problems in a repeated measures ANOVA with lesion as a between-subjects factor and problem as a within-subjects factor (see Table 17 in Appendix B). This analysis revealed no significant main effects of either lesion, $F(1,22)=1.52$, $p>.05$, or problem, $F(3,66)=2.45$, $p>.05$, and no significant interaction between these two variables, $F(3,66)=1.74$, $p>.05$.

Eleven SHAM and nine PRH rats learned a second postsurgery problem. PRH and SHAM rats did not differ in their acquisition of this second postsurgery problem, $t(18)=.91$, $p>.05$. Acquisition of this second problem was compared to acquisition of the first postsurgery problem as well as the presurgery problems in a repeated measures ANOVA with lesion as a between-subjects variable and problem as a within-subjects variable (see Table 18 in Appendix B). This analysis revealed no significant main effects of either lesion, $F(1,18)=1.50$, $p>.05$, or problem, $F(4,72)=1.92$, $p>.05$, and no significant interaction between these two variables, $F(4,72)<1$.

Postsurgery Results: Retention of Presurgery Object-Discriminations. PRH and SHAM rats did not differ in their retention of the presurgery problems and there were no differences between the three problems in terms of how well they were retained. Figure 13 shows the mean number of correct choices made by the PRH and SHAM groups on the three presurgery object discrimination problems summed across the three test days. A repeated measures ANOVA with lesion as a between-subjects variable and with

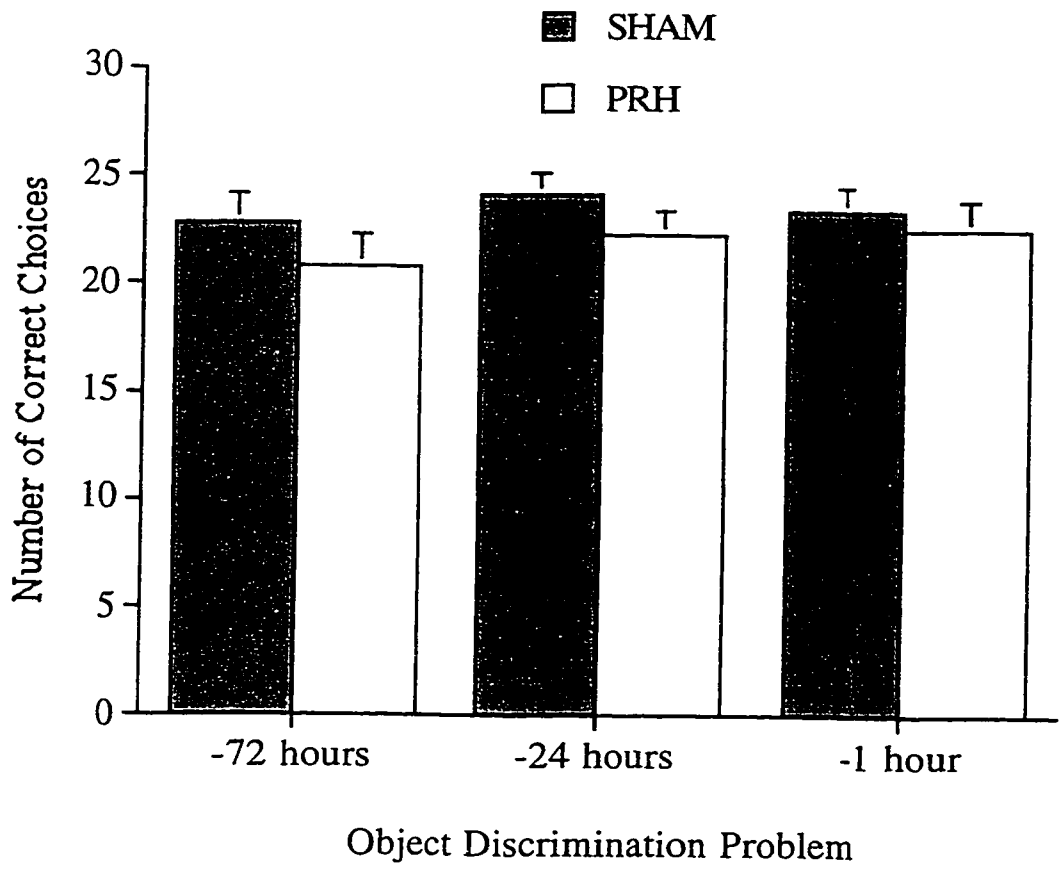


Figure 13. Mean number of correct choices (+*SE*) made by PRH and SHAM rats during retention testing for the presurgery object discrimination problems.

discrimination problem and test day as within-subjects variables revealed a significant effect of test day, $F(2,44)=6.61$, $p<.05$, indicating that the average number of correct choices increased significantly across test days. PRH and SHAM rats did not differ significantly in the number of correct choices made, $F(1,22)=2.44$, $p>.05$ and none of the remaining main effects or interactions were statistically significant (see Table 19 in Appendix B).

Figure 14 shows the mean number of correct choices on the first block of 5 trials for each of the three presurgery object discrimination problems. A repeated measures ANOVA of the first 5 trials, with lesion as a between-subjects variable and problem as a within-subjects variable, revealed no significant difference between PRH and SHAM rats, $F(1,22)=1.9$, $p>.05$, no differences among the three problems, $F(2,44)=1.42$, $p>.05$, and no significant interaction between these two variables, $F(2,44)=1.19$, $p>.05$ (see Table 20 in Appendix B).

Place-Memory Problem

Preliminary Training: Acquisition of the visible-platform task. The four groups were well matched in terms of their performance on the visible-platform task in the water maze. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects variables and trial as a within-subjects variables revealed a significant effect of trial, $F(14,280)=27.09$, $p<.05$, indicating that the average escape latency

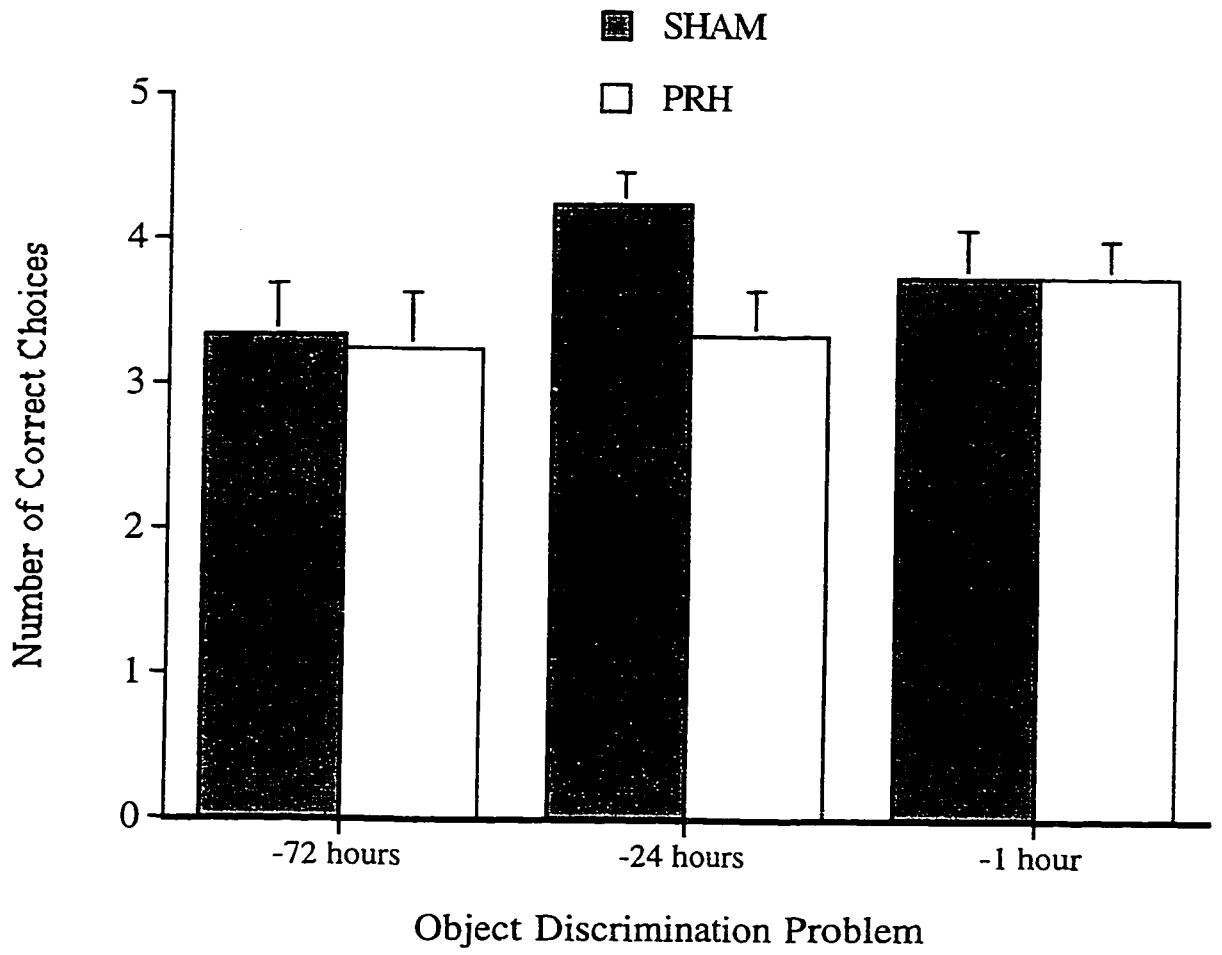


Figure 14. Mean number of correct choices (+*SE*) made by PRH and SHAM rats on the first 5 trials of retention testing.

decreased across trials. None of the remaining main effects or interactions were statistically significant (see Table 21 in Appendix B).

Presurgery Results: Acquisition of the Place-Memory Problem. Figure 15 shows the mean presurgery escape latencies on the place-memory problem for all four groups of rats. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects factors and trial as a within-subjects factor revealed a significant effect of trial, $F(14,280)=16.09, p<.05$, indicating that the average escape latency decreased across trials. In addition, there was a significant lesion X learning-to-lesion interval X trial interaction, $F(14,280)=1.97, p<.05$. As shown in Figure 15, this interaction is due to the SHAM/-72 hour group, that required more trials than the other groups to reach asymptotic performance. None of the remaining main effects or interactions were statistically significant (see Table 22 in Appendix B).

The four groups were well matched in terms of the percent of time they spent in the correct maze quadrant during the presurgery probe. The rats' performance was compared to what would have been expected by chance. Three of the groups, including the SHAM/-72 hour group, $t(5)=2.93, p<.05$, the SHAM/-3 hour group, $t(5)=2.66, p<.05$, and the PRH/-3 hour group, $t(5)=3.47, p<.05$, demonstrated significantly above-chance performance. As shown in Figure 16, the performance of the PRH/-72 hour group was similar to that of the other groups although it did not differ significantly from chance, $t(5)=2.29, p>.05$. An ANOVA with lesion and learning-to-lesion interval as between-

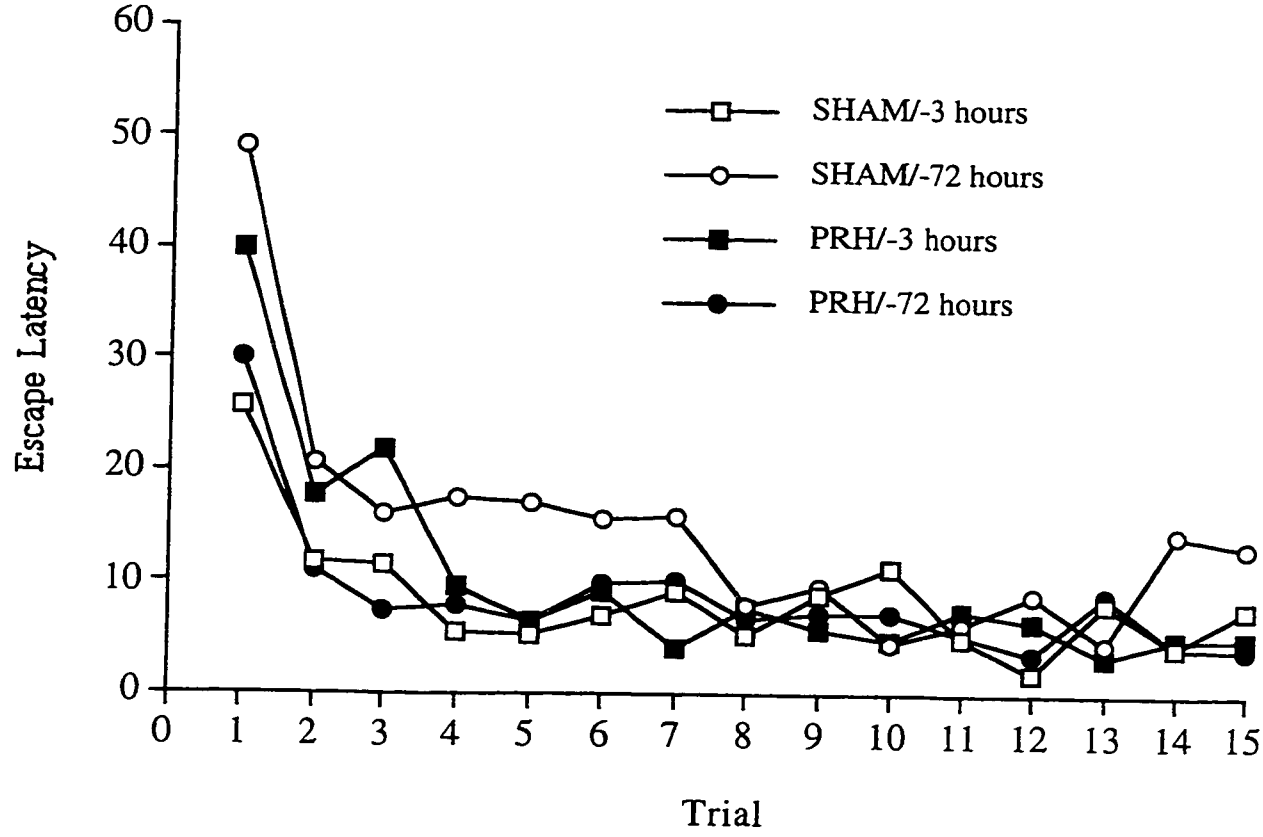


Figure 15. Mean latencies required to locate the hidden platform on each presurgery training trial. Results are shown for all four groups. *SE*'s (not shown) range from .16 to 9.69.

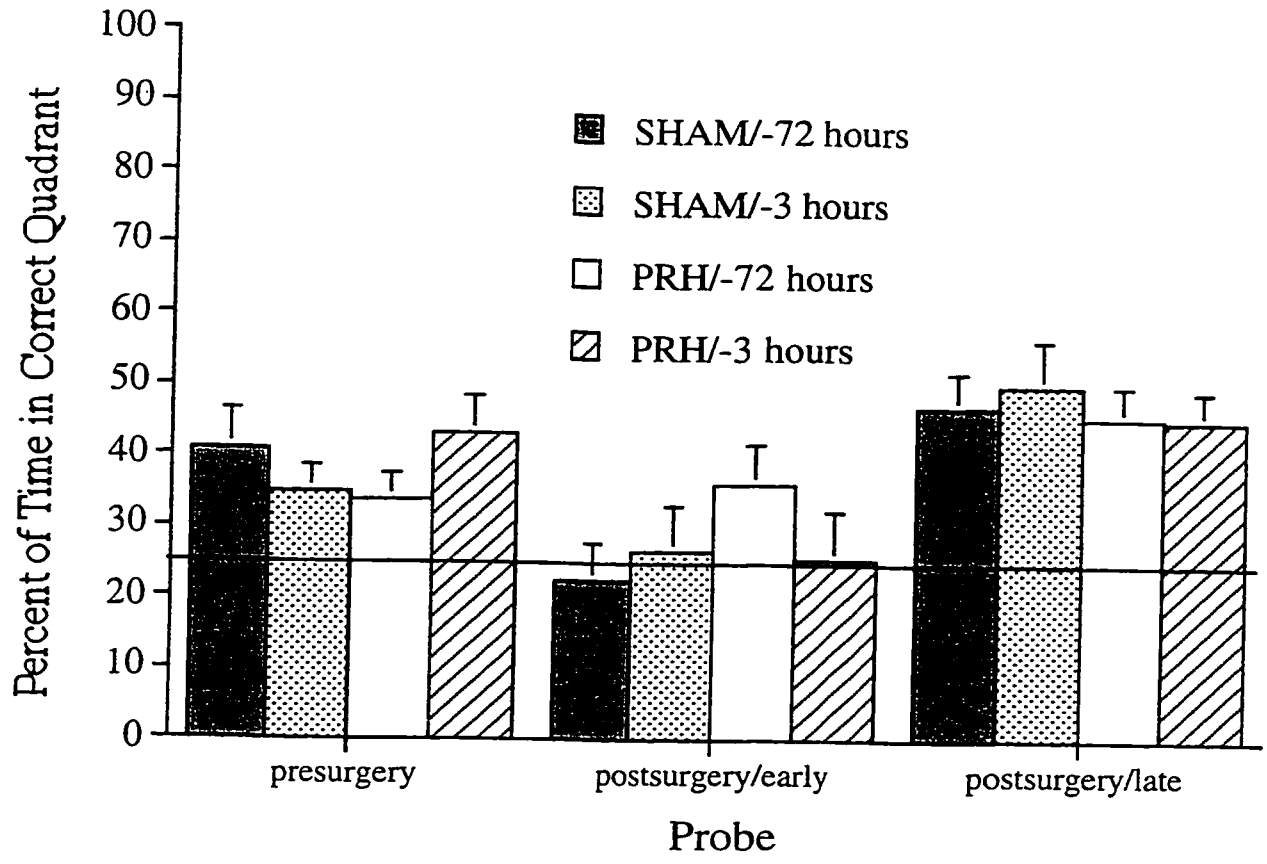


Figure 16. The percent of time (+*SE*) spent in the correct maze quadrant during the three probe trials. Results are shown for all four groups. The horizontal line represents chance performance.

subjects factors revealed no significant effect of lesion, $F(1,20)<1$, no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant interaction between these two variables, $F(1,20)=2.84$, $p>.05$ (see Table 23 in Appendix B).

Postsurgery Results: Swim Latencies. There were no differences among the four groups in terms of their average postsurgery escape latency. Figure 17 shows the average postsurgery escape latencies for each of the four groups. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects factors and trial as a within-subjects factor revealed a significant effect of trial, $F(13,260)=9.94$, $p<.05$, indicating that the average escape latency decreased across trials. There was no significant difference between PRH and SHAM rats, $F(1,20)<1$, and none of the remaining main effects or interactions were statistically significant (see Table 24 in Appendix B).

Postsurgery trial 1 escape latencies were compared to presurgery trial 1 escape latencies to assess how well the rats remembered the previously learned platform location. Figure 18 shows the average pre- and postsurgery trial 1 escape latencies for all four groups. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects factors and trial (pre- vs postsurgery) as a within subjects factor revealed a significant effect of trial, $F(1,20)=9.56$, $p<.05$, indicating that the average escape latency across groups was lower on the first postsurgery trial than on the first presurgery trial. Further analysis of this effect revealed, however, that none of the individual groups demonstrated a significant decrease in trial 1 escape latency from pre- to

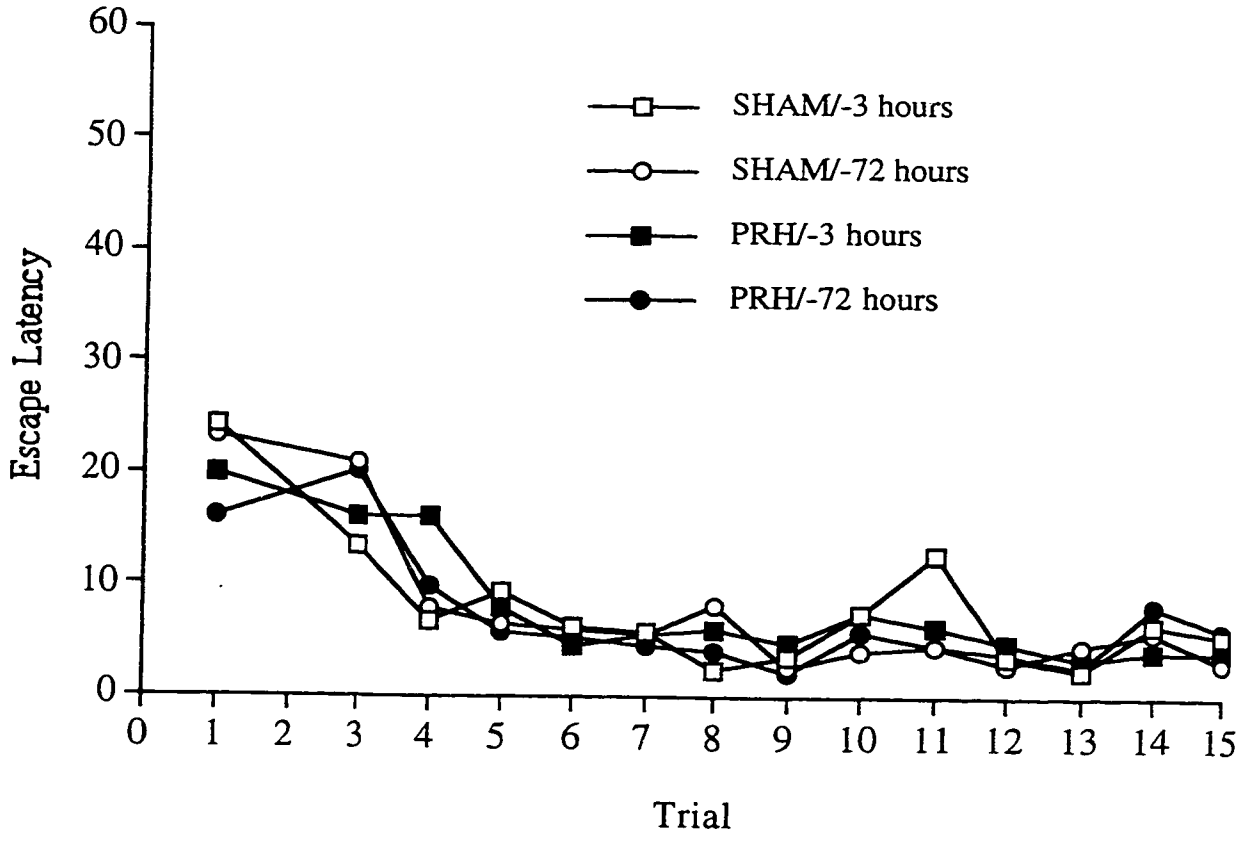


Figure 17. Mean latencies required to locate the hidden platform on each postsurgery testing trial. Results are shown for all four groups. *SE*'s (not shown) range from 0.16 to 11.33.

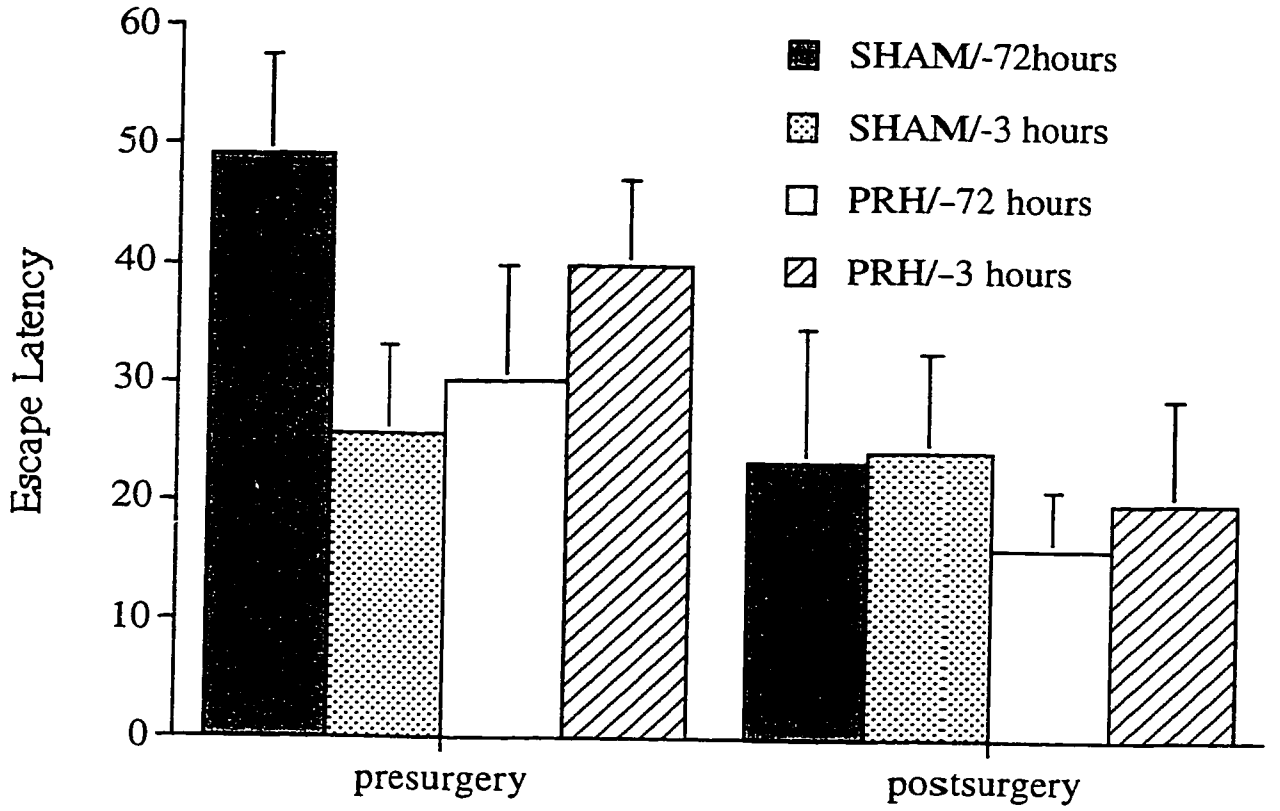


Figure 18. Mean latencies (+*SE*) required to locate the hidden platform on the first presurgery and the first postsurgery trials. Results are shown for all four groups.

postsurgery, all p's >.05. None of the remaining main effects or interactions were statistically significant (see Table 25 in Appendix B).

Postsurgery Results: Probe Trials. Figure 16 shows the percentage of time spent in the correct maze quadrant during the probe trials by each of the four groups. Overall, there were no differences between the PRH and SHAM groups in their performance on the probe trials.

The early postsurgery probe assessed the rats' retention of the previously learned platform location. An ANOVA with lesion and learning-to-lesion interval as between-subjects factors revealed no significant effect of lesion, $F(1,20)<1$, no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant interaction between these two variables, $F(1,20)=1.45$, $p>.05$ (see Table 26 in Appendix B). In addition, the performance of all four groups was compared to what would have been expected by chance (ie. 25% of their time in the correct maze quadrant). None of the groups differed significantly from chance performance (all p's >.05).

The late postsurgery probe, was designed to assess reacquisition of the platform location. All of the groups improved to the point where they all demonstrated significantly above-chance performance (all p's <.05). An ANOVA with lesion and learning-to-lesion interval as between-subjects factors revealed no significant effect of lesion, $F(1,20)<1$, no significant effect of learning-to-lesion interval, $F(1,20)<1$, and no significant lesion X learning-to-lesion interval interaction, $F(1,20)<1$ (see Table 27 in

Appendix B).

The rats' performance on the postsurgery probes was compared to that on the presurgery probe. A repeated measures ANOVA with lesion and learning-to-lesion interval as between-subjects variables and probe trial (presurgery vs early postsurgery vs late postsurgery) as a within-subjects variable revealed a significant effect of probe, $F(2,40)=14.22$, $p<.05$ (see Table 28 in Appendix B). Further analysis of the probe effect revealed that the rats spent less time in the correct maze quadrant during the early postsurgery probe compared to both the presurgery probe, $t(23)=3.05$, $p<.05$, and the late postsurgery probe, $t(23)=4.81$, $p<.05$. In addition, the rats spent more time in the correct quadrant during the late postsurgery probe compared to the presurgery probe, $t(23)=2.51$, $p<.05$.

Discussion

The main findings were that perirhinal cortex lesions do not cause retrograde amnesia for object discrimination problems and do not cause impairments on a place-memory problem in rats.

Lesions of the perirhinal cortex do not cause retrograde amnesia for object discrimination problems learned prior to surgery, as demonstrated by: 1) the lack of a significant group difference in the number of correct choices made across test days and, 2) the lack of a significant group difference in the number of correct choices made on the first five trials of retention testing. This finding is consistent with those of Astur et al. (1995)

who found that perirhinal cortex lesions did not cause retrograde amnesia for object discrimination problems in rats. This finding is inconsistent, however, with the finding by Thornton and Murray (1996) that rhinal cortex lesions caused retrograde amnesia for object discrimination problems in monkeys. One potential reason for this discrepancy is that monkeys in the Thornton and Murray (1996) experiment likely sustained more damage to the entorhinal cortex than did rats in either this experiment or in the Astur et al. (1995) experiment. The role of the entorhinal cortex in memory for object discrimination problems in rats should, therefore, be examined in future experiments.

Perirhinal cortex lesions caused a transient deficit on the ability of rats to acquire object discrimination problems. PRH rats were impaired on the first postsurgery object discrimination problem but not on the second postsurgery problem.

Lesions of the perirhinal cortex do not cause impairments on a place-memory problem in rats, as demonstrated by: 1) the lack of a significant difference between PRH and SHAM rats in reacquiring the task, and 2) the lack of significant differences between PRH and SHAM rats on the postsurgery probe trials. Interpretation of the results of the place-memory testing is complicated by the fact that none of the groups showed good retention of the place-memory task they had acquired prior to surgery. Although the average escape latency across groups was lower on the first postsurgery trial than it was on the first presurgery trial, none of the individual groups demonstrated a significant decrease in escape latency from the first presurgery to the first postsurgery trial. In addition, none of the groups demonstrated a preference for the correct maze quadrant

during the early postsurgery probe trial that was conducted on the second postsurgery trial. The fact that all of the groups demonstrated poor retention of the place-memory problem renders it impossible to determine whether perirhinal cortex lesions cause retrograde amnesia for spatial information. Nevertheless, it is clear that lesions of the perirhinal cortex did not cause impairment on the place-memory problem. This finding is consistent with previous reports that perirhinal cortex lesions do not cause impairments on spatial memory tasks (Astur, et al., 1995; Ennaceur, Neave & Aggleton, 1996; Wiig & Bilkey, 1994a). This finding is inconsistent, however, with reports that perirhinal cortex lesions cause impairment on spatial memory tasks (Wiig & Bilkey, 1994b; Nagahara, Otto & Gallagher, 1995). One potential reason for this discrepancy is that rats in the this experiment as well as in the Astur et al. (1995), Ennaceur et al. (1996), and Wiig & Bilkey (1994a) experiments received presurgery training, whereas rats in the Wiig & Bilkey (1994b) Nagahara et al. (1995) experiments did not. It may be that the perirhinal cortex plays some role in the initial acquisition of place-memory tasks but not in the retention of such tasks.

In sum, the main findings of this experiment are that perirhinal cortex lesions do not cause retrograde amnesia for object discrimination problems and do not cause deficits on a place-memory task. It therefore appears that the perirhinal cortex does not play an essential role in the consolidation of either spatial or nonspatial memory.

GENERAL DISCUSSION

The main findings were; 1) hippocampal lesions, but not perirhinal cortex lesions, impaired performance on a place-memory task, and 2) neither hippocampal nor perirhinal cortex lesions caused significant retention deficits for object discrimination problems that were acquired prior to surgery. Overall, these findings do not support the conclusion that the hippocampal formation and perirhinal cortex are serial-components of a single memory system in which the mnemonic functions of the hippocampal formation are dependent on information supplied through the perirhinal cortex (Eichenbaum et al., 1994). As well, these findings neither the hippocampus nor the perirhinal cortex play an essential role in the consolidation of long-term memory for object discrimination problems.

HPC rats, but not PRH rats, were impaired on the place-memory task. HPC rats required significantly longer escape latencies to locate the hidden platform during postsurgery testing than SHAM rats and spent significantly less time in the correct quadrant than did SHAM rats during the postsurgery probe trials. In contrast, PRH rats did not differ significantly from SHAM rats in either their escape latencies or in the amount of time spent in the correct quadrant during postsurgery probe trials.

The finding that hippocampal lesions impair place-memory ability was entirely expected in light of numerous reports that such lesions disrupt performance on similar tasks (see review by Barnes, 1988). Moreover, the finding that perirhinal cortex lesions do not impair place-memory ability is consistent with some previous experiments (Astur,

et al., 1995; Ennaceur, Neave & Aggleton, 1996; Wiig & Bilkey, 1994a). This finding is inconsistent, however, with reports that perirhinal cortex lesions impair performance on some place-memory tasks. (Wiig & Bilkey, 1994b; Nagahara, Otto & Gallagher, 1995). One potential reason for this discrepancy is that rats in Experiment 2 as well as in the Astur et al. (1995), Ennaceur et al. (1996), and Wiig & Bilkey (1994a) experiments received presurgery training, whereas rats in the Wiig & Bilkey (1994b) and Nagahara et al. (1995) experiments did not. It is possible that the perirhinal cortex is involved in the initial acquisition of place-memory tasks but not in the retention of such tasks.

Neither perirhinal cortex lesions nor hippocampal lesions caused significant retention deficits for the preoperatively acquired object discrimination problems. Neither HPC nor PRH rats differed significantly from SHAM rats in the number of correct choices made across test days, nor did they differ significantly from SHAM rats in the number of correct choices made on the first five trials of retention testing. These results are consistent with those of previous experiments in which rats with hippocampal lesions (Astur et al., 1994) as well as those with perirhinal cortex lesions (Astur et al., 1995) were unimpaired in their retention of preoperatively acquired object discriminations (Astur et al., 1995). This finding is inconsistent, however, with a previous experiment in which monkeys with rhinal cortex ablations displayed retrograde amnesia for preoperatively acquired object discriminations (Thornton & Murray, 1996).

It should be noted, however, that although HPC rats showed good retention of the object discrimination problems, their scores were moderately lower than those obtained

by SHAM rats. This difference approached, but did not meet the criterion of statistical significance (p=.10). The results of Experiment 1A, therefore, do not entirely rule out the possibility that the hippocampal formation plays a role in the consolidation of memory for object discrimination problems.

The small difference between HPC and SHAM rats in their retention scores for the -1 hour problem was not due to the amnestic effects of the diazepam that had been administered to the HPC rats. The main finding of Experiment 1B was that diazepam did not cause retrograde amnesia for an object discrimination problem learned 1 hour prior to drug treatment, as demonstrated by the lack of a significant difference between VAL and SAL rats in the number of correct choices made during retention testing for the pretreatment object discrimination.

Neither perirhinal cortex lesions nor hippocampal lesions caused significant, long-lasting impairment in the acquisition of object discrimination problems. Although PRH rats required more trials to reach criterion on the first postsurgery problem than did SHAM rats, there was no group difference between PRH and SHAM rats in the acquisition of the second postsurgery problem. Similarly, HPC rats did not differ significantly from SHAM rats in the number of trials required to reach criterion on either the first or the second postsurgery problem. These findings are consistent with previous reports that neither perirhinal cortex lesions (Astur et al., 1995; Gaffan & Murray, 1992), nor hippocampal lesions (Astur et al., 1994; Ridley et al., 1995; Vnek & Rothblat, 1996) impair the ability to acquire object discrimination problems.

According to the model put forth by Eichenbaum et al. (1994), the hippocampal formation operates on information it receives through its afferent connections from the rhinal cortex. A prediction that arises from this serial-processing model of temporal lobe function is that only one type of functional dissociation should be possible: a particular memory ability could be impaired by rhinal cortex lesions but spared by hippocampal lesions. The present experiments, however, produced the opposite pattern of results. Rats with hippocampal lesions, but not those with perirhinal cortex lesions, were impaired on a place-memory problem. Such a pattern of results should not have occurred if the mnemonic functions of the hippocampal formation are dependent on information supplied through the perirhinal cortex. These results do not support the conclusion that the hippocampal formation and perirhinal cortex are serial components of a single memory system. It is possible, however, that hippocampal function is disrupted only by complete lesions of the rhinal cortex. As shown in Figures 10 and 11, rats in Experiment 2 sustained large lesions of the perirhinal cortex as well as a minor amount of damage to the entorhinal cortex. It may be that both the entorhinal and perirhinal cortices must be completely lesioned to disrupt the afferent connections to the hippocampal formation.

The present results do not entirely support the conclusion that the hippocampal formation and perirhinal cortex are components of dissociable memory systems. Although the role of the hippocampal formation in spatial memory was, once again, confirmed, the mnemonic functions of the perirhinal cortex remain unclear. The prediction that perirhinal cortex lesions would cause retrograde amnesia for object

discrimination problems was not confirmed as PRH rats did not differ significantly from SHAM rats in their retention of preoperatively acquired problems. This finding does not support the hypothesis that the perirhinal cortex plays a preferential role in memory for objects. This hypothesis is supported by experiments in which perirhinal cortex lesions caused impairments in object recognition in both rats (Ennaceur, Neave & Aggleton, 1996; Mumby & Pinel, 1994) and monkeys (Meunier, Bachevalier, Mishkin & Murray, 1993; Zola-Morgan, Squire, Amaral & Suzuki, 1989). According to the findings of both Experiment 2 as well as those of Astur et al. (1995), the perirhinal cortex does not play a role in the long term retention of object discrimination problems. It may be, therefore, that the role of this structure in memory for objects is restricted to the short term retention of individual objects (Mumby & Pinel, 1994; Murray, 1996).

Consolidation theories of medial temporal lobe function maintain that the hippocampal formation plays an essential role in the formation of long term memory, either by temporarily storing memory for events, or by playing an active role in guiding subsequent storage in neocortical areas (Eichenbaum et al., 1994; McClelland et al., 1995; Squire & Zola-Morgan, 1991). Zola-Morgan & Squire (1990) found that large lesions of the medial temporal lobe caused temporally-graded retrograde amnesia for object discrimination problems in monkeys. It is not clear, however, whether the damage sustained by the hippocampal formation was responsible for the memory deficits exhibited by lesioned monkeys. Astur et al. (1994) found that hippocampal formation lesions did not cause retrograde amnesia for object discriminations in rats. Experiment 1A

was designed to investigate the possibility that the hippocampal formation does play a role in the consolidation of long term memory, but that this role lasts for a shorter time than one week, which was the shortest learning-to-lesion interval used in the Astur et al. experiment (1994). Based on the results of Experiment 1A, it appears that hippocampal lesions do not disrupt the consolidation of memory for object discrimination problems. Overall, HPC rats showed good retention of the object discrimination problems they had learned prior to surgery. Although their scores were moderately lower than those obtained by SHAM rats, the mean retention scores obtained by HPC rats on each of the three presurgery problems were above chance, indicating that the HPC rats had not forgotten these problems. Moreover, there was no significant interaction between lesion and the time at which the problems were originally learned. That is, the retention scores of the HPC rats did not vary significantly according to the time at which the problems were originally learned. These results suggest that the hippocampus does not play a necessary role in the consolidation of long-term memory.

If the retrograde amnesia exhibited by monkeys in the Zola-Morgan and Squire (1990) experiment was not due to the hippocampal damage, then it may have been due to the damage sustained by adjacent rhinal cortex. This hypothesis was investigated in Experiment 2 and the results are consistent with a previous finding that perirhinal cortex lesions do not cause retrograde amnesia for object discrimination problems in rats (Astur et al., 1995). Thornton and Murray (1996), however, found that monkeys with combined lesions of the perirhinal and entorhinal cortices exhibit retrograde amnesia for object

discriminations. The combined results of these experiments suggest that more than one medial temporal lobe structure must be damaged in order to disrupt the consolidation of long term memory for object discrimination problems. Future experiments, therefore, should be performed to investigate the effects of various combinations of lesions involving the hippocampal formation, perirhinal cortex, and entorhinal cortex, on the ability to remember preoperatively-acquired object discrimination problems.

In sum, the main findings of the present experiments were: 1) hippocampal formation lesions, but not perirhinal cortex lesions, impair place-memory abilities in rats, and 2) neither hippocampal formation nor perirhinal cortex lesions cause significant retention deficits for object discrimination problems that were acquired prior to surgery. Overall, the present findings do not support the conclusion that the hippocampal formation and perirhinal cortex are serial components of a single memory system (Eichenbaum et al., 1994), nor do they provide convincing evidence that either the hippocampal formation or perirhinal cortex plays an essential role in long-term memory formation.

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APPENDIX A

Stereotaxic coordinates used to make NMDA lesions of the hippocampal formation.

Table 1

Stereotaxic Coordinates Used to Make NMDA Lesions of the Hippocampal Formation. All Values are Listed as the Number of Millimetres Relative to Bregma.

Injection Site	Anteroposterior	Mediolateral	Dorsoventricular
1	-3.1	+/- 1.0	-3.6
2	-3.1	+/- 2.0	-3.6
3	-4.1	+/- 2.0	-4.0
4	-4.1	+/- 3.5	-4.0
5	-5.0	+/- 3.0	-4.1
6	-5.0	+/- 5.2	-5.0
7	-5.0	+/- 5.2	-7.3
8	-5.8	+/- 4.4	-4.4
9	-5.8	+/- 5.1	-6.2
10	-5.8	+/- 5.1	-7.5

APPENDIX B

Analysis of variance source tables

Table 1

Analysis of Variance for the Number of Trials Required by HPC and SHAM rats to Reach Criterion During Original Learning of the -1 hour, -24 hour, and -72 hour Object Discriminations Problems

Source	SS	df	MS	F	P
Between Subjects					
Lesion	922.09	1	922.09	.96	.34
Error	20175.24	21	960.73		
Within Groups					
Problem	1733.83	2	866.91	.73	.49
Lesion X Problem	703.86	2	351.93	.30	.75
Error	49916.98	42	1188.50		

Table 2

Analysis of Variance for the Number of Trials Required by HPC and SHAM rats to Reach Criterion During Original Learning of the Presurgery Object Discrimination Problems and the First Postsurgery Object Discrimination Problem

Source	SS	df	MS	F	P
Between Subjects					
Lesion	90.79	1	90.79	.08	.79
Error	25225.93	21	1201.23		
Within Groups					
Problem	37753.42	3	12584.47	10.12	.00
Lesion X Problem	2660.03	3	886.68	.71	.55
Error	78312.30	63	1243.05		

Table 3

Analysis of Variance for the Number of Correct Choices Made by HPC and SHAM Rats During Retention Testing For the -1 Hour, -24 Hour, and -72 Hour Object Discrimination Problems.

Source	SS	df	MS	F	P
Between Subjects					
Lesion	14.43	1	14.43	2.97	.10
Error	101.95	21	4.86		
Within Groups					
Test Day	31.44	2	15.72	9.21	.01
Lesion X Test Day	3.15	2	1.58	.92	.41
Error	71.71	42	1.71		
Problem	7.96	2	3.98	1.0	.38
Lesion X Problem	6.81	2	3.40	.85	.43
Test Day X Problem	3.88	4	.97	.63	.64
Lesion X Test Day X Problem	2.60	4	.65	.42	.79
Error	129.44	84	1.54		

Table 4

Analysis of Variance for the Number of Correct Choices Made by HPC and SHAM Rats On the First Five Trials of Retention Testing For the -1 Hour, -24 Hour, and -72 Hour Object Discrimination Problems.

Source	SS	df	MS	F	P
Between Subjects					
Lesion	.89	1	.89	.60	.45
Error	30.88	21	1.47		
Within Groups					
Problem	1.51	2	.75	.68	.51
Lesion X Problem	2.19	2	1.09	.99	.38
Error	46.30	42	1.10		

Table 5

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Visible Platform During Preliminary Training in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	28.80	1	28.80	.34	.58
Learning-to-lesion interval	64.80	1	64.80	.76	.41
Lesion X Learning-to-lesion interval	32.09	1	32.09	.38	.56
Error	680.62	8	85.08		
Within Groups					
Trial	21825.58	14	1558.97	16.84	.01
Lesion X Trial	1041.53	14	74.40	.80	.66
Learning-to-lesion interval X Trial	1947.87	14	139.13	1.50	.12
Lesion X Learning-to-lesion interval X Trial	365.91	14	26.14	.28	.99
Error	10371.38	112	92.60		

Table 6

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Hidden Platform During Presurgery Training in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	3132.31	1	3132.31	3.51	.08
Learning-to-lesion interval	3304.52	1	3304.52	3.70	.07
Lesion X Learning-to-lesion interval	2921.25	1	2921.25	3.27	.09
Error	17851.60	20	892.58		
Within Groups					
Trial	18420.35	14	1315.74	7.52	.01
Lesion X Trial	3035.71	14	216.84	1.24	.25
Learning-to-lesion interval X Trial	1779.48	14	127.11	.73	.75
Lesion X Learning-to-lesion interval X Trial	1500.59	14	26.14	.28	.99
Error	10371.38	280	174.98		

Table 7

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Presurgery Probe Trial by HPC and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	18.38	1	18.38	.15	.70
Learning-to-lesion interval	15.04	1	15.04	.13	.73
Lesion X Learning-to-lesion interval	63.38	1	63.38	.53	.47
Error	2388.83	20	119.44		

Table 8

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Hidden Platform During Postsurgery Testing in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	25166.32	1	25166.32	42.66	.00
Learning-to-lesion interval	21.86	1	21.86	.04	.85
Lesion X Learning-to-lesion interval	416.52	1	416.52	.71	.41
Error	11799.37	20	589.97		
Within Groups					
Trial	9469.22	13	728.40	3.05	.00
Lesion X Trial	3960.47	13	304.65	1.27	.23
Learning-to-lesion interval X Trial	3555.69	13	273.51	1.14	.32
Lesion X Learning-to-lesion interval X Trial	2057.12	13	158.24	.66	.80
Error	62138.27	260	238.99		

Table 9

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Hidden Platform on the First Presurgery and the First Postsurgery Trials

Source	SS	df	MS	F	P
Between Subjects					
Lesion	1666.16	1	1666.16	3.84	.07
Learning-to-lesion interval	512.21	1	512.21	1.18	.29
Lesion X Learning-to-lesion interval	72.52	1	72.52	.17	.69
Error	8677.09	20	433.85		
Within Groups					
Trial	14.08	1	14.08	.03	.86
Lesion X Trial	397.90	1	397.90	.94	.34
Learning-to-lesion interval X Trial	521.40	1	521.40	1.23	.28
Lesion X Learning-to-lesion interval X Trial	252.08	1	252.08	.60	.45
Error	8458.94	20	422.95		

Table 10

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Early Postsurgery Probe Trial by HPC and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	962.67	1	962.67	9.64	.01
Learning-to-lesion interval	16.67	1	16.67	.17	.69
Lesion X Learning-to-lesion interval	73.50	1	73.50	.74	.40
Error	1997.67	20	1997.67		

Table 11

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Late Postsurgery Probe Trial

Source	SS	df	MS	F	P
Between Subjects					
Lesion	3151.04	1	3151.04	9.64	.00
Learning-to-lesion interval	.38	1	.38	.00	.97
Lesion X Learning-to-lesion interval	40.04	1	40.04	.18	.68
Error	4539.17	20	226.96		

Table 12

Analysis of Variance for the Percent of Time Spent in the Correct Quadrant During the Presurgery , Early Postsurgery, and Late Postsurgery Probe Trials by HPC and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	2787.56	1	2787.56	13.16	.00
Learning-to-lesion interval	18.00	1	18.00	.08	.77
Lesion X Learning-to-lesion interval	10.89	1	10.89	.05	..82
Error	4235.56	20	211.78		
Within Groups					
Probe	6885.25	2	3442.62	29.36	.00
Lesion X Probe	1344.53	2	672.26	5.73	.01
Learning-to-lesion interval X Probe	14.08	2	7.04	.06	.94
Lesion X Learning-to-lesion interval X Probe	166.03	2	83.01	.71	.50
Error	4690.11	40	117.25		

Table 13

Source Table for the Simple Effects Analysis of the Percent of Time Spent in the Correct Quadrant During the Presurgery, Early Postsurgery, and Late Postsurgery Probe Trials

Source	df	MS	F	P
Simple Effects of Lesion				
Presurgery Probe	1	18.375	.154	.70
Error	20	119.44		
Early Postsurgery Probe	1	962.67	9.64	.01
Error	20	99.88		
Late Postsurgery Probe	1	3151.04	13.88	.00
Error	20	226.96		

Table 14

Analysis of Variance for the Number of Trials Required by VAL and SAL rats to Reach Criterion on the Presurgery and Postsurgery Object Discrimination Problems

Source	SS	df	MS	F	P
Between Subjects					
Group	12.00	1	12.00	.01	.94
Error	8796.00	4	2199.00		
Within Groups					
Problem	48.00	1	48.00	.14	.73
Group X Problem	65.33	1	65.33	.19	.69
Error	1374.67	4	343.67		

Table 15

Analysis of Variance for the Number of Correct Choices Made by VAL and SAL rats During Retention Testing for the Presurgery Object Discrimination Problem

Source	SS	df	MS	F	P
Between Subjects					
Group	0.00	1	0.00	0.00	n/a
Error	1.78	4	.44		
Within Groups					
Test day	.78	2	.39	1.40	.30
Group X Test day	.33	2	.17	.60	.57
Error	2.22	8	.28		

Table 16

Analysis of Variance for the Number of Trials Required by PRH and SHAM rats to Reach Criterion During Original Learning of the -1 hour, -24 hour, and -72 hour Object Discriminations Problems

Source	SS	df	MS	F	P
Between Subjects					
Lesion	32.00	1	32.00	.02	.88
Error	32562.17	22	1480.10		
Within Groups					
Problem	839.25	2	419.63	.31	.73
Lesion X Problem	248.08	2	124.04	.09	.91
Error	58656.00	44	1333.09		

Table 17

Analysis of Variance for the Number of Trials Required by PRH and SHAM rats to Reach Criterion During Original Learning of the Presurgery Object Discrimination Problems and the First Postsurgery Object Discrimination Problem

Source	SS	df	MS	F	P
Between Subjects					
Lesion	2166.00	1	2166.00	1.52	.23
Error	31264.33	22	1421.11		
Within Groups					
Problem	12239.75	3	4079.92	2.45	.07
Lesion X Problem	8698.08	3	2899.36	1.74	.17
Error	109743.67	66	1662.78		

Table 18

Analysis of Variance for the Number of Trials Required by PRH and SHAM rats to Reach Criterion During Original Learning of the Presurgery and Postsurgery Object Discrimination Problems

Source	SS	df	MS	F	P
Between Subjects					
Lesion	2244.63	1	2244.63	1.50	.24
Error	27011.41	18	1500.63		
Within Groups					
Problem	12095.64	4	3023.91	1.92	.12
Lesion X Problem	4508.91	4	1127.23	.71	.58
Error	113576.65	72	1577.45		

Table 19

Analysis of Variance for the Number of Correct Choices Made by PRH and SHAM Rats During Retention Testing For the -1 Hour, -24 Hour, and -72 Hour Object Discrimination Problems.

Source	SS	df	MS	F	P
Between Subjects					
Lesion	14.52	1	14.52	2.44	.13
Error	131.02	22	5.96		
Within Groups					
Test Day	23.68	2	11.84	6.61	.00
Lesion X Test Day	.84	2	.42	.24	.79
Error	78.82	44	1.79		
Problem	9.59	2	4.80	.73	.49
Lesion X Problem	1.59	2	.80	.12	.89
Error	290.15	44	6.59		
Test Day X Problem	3.94	4	.98	.53	.72
Lesion X Test Day X Problem	12.88	4	3.22	.1.72	.15
Error	164.52	88	1.87		

Table 20

Analysis of Variance for the Number of Correct Choices Made by PRH and SHAM Rats On the First Five Trials of Retention Testing For the -1 Hour, -24 Hour, and -72 Hour Object Discrimination Problems.

Source	SS	df	MS	F	P
Between Subjects					
Lesion	2.00	1	2.00	1.9	.18
Error	23.11	22	1.05		
Within Groups					
Problem	3.69	2	1.85	1.42	.25
Lesion X Problem	3.08	2	1.54	1.19	.32
Error	57.22	44	1.30		

Table 21

Analysis of Variance for the Latencies Required by PRH and SHAM rats to Locate the Visible Platform During Preliminary Training in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	416.03	1	416.03	.80	.38
Learning-to-lesion interval	1099.00	1	1099.00	2.12	.16
Lesion X Learning-to-lesion interval	437.80	1	437.80	.85	.37
Error	10343.81	20	517.19		
Within Groups					
Trial	35873.98	14	2562.43	27.09	.00
Lesion X Trial	779.85	14	55.70	.59	.87
Learning-to-lesion interval X Trial	1222.87	14	87.35	.92	.53
Lesion X Learning-to-lesion interval X Trial	1058.07	14	75.58	.80	.67
Error	26485.36	280	94.59		

Table 22

Analysis of Variance for the Latencies Required by PRH and SHAM rats to Locate the Hidden Platform During Presurgery Training in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	423.15	1	423.15	.59	..45
Learning-to-lesion interval	476.33	1	476.33	.67	.42
Lesion X Learning-to-lesion interval	1402.25	1	1402.25	1.96	.18
Error	14303.43	20	715.17		
Within Groups					
Trial	19828.86	14	1416.35	16.09	.00
Lesion X Trial	426.28	14	30.45	.35	..99
Learning-to-lesion interval X Trial	934.43	14	66.74	.75	.71
Lesion X Learning-to-lesion interval X Trial	2431.90	14	173.71	1.97	.02
Error	24644.93	280	88.02		

Table 23

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Presurgery Probe Trial by PRH and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	1.04	1	1.04	.01	.93
Learning-to-lesion interval	15.04	1	15.04	.12	.73
Lesion X Learning-to-lesion interval	360.37	1	360.37	2.84	.11
Error	2540.17	20	127.01		

Table 24

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Hidden Platform During Postsurgery Testing in the Water Maze

Source	SS	df	MS	F	P
Between Subjects					
Lesion	3.07	1	3.07	.02	.89
Learning-to-lesion interval	27.26	1	27.26	.17	.69
Lesion X Learning-to-lesion interval	7.53	1	7.53	.05	.83
Error	3301.26	20	165.06		
Within Groups					
Trial	8853.75	13	681.06	9.94	.00
Lesion X Trial	491.44	13	37.80	.55	.89
Learning-to-lesion interval X Trial	536.01	13	41.23	.60	.85
Lesion X Learning-to-lesion interval X Trial	351.27	13	27.02	.39	.97
Error	17809.04	260	68.50		

Table 25

Analysis of Variance for the Latencies Required by HPC and SHAM rats to Locate the Hidden Platform on the First Presurgery and the First Postsurgery Trials

Source	SS	df	MS	F	P
Between Subjects					
Lesion	196.43	1	196.43	.34	.56
Learning-to-lesion interval	62.34	1	62.34	.11	.74
Lesion X Learning-to-lesion interval	994.63	1	994.63	1.74	.20
Error	11419.55	20	570.98		
Within Groups					
Trial	2804.49	1	2804.49	9.56	.01
Lesion X Trial	34.85	1	34.85	.12	.73
Learning-to-lesion interval X Trial	253.46	1	253.46	.86	.36
Lesion X Learning-to-lesion interval X Trial	681.77	1	681.77	.2.32	.14
Error	5868.58	20	293.43		

Table 26

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Early Postsurgery Probe Trial by PRH and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	228.17	1	228.17	.98	.33
Learning-to-lesion interval	66.67	1	66.67	.29	.60
Lesion X Learning-to-lesion interval	337.5	1	337.5	1.45	.24
Error	4645.67	20	232.28		

Table 27

Analysis of Variance for the Percent of Time Spent in the Correct Maze Quadrant During the Late Postsurgery Probe Trial by PRH and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	66.67	1	66.67	.43	.52
Learning-to-lesion interval	8.17	1	8.17	.05	.82
Lesion X Learning-to-lesion interval	16.67	1	16.67	.11	.75
Error	3079.00	20	153.95		

Table 28

Analysis of Variance for the Percent of Time Spent in the Correct Quadrant During the Presurgery , Early Postsurgery, and Late Postsurgery Probe Trials by PRH and SHAM rats

Source	SS	df	MS	F	P
Between Subjects					
Lesion	21.12	1	21.12	.11	.75
Learning-to-lesion interval	.68	1	.68	.00	.95
Lesion X Learning-to-lesion interval	4.01	1	4.01	.02	..89
Error	3990.06	20	199.50		
Within Groups					
Probe	4462.75	2	2231.38	14.22	.00
Lesion X Probe	274.75	2	137.38	.88	.42
Learning-to-lesion interval X Probe	89.19	2	44.60	.28	.75
Lesion X Learning-to-lesion interval X Probe	710.53	2	355.26	2.26	.12
Error	6274.78	40	156.87		