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Functional Dissociation Between the Hippocampal Formation and Perirhinal Cortex: Evidence for Independent Memory Systems in the Medial Temporal Lobe

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A Thesis

in

the Department

of

Psychology

Presented in Partial Fulfilment of the Requirements
for the Degree of Master of Arts at
Concordia University
Montreal, Quebec, Canada

August 1997

ABSTRACT

Functional Dissociation Between the Hippocampal Formation and Perirhinal Cortex: Evidence for Independent Memory Systems in the Medial Temporal Lobe

Melissa Glenn

Current views about the functional organization of memory in the medial temporal lobe of the mammalian brain suggest that the hippocampal formation (HPC) and the perirhinal cortex (PRh) are serial components in a unitary memory system. Contradictory to this view, evidence from numerous studies with monkeys and rats suggest that there are at least two independent memory systems within the medial temporal lobe. It appears that the PRh is critically involved in object-recognition memory, but the HPC does not make a significant contribution to this type of memory. Spatial memory appears to rely on the integrity of the HPC. It is not clear what role, if any, the PRh has in supporting spatial memory. The aim of this thesis was to assess the validity of these two views about the functional organization of memory and the contribution of the HPC and PRh to object-recognition and spatial memory. In Experiment 1, rats were presurgically trained on a spatial memory task, delayed matching-to-place task, in a water maze. Lesions of the HPC produced deficits on this task, whereas lesions of the PRh did not affect performance. In Experiment 2, rats were presurgically trained on a spatial memory task and an object-recognition task; delayed matching-to-place and delayed nonmatching-to-sample, respectively. PRh lesions produced deficits on the delayed nonmatching-to-sample task, but had no effect on performance on the delayed matching-to-place task. By contrast, HPC lesioned rats were impaired on delayed matching-to-place, but did not display deficits on delayed nonmatching-to-sample. These results are consistent with current findings and support the view that multiple, independent memory systems exist within the medial temporal lobe and the PRh is a central component in a circuit that is critically involved in processing object information, whereas the HPC is a central component in a circuit that is critically involved in processing spatial information.

ACKNOWLEDGEMENTS

There are many people that I would like to express my gratitude to for supporting me, professionally and personally, over the last few years.

To Dave Mumby, my graduate supervisor, I would like to extend my deepest appreciation. His guidance and instruction, patience and consideration, and above all, his dedication, have been an immeasurable source of strength for me.

I would like to thank Barbara Woodside for being a part of my committee and for reading an earlier draft of this thesis. I would also like to thank her for supporting and encouraging me, and for expressing interest in and providing input to my thesis work. I would also like to thank Jane Stewart for her work as a member of my committee.

I am truly grateful to Alf and Jodye. Not a day has passed without a word of encouragement or reassurance from them. Their endless humour and (at times questionable) wit, never ceases to make me smile. I want to thank them both for always being there for me, and for being such amazing friends.

I would also like to thank Colleen, Tod, Hugo, Linda, Naomi, Van, and Danielle for their friendship and support, for always lending a listening ear, and for providing words of kindness and consolation when I really needed it the most.

Thank you to members of the Woodside/Mumby lab, past and present, for all the assistance and guidance they provided. Thank you also to Stella, Linda, Christiana, and Viijay for their help with various portions of the data collection.

A special thank you to Owen for his encouraging words, his understanding and sensitivity, and particularly for standing by me during the most difficult time in the completion of this thesis.

Finally, I want to thank my family for their love and support. I dedicate this thesis to my Mom and Dad. Without their unconditional acceptance of all my endeavors, and the faith they have in me, this thesis would not have been possible.

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Neurobiological research on learning and memory has revealed that there are multiple, functionally and anatomically independent, memory systems within the mammalian brain. The medial temporal lobe is a brain region that appears to be critical for certain kinds of memory abilities, but there is some disagreement about whether these abilities reflect the functions of a unitary memory system, or multiple systems made up of different temporal lobe structures.

According to the unitary-system view there is a serial flow of information from the neocortex through a circuit consisting of medial temporal lobe structures, each of which play a specific role in processing information. According to the multiple-systems view certain structures within the medial temporal lobe function independently as components of separate systems that are specialized to process different kinds of information.

The aim of this thesis was to test the prediction that the functions of two medial temporal lobe structures, the hippocampal formation (HPC--including the dentate gyrus, hippocampus proper, and the subicular complex) and the perirhinal cortex (PRh), reflect independent memory systems that are dissociable in terms of their role in processing different kinds of information. Specifically, the hypothesis was that the HPC is critical for spatial memory abilities, but not for object recognition, and the PRh is critical for object recognition, but not for spatial memory abilities. In Experiment 1 rats with lesions of the HPC or PRh were tested on a spatial memory task, both before and after surgery. In Experiment 2 rats with lesions of the HPC or PRh were tested on an object-recognition task and a spatial memory task, both before and after surgery.

The following introduction and literature review has five main sections. The first section is an overview of the anatomy of the medial temporal lobes. Because much of our knowledge about the anatomical organization of memory and the role of medial temporal lobe structures in object-recognition comes from the study of human amnesia, the second section describes medial temporal lobe amnesia, important human cases of this amnesia, and animal models of medial temporal lobe amnesia. The third section reviews studies that examined the contribution of the HPC and PRh to object-recognition memory. The fourth section reviews studies that examined the contribution of the HPC and PRh to spatial

memory. Finally, the fifth section discusses models of the functional relations between these two structures.

1. Anatomy of the Medial Temporal Lobe

Figure 1 shows a schematic view of the connectivity of the medial temporal lobe. The medial temporal lobe is comprised of the HPC, the amygdala, the rhinal cortex, the parahippocampal cortex in monkeys and the postrhinal cortex in rats, and temporal association cortices. The rhinal cortex is situated adjacent to the HPC and refers to the PRh and the entorhinal cortices (Burwell, Witter, and Amaral, 1995; Witter, Groenewegen, Lopes da Silva, and Lohman, 1989). The PRh and entorhinal cortex receive projections from polymodal association cortices (Burwell et al., 1995; Witter and Amaral, 1991). The PRh also receives projections from unimodal association cortices (Burwell et al., 1995; Deacon, Eichenbaum, Rosenberg, and Eckmann, 1983). The PRh transmits highly processed information received from the neocortex to the entorhinal cortex (Burwell et al., 1995; Suzuki, 1996). This projection comprises the majority of the output of the PRh (Burwell et al., 1995; Suzuki, 1996). There are also some projections from the PRh to the HPC, amygdala, and the diencephalon (Kosel, van Hoesen, and Rosene, 1983; Burwell et al., 1995). The entorhinal cortex projects densely to the dentate gyrus of the HPC via the perforant path (Insausti, Amaral, and Cowan, 1987; Witter and Amaral, 1991). There are also projections from the entorhinal cortex to the CA1 cell field of the hippocampus, and to the subiculum (Insausti et al., 1987). The HPC returns projections to the PRh and entorhinal cortex (Insausti et al, 1987; Amaral and Witter, 1989; Burwell, et al., 1995; Suzuki, 1996). There are also reciprocal connnections between the HPC and the amygdala, and between the HPC and the diencephalon via the fimbria-fornix system (Amaral and Witter, 1989).

The connectivity of medial temporal lobe structures indicates that there is a major pathway from neocortex through the PRh and entorhinal cortex to the HPC. However, each of these areas also have independent connections with neocortex and subcortical regions. These anatomical findings can, therefore, support either the unitary-system or the

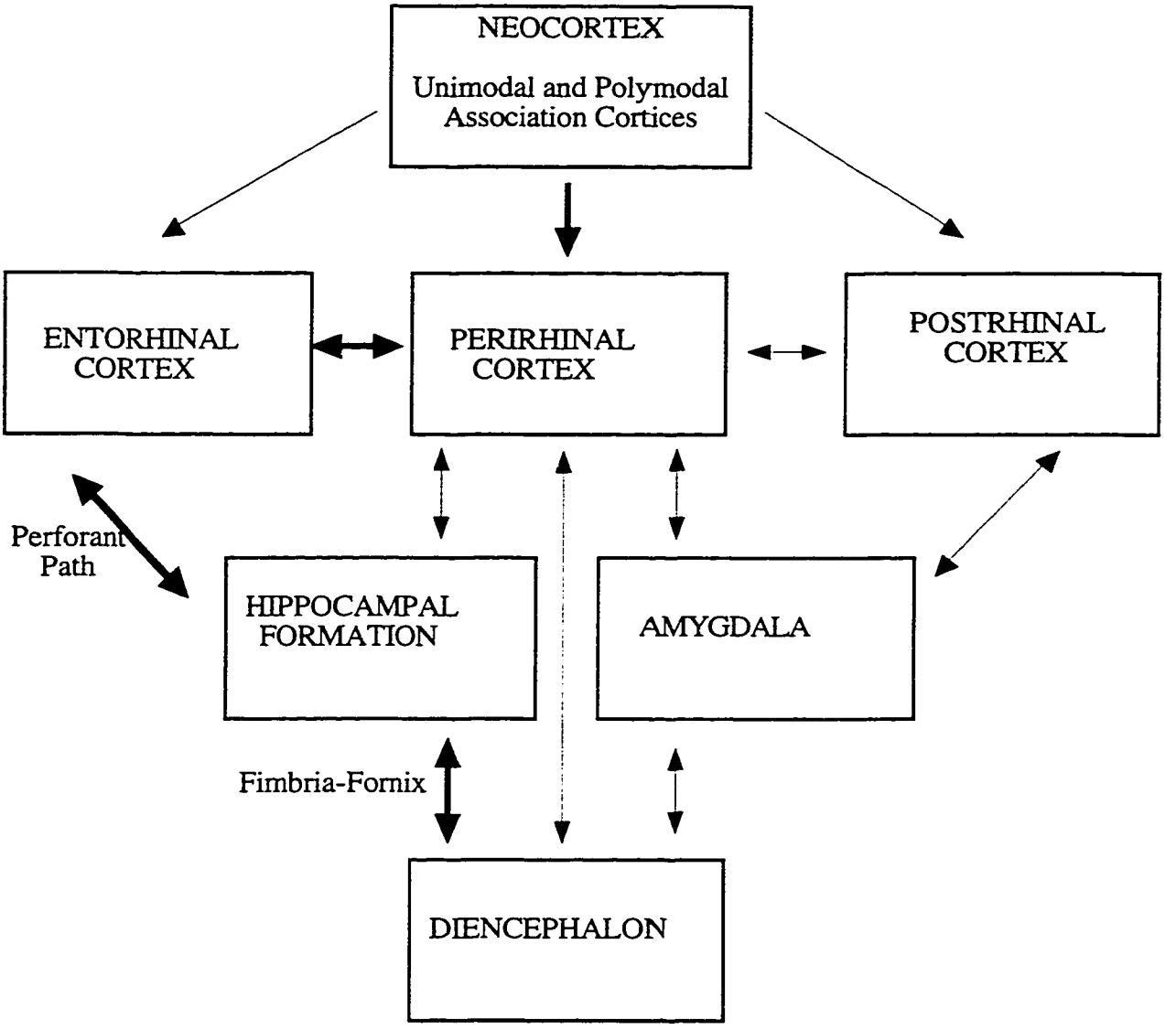


Figure 1. A schematic diagram showing the structures and connections of the medial temporal lobe.

multiple-system views. On the one hand, the pattern of dense projections from association cortices to the PRh and entorhinal cortex to the HPC may be interpreted as evidence for a single, critical pathway through which information is transmitted until processed by the HPC. On the other hand, there are routes that information output from structures, such as the PRh cortex, could take to other brain regions without involving the HPC.

2. Medial Temporal Lobe Amnesia

Observations of humans who have sustained brain damage in the medial temporal lobe provide important clues to the functional organization of memory in the medial temporal lobe. They also provide a basis for the design and implementation of animal models. These animal models are fundamental to our understanding of how the mammalian brain functions because they create controlled environments within which the effects of precise brain lesions on specific behaviours can be assessed. Also, with these animal models the extent of surgical lesions can be easily verified, whereas in humans analyses of brain damage are not possible until the death of the patient, or are limited to imaging methods, which can be costly, invasive, and inaccurate.

Amnesia is defined as a loss of memory in the absence of other cognitive disabilities. It is differentiated from generalized dementia which is classified as an overall reduction in cognitive functioning, including memory (Cohen and Squire, 1980). Amnesia is often the result of brain damage, either through accidental trauma or surgical lesion. The type of memory abilities impaired in the amnesic syndrome include memories associated with facts or events, sometimes referred to as declarative memory (Squire, 1986; Squire and Zola-Morgan, 1991). This type of memory is contrasted with nondeclarative memory, which is not impaired in the amnesic syndrome. Nondeclarative memory refers to procedural learning and implicit memory abilities, such as perceptual and motor skill learning, classical conditioning, and priming (Cohen and Squire, 1980; Squire, 1986; Squire and Zola-Morgan, 1991). Short-term memory abilities are also not impaired (Milner, Corkin, and Teuber, 1968).

Amnesia can be either anterograde or retrograde. Anterograde amnesia is an

inability to form new memories following the onset of amnesia. Retrograde amnesia is a loss of memories that were acquired prior to the onset of amnesia. Amnesia is typically associated with damage to one of either two brain regions: the diencephalon or the medial temporal lobe. This thesis focuses on medial temporal lobe amnesia.

2.1. Amnesia in Humans: Patient H.M. and Patient R.B.

In 1957 Scoville and Milner reported the case of a patient, referred to as H.M., who underwent a radical bilateral resection of the medial temporal lobe in an attempt to alleviate debilitating seizures (Scoville and Milner, 1957). Based on the surgeon's estimate, the lesion was reported to extend approximately 8 cm from the midpoints of the tips of the temporal lobes and to extend laterally to the temporal horns. This lesion would include a large portion of the HPC, the amygdala, and surrounding cortical areas (PRh, entorhinal cortex, and parahippocampal gyrus). Corkin, Amaral, Gonzalez, Johnson, and Hyman (1997) reported findings from a magnetic resonance imaging (MRI) assessment of H.M.s medial temporal lobe lesion. It was observed that the amount of HPC tissue reported removed was overestimated by Scoville and Milner (1957). Corkin et al. (1997) observed that the lesion does include large portions of the HPC, but it is not as large or as complete as was previously thought. The lesion also includes substantial portions of the PRh, amygdala, entorhinal cortex, and rostral portions of the posterior parahippocampal gyrus. There was some sparing of the ventral portions of the PRh and the temporal stem.

Following H.M.'s surgery, Scoville and Milner (1957) reported some success at attenuating the seizures, however, H.M. had sustained a severe memory impairment. An important observation was that the memory deficits occurred in the absence of other cognitive abnormalities (Scoville and Milner, 1957). Assessments of H.M. conducted after the surgery showed a profound anterograde amnesia, and temporally graded retrograde amnesia--memories from about 19 months before the surgery were completely lost, there was partial loss of memory for the preceding 3 years, and earlier memories were intact (Scoville and Milner, 1957). One of H.M.'s most striking anterograde deficits is impaired recognition memory. For example, he is unable to recognize hospital staff that he sees

several times per day, and he rereads books or magazines without remembering having read them previously (Scoville and Milner, 1957). He is also reported to have impaired spatial memory (Milner et al., 1968). His I.Q. and personality were not changed, and perception, abstract thinking, and motivation were reported to be normal (Scoville and Milner, 1957; Milner et al., 1968). H.M. is able to acquire new motor skills (Milner et al., 1968). He is also able to retain information for short periods of time when distractions are kept minimal during retention delays, though acquisition is slow (Milner et al., 1968). As discussed earlier this pattern of memory deficits is consistent with the defined parameters of medial temporal lobe amnesia--impaired declarative memory for events and information, but spared skill learning and intact short-term memory.

In addition to the case of H.M., Scoville and Milner (1957) reported a number of other cases in which similar bilateral resections of medial temporal lobe tissue were performed. It was noted by the authors that those patients sustaining the most extensive damage to the HPC had the most severe memory impairments. This led many researchers to suspect that the HPC is critically involved in memory.

In 1986, Zola-Morgan, Squire, and Amaral reported the case of another human amnesic, R.B (see also Squire, 1986). This patient, like H.M., sustained a marked deficit in memory in the absence of other cognitive abnormalities. R.B. became amnesic after an ischemic episode that occurred during a cardiac bypass operation. He lived for 5 more years and after his death an analysis of his brain revealed a substantial loss of cells in the CA1 cell field of the hippocampus proper. There was also some loss of cells in other brain regions, but only the damage in the HPC was extensive and bilateral. The case of R.B. provided compelling evidence that HPC damage was sufficient to cause the major symptoms of amnesia, including impaired recognition memory. The contribution of the damage to other areas was considered minimal as those areas were not thought to be important for memory.

Evaluations of other human amnesics revealed spared abilities in visual discrimination learning, the acquisition of new motor skills, and short-term memory (Milner, et al., 1968; see also Graf, Squire, and Mandler, 1984; Squire, Zola-Morgan, and

Chen, 1988; Squire and Zola-Morgan, 1991). They were able to recognize visual stimuli after very short delays, but as the delay period was lengthened beyond a few seconds or if there was distraction during the delay period, their performance rapidly worsened (Aggleton, et al. 1988; Squire and Zola-Morgan, 1991).

2.2. Delayed Nonmatching-to-Sample (DNMS)

The development of a successful animal model of amnesia was largely dependent on the determination of the types of memories impaired in human amnesics, and the development of tasks for nonhuman animals that would reflect the same types of abilities (Gaffan, 1974). A breakthrough in modeling human amnesia with animals came with the development of a test of object-recognition referred to as the trial-unique delayed nonmatching-to-sample task (DNMS). This task involves showing the subject a stimulus, usually an object, which is referred to as the sample. This sample stimulus is paired with a reward. After a delay period during which the sample is not visible to the subject, it is presented again, this time with another, different stimulus, referred to as the novel stimulus. The subject is rewarded for selecting the novel object. The subject receives many trials in this manner, and different object pairs are used on each trial. The DNMS task is sensitive to the impaired memory abilities of human amnesics, namely stimulus recognition with relatively long retention delays (Gaffan, 1974; Mishkin and Delacour, 1975). DNMS performance can be assessed at very short retention delays, and, to further tax memory, the delays can be lengthened, or the subject can be distracted during the delay. Like humans, the performance of monkeys declines as the retention delay is lengthened or if there is distraction during the delay period. Thus, the DNMS task appears to provide a good animal model of human amnesia.

The more recent development of object-based DNMS procedures for rats (Aggleton, 1985; Rothblat and Hayes, 1987; Mumby, Pinel, and Wood, 1990) made it possible to assess visual object-recognition memory performance in rats. The version of DNMS adapted for use with rats by Mumby et al. (1990) was used in an experiment of this thesis. Mumby et al. (1990) reported that rats were able to learn DNMS at brief delays, and

continued to perform successfully, that is, above chance levels, at delays as long as 600 seconds.

3. Contribution of Medial Temporal Lobe Structures to Object-Recognition Memory

Using the DNMS task with animals not only provided important clues to understanding amnesia, it also provided critical information about the functional organization of object-recognition memory within the medial temporal lobe. This section discusses studies that were conducted to determine the contribution of individual medial temporal lobe structures to impaired object-recognition using DNMS.

3.1. The HPC and Object-Recognition Memory

The observation by Scoville and Milner (1957) that patients with the most extensive removal of HPC tissue had the most severe memory impairments, and the case of patient R.B. (Squire, 1986; Zola-Morgan et al., 1986), led many researchers to suspect that the functions of the HPC were critical for normal object-recognition memory. In 1978, Mishkin observed severe DNMS deficits following combined, but not separate removal of the HPC and amygdala in monkeys (Mishkin, 1978). He found that monkeys with HPC+amygdala lesions, unlike monkeys with lesions of only the HPC or the amygdala, were severely impaired in reacquiring a presurgically learned DNMS task at a brief delay (10 seconds). The monkeys with the HPC+amygdala lesions required significantly more trials to relearn DNMS following surgery. After the monkeys reattained criterion performance on DNMS at the brief delay, Mishkin lengthened the delays to 30, 60, and 120 seconds. Again, the monkeys with the HPC+amygdala lesions, but not those with the single lesions, were severely impaired, performing just above chance. Mishkin's findings were replicated by others (Mahut, Zola-Morgan, and Moss, 1981; Zola-Morgan, Squire, and Mishkin, 1982; Saunders, Murray, and Mishkin, 1984; Zola-Morgan and Squire, 1985). Thus, it appeared that the HPC and the amygdala were contributing equally to object-recognition memory.

Rats with lesions of the HPC, or the fimbria-fornix--a major source of reciprocal connections between the HPC and subcortical structures--did not show an impairment on DNMS (Aggleton, Hunt, and Rawlins, 1986; Rothblat and Kromer, 1991; Mumby, Wood, and Pinel, 1992). Aggleton, Blindt, and Rawlins (1989) found that rats with combined HPC+amygdala lesions were impaired on DNMS at delays up to 60 seconds, though they were not impaired during acquisition of DNMS. By contrast, Mumby et al. (1992) reported that rats with combined HPC+amygdala lesions were not impaired on DNMS with retention delays as long as 120 seconds. Mumby et al. (1992) proposed that, at least in rats, damage to the HPC and amygdala do not produce DNMS deficits unless damage to the rhinal cortex is also present.

The rats in the Mumby et al. (1992) study received extensive presurgery training, whereas the rats in the Aggleton et al. (1989) study were not trained prior to surgery. Previous findings showed that monkeys without any presurgery training show more severe DNMS deficits following lesions of the HPC (Zola-Morgan and Squire, 1986; also see Squire and Zola-Morgan, 1991) than those trained on DNMS prior to surgery (Mishkin, 1978; Murray and Mishkin, 1984). Presurgery training provides a clearer interpretation of postsurgery performance deficits by eliminating the possibility that animals are not able to acquire non-mnemonic skills required for successful performance on the task.

Zola-Morgan and Squire (1986) reported that lesions restricted to the HPC and the adjacent cortex, which spared the amygdala, were sufficient to produce a significant DNMS impairment in monkeys (Zola-Morgan and Squire, 1986). This finding was inconsistent with findings in rats (Aggleton et al., 1986; Rothblat and Kromer, 1991; Mumby et al., 1992). Zola-Morgan, Squire, and Amaral (1989) found that lesions restricted to the amygdala, that spared the adjacent cortex and the HPC, did not disrupt DNMS performance in monkeys. This finding was consistent with reports that amygdala lesions in rats did not impair DNMS performance (Aggleton et al., 1986; Mumby et al., 1992). The amygdala is no longer believed to make a significant contribution to object-recognition memory (Zola-Morgan et al., 1989; Squire and Zola-Morgan, 1991; Murray, Gaffan, and Flint, 1996).

Mumby et al. (1992) proposed a number of explanations to account for the

discrepancy between the DNMS performance of monkeys (Mishkin, 1978) and rats (Mumby et al., 1992) with HPC+amygdala lesions. Rats and monkeys may solve the DNMS task in different ways, thus relying on the functions of different brain regions. It is also possible that the lesions were not comparable. Due to differences in the topography of the monkey brain, different cortical areas were damaged when aspirating the HPC and amygdala in rats. The ventral approach used to aspirate the HPC and amygdala in monkeys results in additional damage to the rhinal cortex, but in rats the dorsal approach results in additional damage to parietal cortex, and usually spares the rhinal cortex. Thus, an important difference between the HPC+amygdala lesions in monkeys and rats was the extent of additional damage to the rhinal cortex.

The recent development of stereotaxic lesion procedures for monkeys, guided by MRI, enabled researchers to lesion the HPC in monkeys while sparing adjacent structures. Selective lesions of the HPC and amygdala, that did not include damage to the rhinal cortex, were found to spare recognition memory in monkeys (O'Boyle, Murray, and Mishkin, 1993). This finding was consistent with previous findings in rats (Aggleton et al., 1986; Rothblat and Kromer, 1991; Mumby et al., 1992), and indicated that the HPC is not an important structure for object-recognition memory. In the following section the evidence that the rhinal cortex makes an independent and significant contribution to object-recognition memory is discussed.

3.2. The PRh and Object-Recognition Memory

Murray and Mishkin (1986) examined DNMS performance of monkeys with lesions of either the HPC plus rhinal cortex or the amygdala plus rhinal cortex. They examined the possibility that the damage to the rhinal cortex made a critical contribution to the DNMS deficits in monkeys with combined HPC+amygdala lesions (Mishkin, 1978). They found that lesions of the amygdala plus rhinal cortex produced severe DNMS deficits, whereas lesions of the HPC plus rhinal cortex produced only a mild impairment . Murray and Mishkin concluded that rhinal cortex damage in the monkeys with combined amygdala plus rhinal cortex lesions disconnected the HPC from neocortical input, thus emulating the

effects of combined HPC+amygdala lesions. They also concluded that the rhinal cortex damage itself does not make a direct contribution to the DNMS deficits observed in monkeys with HPC+amygdala lesions (Mishkin, 1978). This interpretation was consistent with previous interpretations that the HPC and amygdala must both be lesioned to produced DNMS deficits (Mishkin, 1982; Zola-Morgan, et al., 1982), and the damage to rhinal cortex was not critical (Mishkin, 1978). These findings would be later reinterpreted (discussed below).

Researchers investigating the effects of selective rhinal cortex lesions on DNMS performance found that these lesions, which spared the HPC and amygdala, produced deficits in monkeys (Gaffan and Murray, 1992; Suzuki, Zola-Morgan, Squire, and Amaral, 1993; Eacott, Gaffan, Murray, 1994, Meunier, Bachevalier, Mishkin, and Murray, 1993; Meunier, Hadfield, Bachevalier, and Murray, 1996; Murray, Gaffan, and Flint, 1996) and rats (Mumby and Pinel, 1994). Also, Meunier et al. (1993) showed that lesions restricted to the PRh, but not lesions of the entorhinal cortex, produced severe DNMS deficits in monkeys. These findings suggested that the rhinal cortex and the PRh in particular, is critically involved in object-recognition memory. Meunier et al. (1996) reexamined the interpretations made by Murray and Mishkin (1986) that the amygdala plus rhinal cortex lesions produced DNMS deficits because the rhinal cortex lesions had deafferented the HPC. They pointed out that the amygdala plus rhinal cortex lesion included the most rostral portions of rhinal cortex, corresponding to the PRh, whereas the HPC plus rhinal cortex lesions spared this portion of rhinal cortex. Other studies that found DNMS deficits following lesions that included the PRh (Gaffan and Murray, 1992; Suzuki et al., 1993; Meunier et al., 1993; Eacott et al., 1994) supported the conclusion that damage to the PRh, and not the combined lesions of HPC+amygdala, was critical in producing DNMS deficits. Therefore, it was likely that the HPC plus rhinal cortex lesions in the monkeys from the Murray and Mishkin study (1986) did not include enough damage to the PRh to disrupt DNMS performance, whereas the amygdala plus rhinal cortex lesions included substantial PRh damage that disrupted DNMS performance. In addition, the findings that combined lesions of the HPC and amygdala were necessary to produce memory deficits (Mishkin,

1978; Zola-Morgan et al., 1982; Saunders et al., 1984) were likely also due to more extensive rhinal cortex damage in monkeys with HPC+amygdala lesions.

Meunier et al. (1996) interpreted the findings of the abovementioned studies as an indication that there are multiple memory systems within the medial temporal lobe, and that the PRh, but not the HPC or amygdala, is central to a system that supports object-recognition memory. Studies conducted in rats point to a similar conclusion, namely that lesions of the PRh, and not the HPC and/or amygdala, are sufficient to produce DNMS deficits (Mumby et al., 1994).

4. Contribution of Medial Temporal Lobe Structures to Spatial Memory

According to the evidence discussed above, HPC lesions do not impair object-recognition memory, whereas PRh lesions produce deficits. As will be outlined in the following section, the HPC is critically involved in spatial memory. It is not clear what role the PRh plays in spatial memory, or whether the functions of these two structures are also dissociable in terms of the processing of spatial information.

4.1. The HPC and Spatial Memory

An inability of HPC lesioned rats to navigate successfully in different types of mazes is a well documented finding (Douglas, 1967; O'Keefe and Nadel, 1978; Olton and Papas, 1979; Olton, Walker, and Wolf, 1982; Eichenbaum, Otto, and Cohen, 1992; Jarrard, 1993) that has contributed much to our understanding of the neuroanatomy of spatial memory.

O'Keefe and Nadel (1978) proposed that the HPC stores cognitive maps. They hypothesized that through repeated experience within a particular environment an animal would store information about the spatial layout of the environment, including visual, auditory, olfactory, and tactile cues. An animal can quickly navigate in the environment if it is able to remember the location of cues relative to one another. According to O'Keefe and Nadel, the cognitive map is flexible, and can incorporate changes in the position of cues relative to the animal as it moves through the environment.

O'Keefe and Nadel (1978) differentiated between two types of navigation, only one of which they proposed to be dependent on HPC function. One type of navigation is referred to as egocentric spatial memory. This type of memory involves the encoding of a series of movements that can be reenacted reliably on subsequent exposures to an environment to reach a particular location. For example, to get from a point A to a point B the animal could remember that always turning right and then left is sufficient. This egocentric navigation does not require the encoding of cues within the environment and it can be contrasted with another type of navigation referred to as allocentric spatial memory. Allocentric navigation requires the storage of cues external to the animal, within the environment--namely a cognitive map. The cognitive map enables the animal to choose a variety of paths to reach point B from point A, and the animal can get to point B from any position within the environment. According to O'Keefe and Nadel the HPC stores these cognitive maps and therefore supports allocentric, but not egocentric spatial memory.

Studies that assessed the firing patterns of individual cells within the HPC, while a rat was exploring an environment, provide electrophysiological evidence that the HPC has a specialized role in processing spatial information and creating and storing cognitive maps. O'Keefe (1976) was able to identify specific cells in the HPC that would fire only when the rat was within a particular area within a familiar environment. These cells, referred to as place cells, were observed to reliably signal a rat's location in the environment relative to distal cues (O'Keefe, 1976; O'Keefe and Nadel, 1978).

The development of sensitive procedures that can be used to directly assess the ways in which an animal might navigate to a certain location within an environment have contributed a significant amount of knowledge about hippocampal function, as well as knowledge regarding what other structures may contribute to spatial memory. Morris (1981) developed a procedure to assess spatial memory in rats. The task used a circular maze filled with opaque water in which a platform was submerged slightly below the water level. The platform was not visible to a rat swimming in the maze. A rat placed in this maze learns to search the pool for the hidden platform. Once the rat finds the platform, it may climb onto it to escape from the cool water. In the original version of this spatial task

the platform remains stationary throughout training, but release locations into the pool are varied. Cues external to the maze are available and constant, and rats will readily learn the platform's location relative to them.

Morris, Garrud, Rawlins, and O'Keefe (1982) and Sutherland, Whishaw, and Kolb (1983) found that rats with lesions of the HPC were severely impaired on this task, as would have been predicted by O'Keefe and Nadel (1978). Other experiments in which the water maze or other spatial memory procedures were used clearly show that an intact HPC is necessary for an animal to successfully encode and later utilize spatial information about environments (Bouffard and Jarrard, 1988; DiMattia and Kesner, 1988; Devan, Goad, and Petri, 1996; also see Sherry, Jacobs, and Gaulin, 1992; Jarrard, 1993).

4.2. PRh and Spatial Memory

Despite the recent focus on the PRh and its role in object-recognition memory, there have been relatively few examinations of its role in spatial memory. Some studies report that spatial memory is normal following lesions of the PRh cortex in rats. Aggleton, Worburton, and Nakamura (1996) found that rats with PRh lesions were not impaired on a delayed spatial alternation task in a T-maze. Ennaceur, Neave, and Aggleton (1996) also found that PRh lesions did not impair delayed spatial alternation in a T-maze. In addition, they found that rats with PRh lesions performed normally on a delayed nonmatching-to-position task and a spatial discrimination in an operant chamber. Wiig and Bilkey (1994a) found that subtotal lesions of the PRh did not produce an impairment in rats' ability to learn the location of a stationary and hidden platform in a water maze.

By contrast, Wiig and Bilkey (1994b) found that larger lesions of the PRh produced a mild impairment in rats' ability to learn the location of a stationary and hidden platform in a water maze. Nagahara, Otto, and Gallagher (1995) reported deficits on a spatial working memory task with lesions of the PRh in rats. The task was delayed matching to place in a water maze, with retention delays of 30 seconds and 5 minutes. They observed that rats with lesions of the PRh were impaired at the 5 minute delay. The lesions made by Nagahara et al., however, included large portions of the entorhinal cortex, a major

source of input to the HPC.

Several important differences are evident between the studies which suggest that the PRh is involved in spatial memory, and the studies that do not. These differences include the size and location of the PRh lesions, the spatial tasks used, and the amount of presurgery training. This thesis primarily addresses the latter two differences. The stationary platform task in the water maze used by Wiig and Bilkey (1994a; 1994b) requires that the rat learn and remember a single location within an environment over multiple trials. DNMS, the task on which PRh, and not HPC, lesioned animals are impaired, requires subjects to learn and remember a different object on each trial. Therefore, examining the effect of lesions of the PRh on a spatial, one-trial memory task would provide a more complete picture of its role in spatial memory. Nagahara et al. (1995) found that PRh lesions produced deficits on a spatial working memory task, but they did not train the rats prior to surgery. As noted earlier, monkeys with HPC lesions that did not receive presurgery training on DNMS showed a more marked impairment following HPC lesions (Squire and Zola-Morgan, 1991). The possiblity that PRh lesions in rats impair performance on a presurgically acquired spatial memory task was addressed in both experiments in this thesis.

5. Functional Interaction of the HPC and PRh

It is clear from the evidence reviewed above that the HPC is critical for spatial memory, but not object recognition. The PRh, on the other hand, appears critical for object recognition, but it is not clear from the available evidence if it is critical for spatial memory. Models of unitary and multiple medial temporal lobe memory system have attempted to account for these findings.

5.1. Unitary Medial Temporal Lobe Memory System Model

The initial findings that combined, but not separate, lesions of the HPC and amygdala produced severe object-recognition deficits stimulated the development of models to explain this pattern of results. Squire and Zola-Morgan (1988; 1991) view the structures

in the medial temporal lobe as part of a unitary memory system. This system is critical for declarative memory, the type of memory impaired in human amnesia, but it is not essential to nondeclarative memory, the type of memory spared in human amnesia. Proponents of this model view the functions of medial temporal lobe structures as interdependent. Unimodal features of stimuli converge in neocortex, and highly processed multimodal information is relayed to medial temporal lobe cortical areas, including temporal association cortex, PRh and entorhinal cortex, and parahippocampal cortex. These areas relay information to the HPC, the central mnemonic structure that forms and stores declarative memories. Squire and Zola-Morgan's (1991) medial temporal lobe memory system emphasized the importance of the HPC and the adjacent cortices. They view the role of the adjacent cortex as more than just a pathway for information to reach the HPC from neocortex. Instead, the adjacent cortex functions interdependently with the HPC to process and organize information. This model fails to account for findings that lesions of the HPC and amygdala, which spare the rhinal cortex, do not produce DNMS deficits (O'Boyle, Murray, and Mishkin, 1993).

Eichenbaum, Otto, and Cohen (1994) recently developed a model that accounts for the findings that PRh lesions, and not HPC lesions produce DNMS deficits. They also view the structures in the medial temporal lobe as being part of a unitary memory system. They do, however, distinguish two functional units within the system. The HPC, or hippocampus proper, dentate gyrus, and the subiculum, comprises one functional unit which Eichenbaum et al. refer to as the "hippocampal formation". The PRh, entorhinal cortex, and parahippocampal cortex comprise the other functional unit which Eichenbaum et al. refer to as the "parahippocampal region". According to their model the HPC is critically involved in forming relations between stored representations of individual items, regardless of the specific type of information represented by a given item. The parahippocampal region stores intermediate-term representations of individual items and transmits these representations to the HPC for relational processing. In this model, the HPC is critical to spatial memory because this type of memory relies on the relational processing of separate representations of different aspects of an environment. Eichenbaum

et al. do not view the functions of the HPC as critical to object recognition. In their model this type of memory is adequately supported by the representation of single items in the parahippocampal formation. Therefore, the parahippocampal region can support DNMS performance without requiring the functions of the HPC by using intermediate-term representations of objects. The authors also argue that the demonstration that HPC lesions produce DNMS deficits at very long delays (Squire, 1982) is indicative of the inability of the parahippocampal formation to successfully support performance at delays that surpass the capacity of the intermediate-term storage.

Eichenbaum et al.'s (1994) model makes important, testable predictions. According to their model the functions of the HPC are dependent on information relayed to it from the parahippocampal formation. It is, therefore, possible that the parahippocampal formation may function independently of the HPC. The HPC, however, would necessarily require the integrity of the parahippocampal formation to function properly. It would not be possible, according to this model to observe a double dissociation of function between the HPC and the parahippocampal formation. Any memory abilities observed to require HPC function should be impaired following lesions to the parahippocampal formation, as those functions requiring HPC function would necessarily rely on input from the parahippocampal formation. To accurately assess their model, however, it would be necessary to make complete lesions of the parahippocampal region. The experiments in this thesis focused solely on the contribution of the PRh.

5.2. Multiple Medial Temporal Lobe Memory Systems Model

The alternative to a unitary medial temporal lobe memory system is that structures, like the HPC and PRh, may function independently of one another. According to one such view there are at least two separate memory systems within the medial temporal lobe. Mumby et al. (1994) and Meunier et al. (1996) propose that the PRh is a central structure in a memory system designed to store information about objects, including tactile, olfactory, and visual features (see also Mishkin and Murray, 1994 and Murray, 1996). The HPC is not part of this memory system. It has also been proposed that the HPC is a central

structure in a memory system designed to store information about places (Mumby et al., 1994; Aggleton et al., 1996; Ennaceur et al., 1996).

6. General Purpose and Rationale

The view that the HPC is part of a memory system specialized to process spatial information and the PRh is part of a memory system specialized to process object information predicts that lesions of the HPC, but not the PRh, will impair spatial memory, and lesions of the PRh, but not the HPC, will impair object-recognition memory.

Both experiments of this thesis examined the role of the PRh in spatial memory. Rats were trained on an allocentric spatial memory task, delayed matching to place (DMTP). This task was conducted using a water maze. DMTP trials consisted of paired swims in which the rat located a platform in the maze on the first swim, then, following a delay, the second swim permited the rat to return to the same location to escape onto the platform. The primary dependent measure was the latency to escape onto the hidden platform. This task is similar to DNMS in that both procedures involve single trial learning with trial unique stimuli, and they both involve retention delays between the sample and choice phase of trials. There is an important difference between DNMS and DMTP. On each trial of DNMS the animal must remember a specific object, whereas on each trial of DMTP the animal must remember a specific location in the maze.

In Experiment 1 rats were extensively trained on the DMTP task prior to receiving bilateral surgical aspiration of the PRh or bilateral ibotenic acid lesions of the HPC. Based on the hypothesis that these two structures are part of independent memory systems, and that the functions of the HPC are critical to spatial memory and the functions of the PRh are critical to object-recogntion memory, it was predicted that the rats with HPC lesions would show DMTP deficits, but rats with PRh lesions would not be impaired.

Experiment 2 of this thesis sought to determine whether there is a functional double dissociation between the HPC and PRh. Rats were extensively trained on the DMTP task and the DNMS task prior to receiving bilateral surgical aspiration of the PRh or bilateral NMDA lesions of the HPC. In accordance with the multiple memory systems view, it was

expected that the rats with PRh lesions would show DNMS deficits, but not DMTP deficits. By contrast, rats with HPC lesions were expected to show DMTP deficits, but not DNMS deficits.

EXPERIMENT 1

The first experiment of this thesis was designed to examine the role of the PRh in allocentric spatial memory. Findings from previous studies do not consistently indicate that the functions of the PRh are important for spatial memory (Wiig and Bilkey, 1994a, 1994b; Nagahara et al., 1995; Aggleton et al., 1996; Ennaceur et al., 1996). This experiment sought to determine whether the PRh is critically involved in supporting the HPC in processing spatial information by examining the effects of lesions of the PRh or the HPC in pretrained rats on DMTP in a water maze. Consistent with the view that there are multiple memory systems in the medial temporal lobe and the HPC is a critical component in a system that is primarily involved in supporting spatial memory and the PRh is a critical component in a system that is primarily involved in supporting object recognition, it was predicted that HPC lesions, but not lesions of the PRh, would impair performance on the DMTP task.

METHOD

Subjects

The subjects were nineteen adult, male Long-Evans rats (Charles River, Quebec), weighing between 300-350 g at the start of the experiment. The rats were individually housed in plastic opaque (45 x 25 x 20 cm) with continuous access to water, and were fed approximately 25 g of rat chow once per day. The colony room was maintained at 210C with a 12:12 light:dark cycle (lights on at 8 am). All training, testing, and surgical procedures were conducted during the light phase of the cycle.

Apparatus

The water maze was a circular pool, 137 cm in diameter and 46 cm high. A movable platform was constructed of clear Plexiglas with dimensions 10 cm x 10 cm x 28 cm. The water exceeded the height of the platform by approximately 2 cm and was made opaque through the addition of skim milk powder. Water temperature was maintained at approximately 23°C (±1°C). Swim paths were tracked using a VP118 Super Tracker (HVS Image Ltd, Hampton, UK), accompanied by a video monitor (Panasonic, WV-BM900), a video camera (Panasonic, WV-BL200), and a computer (IBM compatible, 486 DX). Data were summarized and extracted using HVSWater software. Extramaze cues, such as posters, laboratory equipment, and sounds from a radio and the computer remained in fixed locations throughout the experiment.

Surgery

All rats were extensively trained on DMTP prior to surgery (see below for details). Between 24 and 72 hours following the completion of presurgery training and testing, rats received either PRh lesions (n=7), HPC lesions (n=7), or Sham lesions (n=5). Rats were given an injection of atropine sulfate (1.0 mg/kg, s.c.) approximately 15 min prior to being anaesthetized with sodium pentobarbital (65 mg/kg, i.p.) . All surgical coordinates were based on Paxinos and Watson's (1992) stereotaxic atlas. A stereotaxic apparatus (David Kopf Instruments, Tajunga, CA) was used. The incisor bar was placed at -3.3 mm relative to the intra-aural line.

For the PRh lesions the scalp was incised along the midline and the skin and muscle were deflected to expose the skull overlying the PRh. An area of the skull, slightly smaller than the PRh, was removed using a dental drill. The underlying PRh was aspirated using a glass Pasteur pipette (1 mm in diameter) attached to a vacuum pump (Gomco Surgical Manufacturing Corp., Buffalo, N.Y., USA). Sterile Gelfoam (Upjohn, Don Mills, Ontario, Canada) was placed in the cavity, the skin and muscle were repositioned, and the wound was sutured.

HPC lesions were made using ibotenic acid (5 µg/µl dissolved in 0.1 M phosphate

buffered saline, PBS pH = 7.4; Sigma Chem. Co., St. Louis, MO)). The ibotenic acid was infused at 10 sites per hemisphere at a flow rate of 0.1 µl/min over a period of 2.5 min for a total injection volume of .25 µl of ibotenic acid per site. The coordinates for the sites, relative to bregma are shown in Appendix A. The injections were made using a micro infusion pump (KD Scientific) and 10 µl Hamilton syringes. The injection cannulae were 30 gauge needles through which the neurotoxic was infused using a connecting 23 gauge needle attached to PE50 tubing that in turn connected to the Hamilton syringes. To allow the neurotoxin to diffuse away from the cannulae, the cannulae were left in place for 2 min following each infusion before being removed. Sham operated rats underwent the same procedure, except the cannulae were lowered only to a point near the dorsal surface of the hippocampus, 2 mm ventral to bregma, and there was no infusion of ibotenic acid.

All rats received topical treatment with an antibiotic powder (Cicatrin) to the incision wound, and 0.2 ml of Ayercillin (sterile penicillin G, i.m.). Hippocampal lesioned rats received 1 mg of diazepam (Hoffmann-La Roche, Mississauga, Ontario, Canada; i.m.) in an injection volume of 0.2 ml, upon awakening, to prevent seizures that sometimes occur following HPC lesions. Rats were permitted to recover for 10 to 14 days during which time food was freely available. One HPC lesioned rat died during recovery leaving 6 rats in the HPC group.

Procedure

Presurgery training: Fixed platform task. Rats were transported to the water maze testing room in groups of 6 or 7 and were singly housed there in covered wire mesh cages. Four equally spaced points along the perimeter of the pool were designated N, S, W, and E and served as release points. On each trial the rat was placed in the pool, facing the wall at one of the release points. The platform was located in the center of the NE quadrant on each trial. The sequence of release points across trials within each session varied, but each release point was used an equal number of times per session. The rat was allowed a maximum of 60 seconds to locate the hidden platform and escape from the water. If the rat did not locate the hidden platform within 60 seconds the experimenter guided it there by

hand. At the end of each trial the rat remained on the platform for 10 s. The primary dependent measure was the rat's latency to escape from the water onto the platform. Each rat received 8 trials per day for 4 days. A probe trial was conducted immediately following the final trial on Day 4. For this trial the platform was removed from the pool and the rat was allowed to swim for 60 s. The dependent measure was the proportion of the 60 second swim time spent in the quadrant of the pool that previously contained the platform.

Presurgery training: Delayed matching-to-place (DMTP) at a 4 second delay. Each delayed matching-to-place trial consisted of two parts: The rat was first allowed to find the hidden platform and escape from the water. Following a 4 second retention delay, which it spent in an opaque plastic cage, the rat was again placed into the pool at the same release point and allowed to find the platform in the same location, and escape from the water. The platform was in the same location for both swims of a trial, but was moved to a different location on successive trials. On each part of the trial the rat had a maximum of 60 seconds to escape onto the platform, and if it failed to do so within the 60 seconds the experimenter guided it to there by hand. There were 4 trials per day.

The rats were gradually introduced to the moving-platform procedure. On the first day, one location was used for all 4 trials. On the second day a different platform location was used for the 4 trials. On the third and fourth day a different platform location was used for the first 2 trials, and another platform location was used for the second 2 trials. On the fifth day, and thereafter, the platform location varied on each successive trial within and across sessions.

A total of ten different platform locations were used (see Figure 2). The particular locations were chosen in order to ensure that any non-spatial strategy that a rat may employ to locate the platform would not be sufficient to adequately support performance--for example, always swimming close to the perimeter of the pool, or always looking in the center of each quadrant. Therefore some of the locations were situated toward the edge of the pool, the centers of the quadrants, and the center of the pool. Rats received 10 sessions with the 4 second delay to ensure they reached asymptotic performance levels before the retention delay was increased.

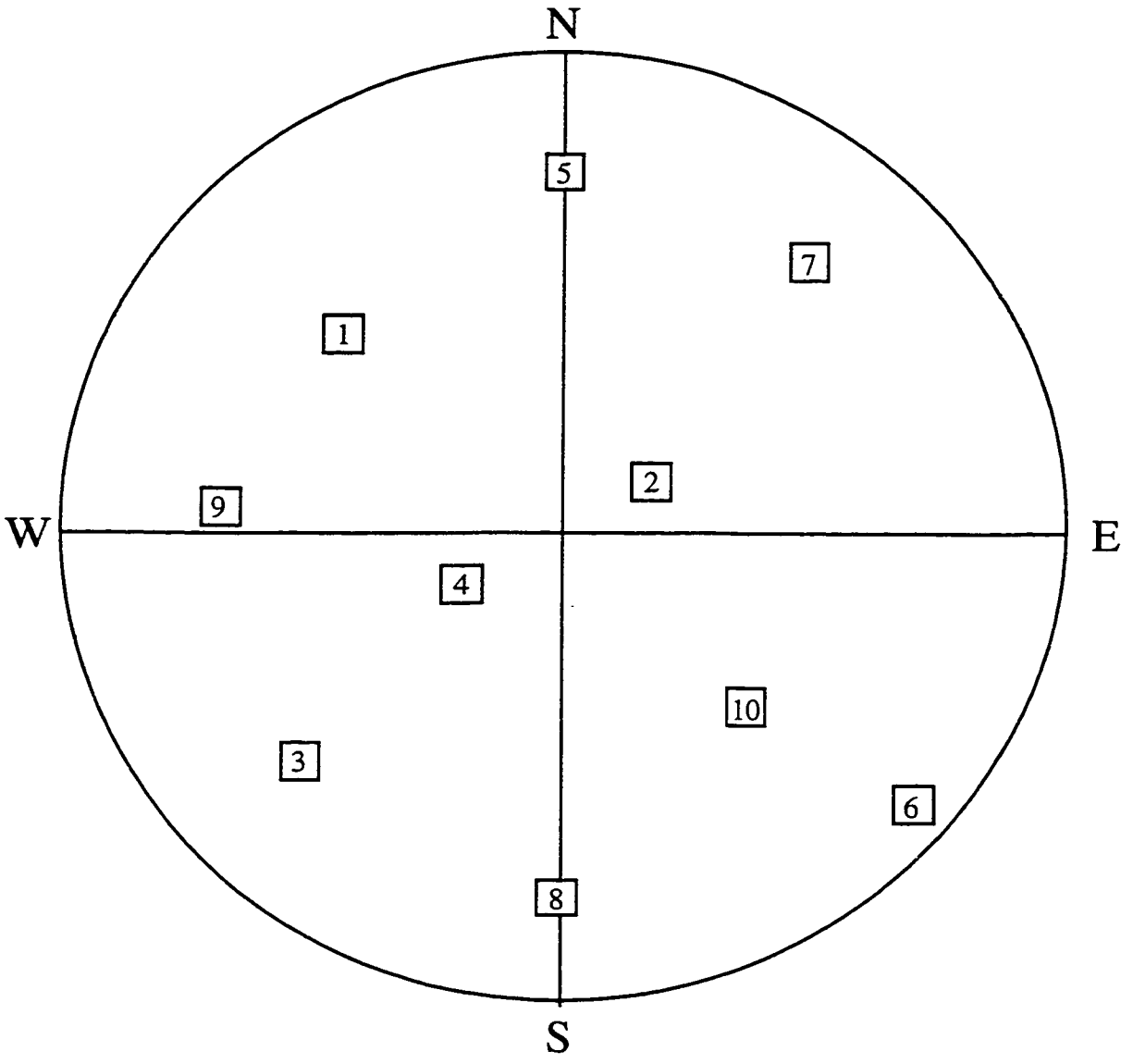


Figure 2. A schematic diagram showing the 10 different platform locations used during training and testing on the DMTP task in the water maze.

Presurgery training: Delayed matching-to-place (DMTP) training at successively longer delays. After the 10 training days with the 4 second delay, the delay period was successively increased to 30, 120, and 300 seconds. Each rat received 4 days (i.e., 16 trials) at each delay before being trained at the next longest delay.

Presurgery testing: Mixed-delay sessions. Following training at each of the longer delays, 15 mixed-delay sessions were conducted. A mixed-delay session consisted of 4 trials, one at each of the four delays (i.e., 4, 30, 60, and 120 seconds). The delays occurred according to a predetermined pseudo-random order so that each delay occurred in each of the 4 trial positions (first trial, second, third, and fourth trial) about equally often. Each of the 10 platform locations were used approximately the same number of times at each delay.

Post-surgery testing: Reacquisition of DMTP at the 4 s delay and mixed-delay sessions. All rats received at least 5 sessions of DMTP retraining at the 4 s delay. Whether or not individual rats received further retraining, beyond the minimum 4 days, was determined by whether they had reattained asymptotic performance. Rats that did not show an asymptotic level of performance, based on their latency to escape onto the platform on the second swim, were further retrained until it was evident that their performance was stable. A rat was to determined to have reached asymptotic performance at the 4 second delay if their mean latency per session did not differ more than 10 s over 3 consecutive sessions, and if there was no more than 1 trial with a 60 second escape latency. After performance reached an asymptote at the 4 s delay, each rat received 15 mixed delay sessions.

DMTP with a visible platform. When all other post-surgery testing was complete a visible platform task was conducted to determine whether all rats were equally proficient at swimming and navigating to a target location. Rats received one session in which the procedure was the same as that for the DMTP procedure with the 4 second delay, except that the platform was visible during the entire session. Black electrical tape was placed around the top 2 cm of the platform. The platform was elongated by attaching a 2 cm plastic box to the bottom. When the elongated platform was placed in the water maze the 2 cm

portion of the platform lined in black tape was above the level of the water, and visible to a rat swimming in the maze.

Histology

Following behavioural testing rats received an overdose of sodium pentobarbital, i.p., and were perfused though the heart with 0.9% saline followed by 10% buffered formalin. Brains were extracted and stored in 10% buffered formalin. Hippocampal lesioned brains were sectioned using a vibratome. PRh lesioned brains were photographed prior to slicing, to obtain a permanent record of the lateral view of the lesion. They were then transfered to a 30% sucrose-formalin solution for 2 days to protect against freeze damage during subsequent sectioning of the frozen brains with a sliding microtome. All brains were sliced at a thickness of 30 μm and every tenth section through the lesion site was retained and mounted on gelatin coated slides and stained with cresyl violet.

Statistical Analyses

The primary dependent measure was the latency of rats to escape onto the hidden platform. Other measures obtained from the postsurgery mixed-delay sessions included savings ratios (computation described below), total distance swam (cm) on the first and second swims of trials, and swim speed (cm/s) for the first and second swims of trials. Mixed factorial analyses of variance were used to analyze the pre- and postsurgery escape latencies, postsurgery savings ratios, path length, and swim speed on the first and second swims of trials at each delay. The between factor in the analyses of variance was Group (HPC, PRh, and Sham), and within factors were Test Time (pre- and postsugery), Delay (4, 30, 120, and 300 seconds), and/or Swim (first and second). Planned pairwise comparisons (t-tests) between each of the groups at each Test Time, Delay, or Swim were computed for the above measures. A critical confidence level of .05 was used for all statistical tests.

RESULTS

Histological Results

Figure 3 shows the location and extent of the HPC lesions. There was minor variability in the extent of the hippocampal damage between rats. The lesions included all or most of the hippocampal cell fields and the dentate gyrus. Damage to the dorsal HPC was most complete and consistently damaged in all rats. Most lesions spared significant portions of the fimbria fornix, corpus callosum, and other white matter. The most variability was observed in the ventral HPC. There was varying amounts of significant sparing of the subicular complex. Cannula tracts were evident in most rats, resulting in unspecific, but minimal and asymmetrical, damage to the overlying pariatel cortex. There was no detectable damage to thalamic structures.

Figure 4 shows the location and extent of the PRh lesions on the lateral surface of the rat brain. Figure 5 shows the coronal view of the location and extent of the PRh lesions. The amount of variability in the size and location of the PRh lesions was greater than that seen in the hippocampal lesions. As seen in Figure 4, the lesions frequently included damage to temporal association cortices, the entorhinal cortex, and the postrhinal cortex. The posterior PRh was consistently lesioned in each rat with the most consistent and symmetrical sparing occurring in the anterior PRh. The entorhinal cortex damage, though sometimes quite significant, was rarely bilateral and typically included only lateral portions of entorhinal cortex. Incidental damage to temporal association cortex was also rarely bilateral within a lesion. Many of the lesions extended to include portions of the ventral HPC. In only a few cases was there significant and bilateral damage.

Behavioural Results

Presurgery training and testing

Fixed platform task. There were no significant differences in the groups' latencies to escape onto the hidden platform during training on the fixed platform task ($F < 1$, see Figure 6). During the probe trial--where the platform was removed from the pool and the rat was permitted to swim in the pool for 60 seconds--all rats showed a similar preference

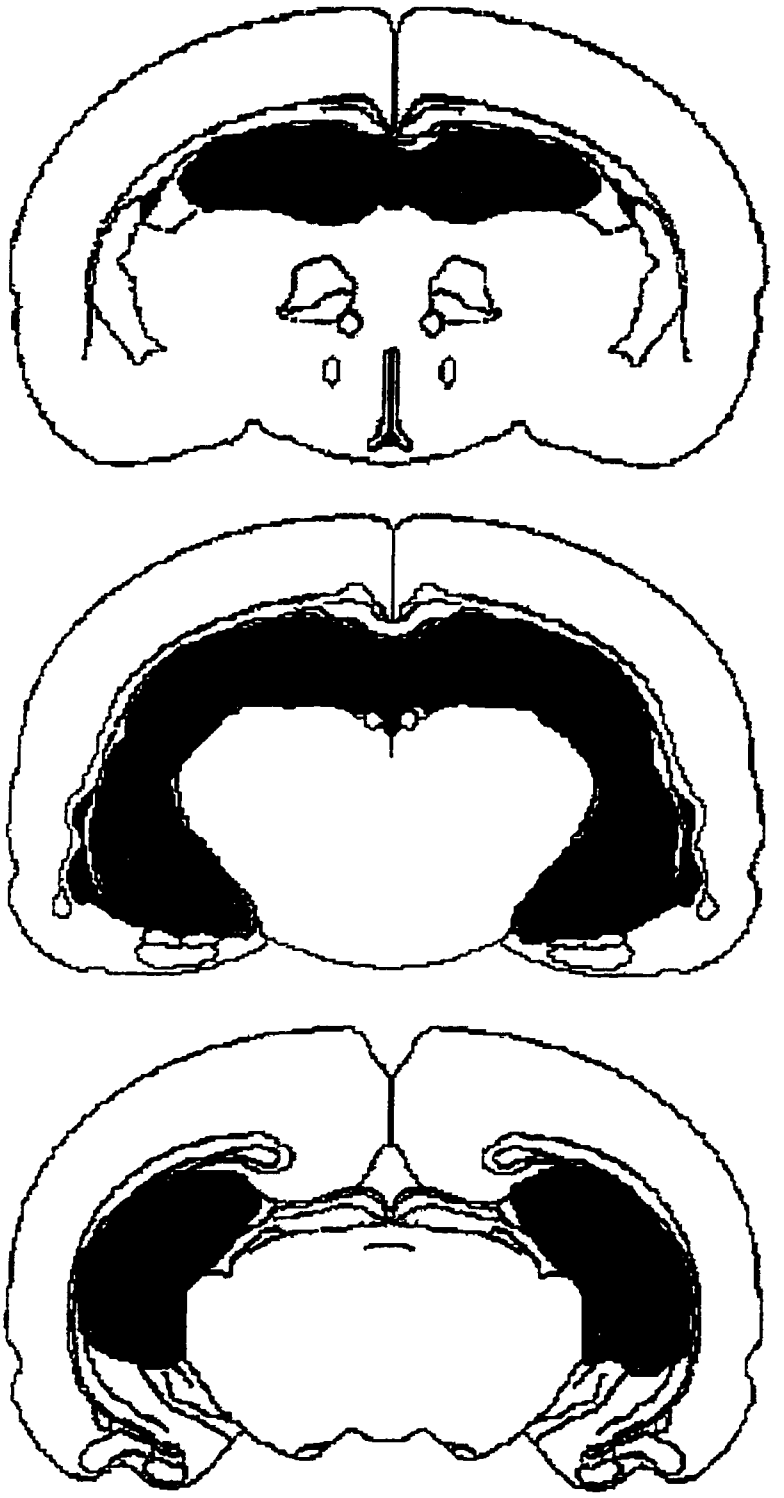


Figure 3. A schematic representationof the coronal view of the largest and smallest HPC lesions. The largest HPC lesion is represented by the light shading and the smallest HPC lesion is represented by the dark shading. (Adapted from Paxinos and Watson, 1968).

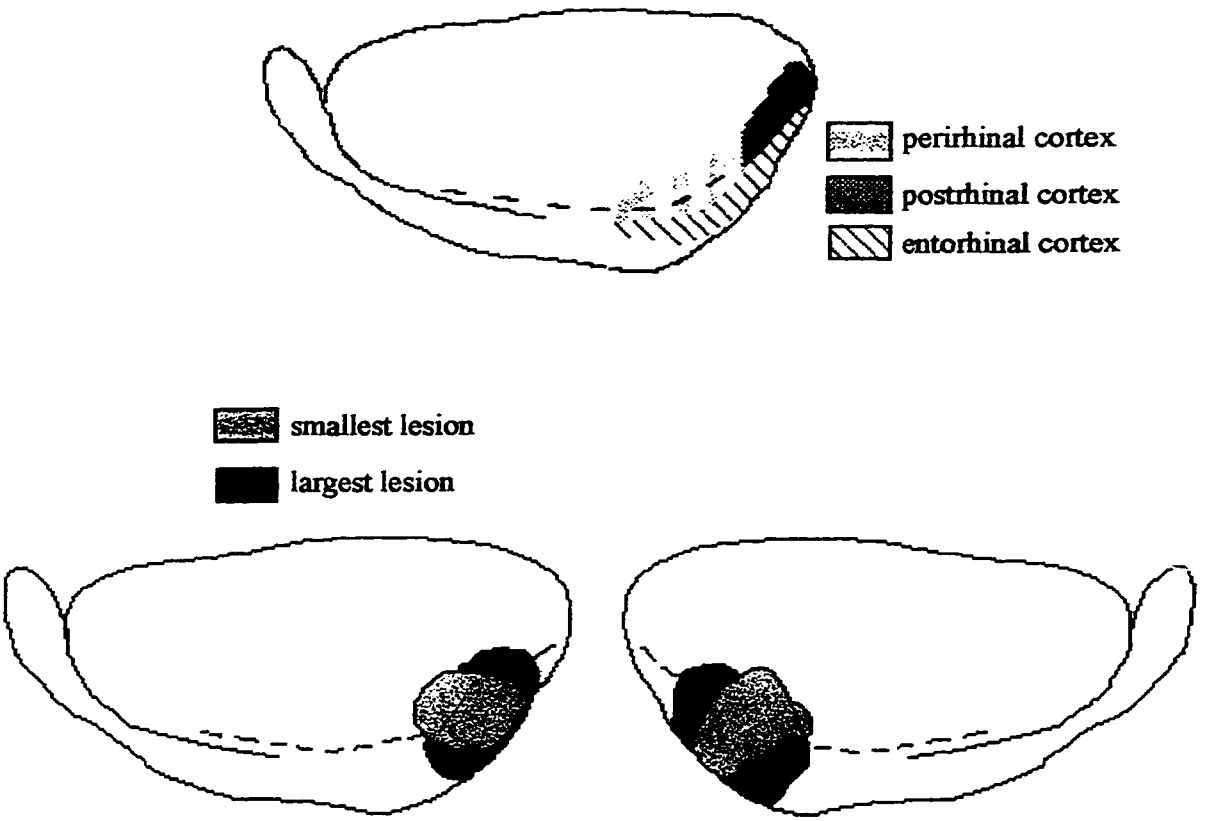


Figure 4. The lateral view of the boundaries of structures in the rhinal cortex are represented in the uppermost schematic diagram. The bottom schematic shows the lateral view of the largest and smallest PRh lesions. (Adapted from Burwell, Witter, and Amaral, 1995).

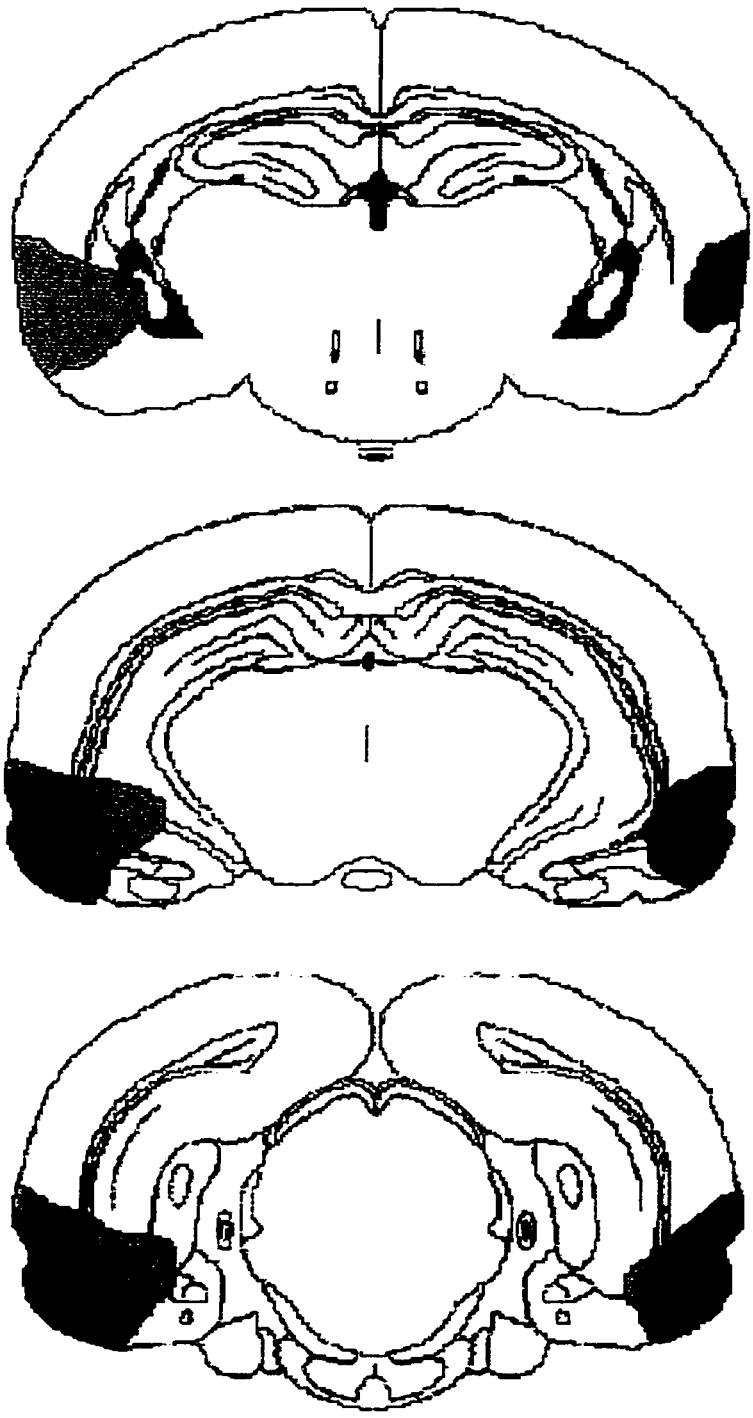


Figure 5. A schematic representation of the coronal view of the largest and smallest PRh lesions. The largest PRh lesions is represented by the light shading and the smallest PRh lesion is represented by the dark shading. (Adapted from Paxinos and Watson, 1986).

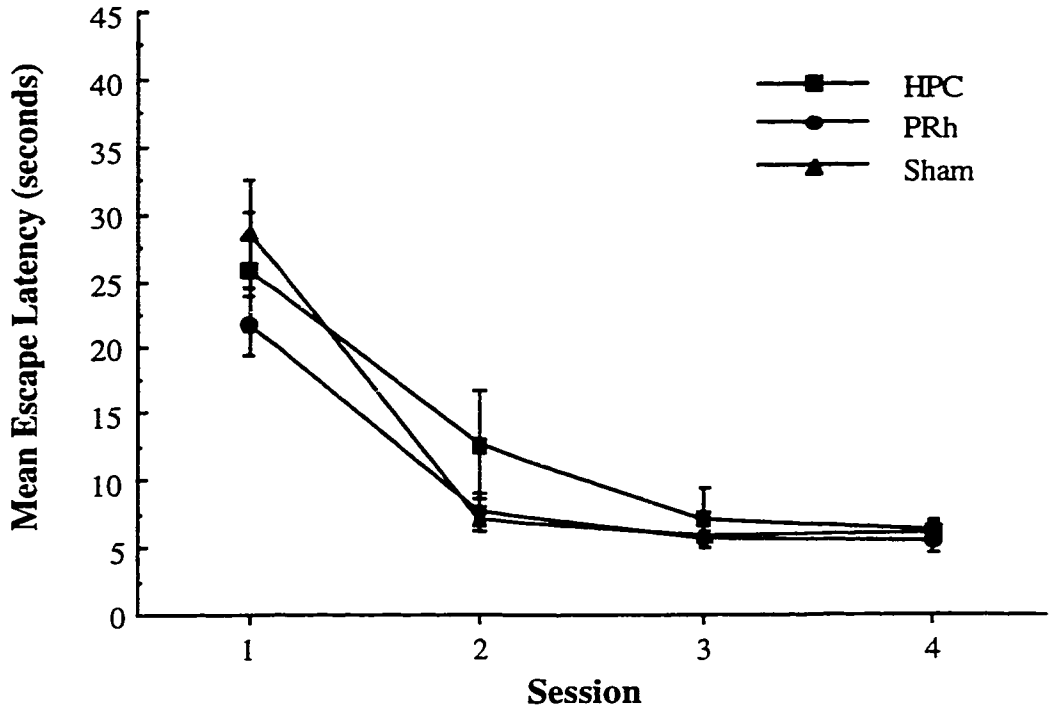


Figure 6. The mean latency of rats to escape onto the hidden platform during presurgery training on the stationary platform task. Error bars represent standard errors of means.

for the quadrant that had contained the platform during the fixed platform training ($F < 1$ Figure 7).

Acquisition of DMTP. All rats readily matched to place at the 4 second delay, showing asymptotic performance between 4 and 6 sessions. The effect of increasing the retention delays to 30, 120 or 300 seconds was neglible as it did not produce any meaningful increases in second swim escape latency ($ps > .05$).

Mixed-delay sessions. The groups were well matched on their performance during the presurgery mixed-delay sessions. The mean escape latencies for each group on the second swim were similar. A mixed factorial analysis of variance on second swim escape latency with Group and Delay as factors confirmed that there were no significant differences between the groups prior to surgery ($F < 1$). The main effect of Delay was also not significant ($F[3,45] = 1.799$, $p = .161$).

Postsurgery testing

Reacquisition of DMTP. Following recovery rats were retrained on DMTP at the 4 second delay. Rats received a minimum of 5 retraining sessions. Figure 8 shows the mean second swim escape latency for each group over the first 5 sessions of reacquisition. An analysis of variance conducted on the mean second swim escape latencies for each group on each of the first 5 reacquisition sessions revealed a significant main effect of Group ($F[2,15] = 13.35$, $p = .001$). Pairwise comparisons revealed that HPC lesioned rats had significantly higher latencies than PRh and Sham lesioned rats ($ps < .05$). The PRh and Sham lesioned rats did not differ significantly ($p > .05$).

One HPC lesioned rat, and 3 PRh lesioned rats, required additional retraining sessions to reach asymptotic performance on the second swim. The 1 HPC rat required 9 retraining sessions before reaching asymptotic performance, 1 PRh rat required 8 sessions, and 2 other PRh rats required 7 sessions. These rats were included in the above analysis of reacquisition performance during the first 5 sessions. Figure 9 shows the mean second swim escape latency of the 1 HPC lesioned rat, and the 3 PRh lesioned rats during reacquisition sessions. The mean second swim escape latency of the HPC lesioned rat on

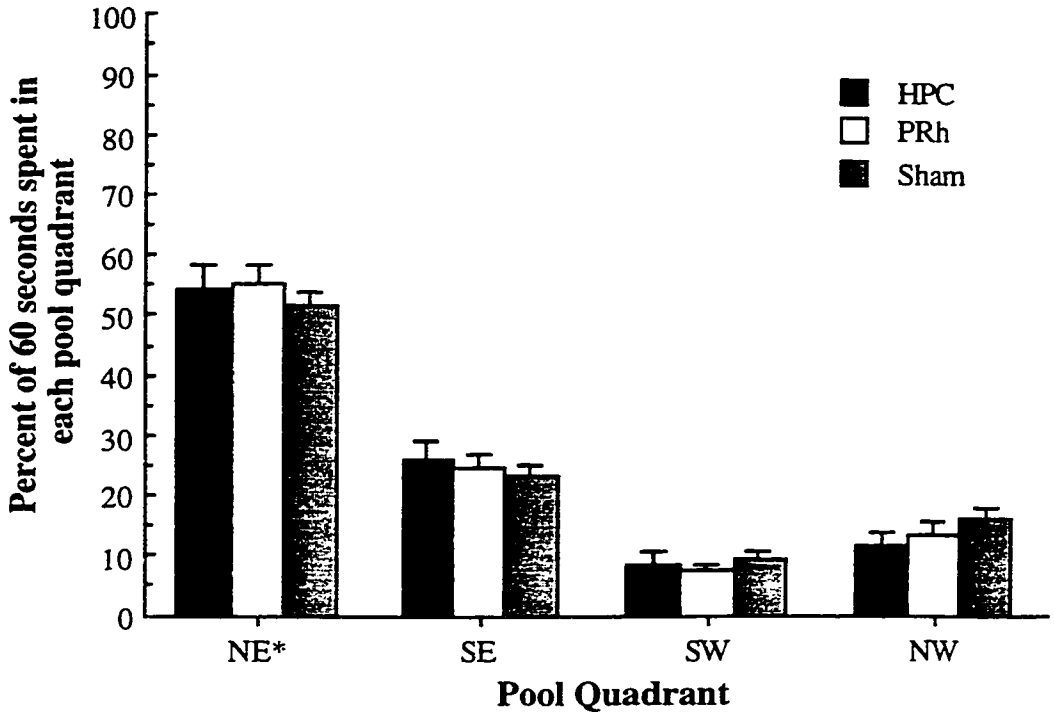


Figure 7. The mean percent of time spent in each quadrant of the pool during the 60 second probe test. Error bars represent standard errors of means. * denotes the quadrant which contained the platform during training on the stationary platform task.

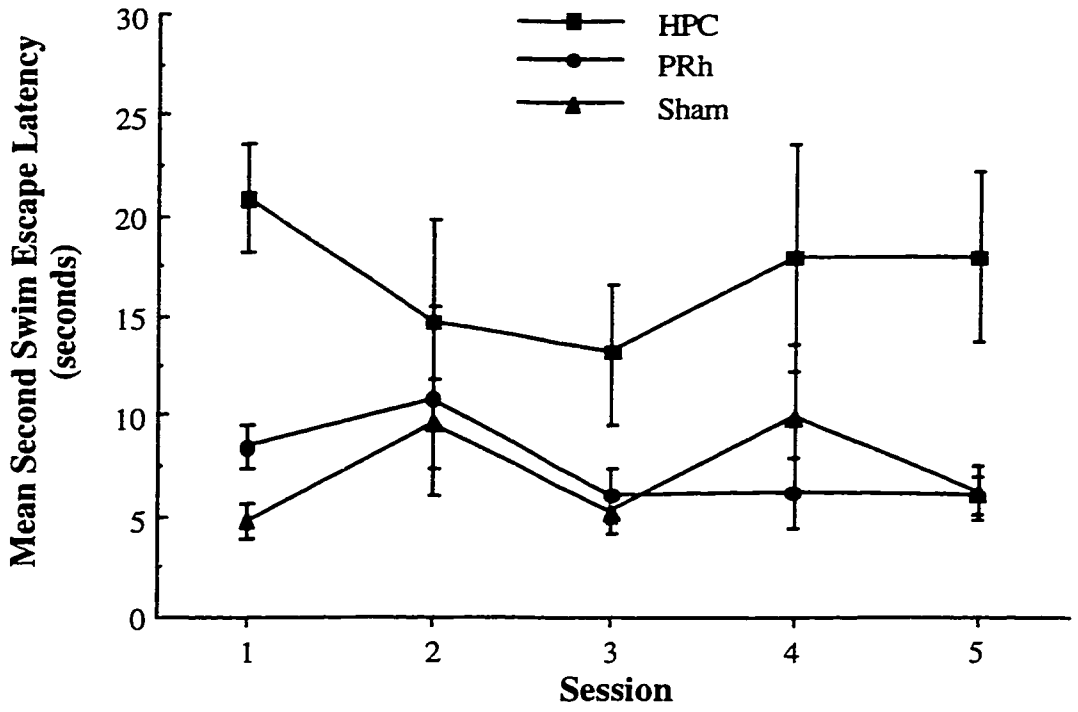


Figure 8. The mean second swim escape latency during postsurgery reacquisition of DMTP at the 4 second delay. Error bars represent standard errors of means.

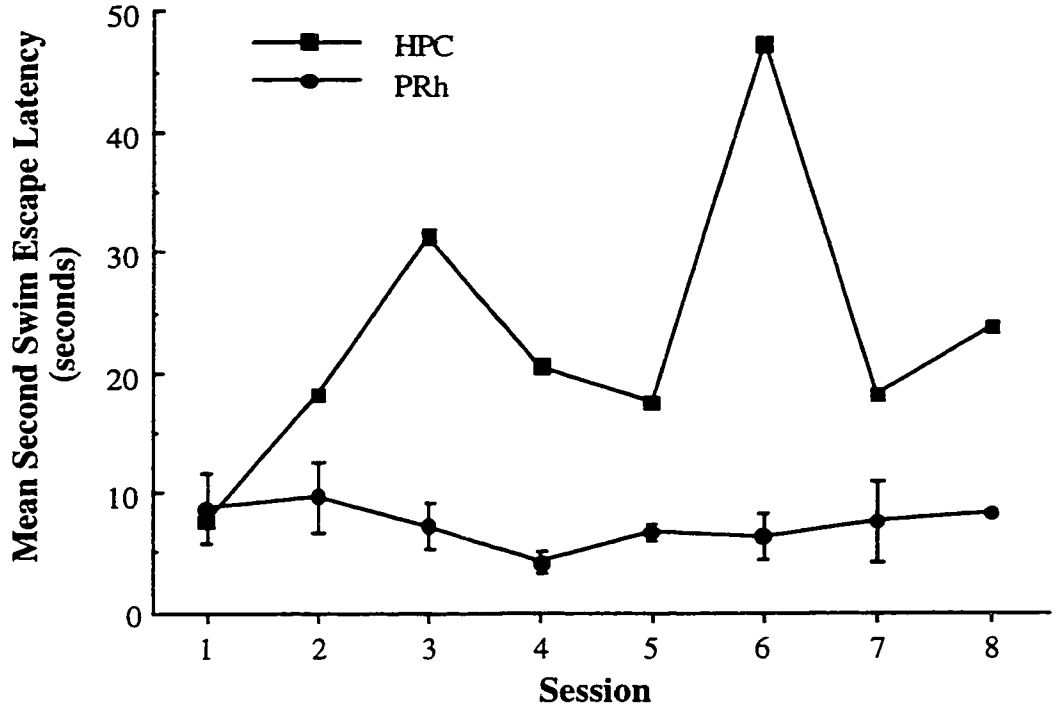


Figure 9. Mean second swim escape latency of the 1 HPC lesioned rat and the 3 PRh lesioned rats that required additional postsurgery DMTP retraining sessions at the 4 second delay. Error bars represent standard errors of means.

each session was longer than that of the Prh lesioned rats. The Prh lesioned rats, unlike the HPC lesioned rat, were unable to meet the asymptote criterion due to very short second swim escape latencies on some sessions.

Mixed-delay sessions. HPC lesioned rats continued to show marked impairments on DMTP during the mixed-delay testing. Rats with PRh lesions continued to perform similarly to Sham lesioned rats. Figure 10 shows the mean second swim escape latency of each group, before and after surgery, at each delay. A mixed factorial analysis of variance on the second swim escape latencies with the between factor Group, and the within factors Delay, and Test Time, revealed significant main effects of Group ($F[2,15] = 24.10$, $p = .001$), and Test Time ($F[1,15] = 14.18$, $p = .002$), and a significant interaction between Group and Test Time ($F[2,15] = 16.320$, $p = .001$). Pairwise comparisons revealed that HPC lesioned rats had significantly higher escape latencies on the second swim than PRh and Sham lesioned rats at all delays ($ps < .05$). Rats with PRh or Sham lesions did not differ significantly ($ps > .05$). Within-group comparisons revealed that HPC lesioned rats had significantly higher second swim escape latencies after surgery relative to their presurgery performance ($F[1,15] = 11.91$, $p = .004$). Neither PRh or Sham lesioned rats displayed such pre- and postsurgery differences in second swim escape latency ($Fs < 1$). There was a minimal overall effect of Delay ($F[3,45] = 2.6233$, $p = .059$). The interactions between Group and Delay, Test Time and Delay, and Group, Test Time, and Delay were not significant ($Fs < 1$).

The rats did not know the platform's location on the first swim. Accordingly, the groups should not differ significantly on first swims. In order to confirm this, a second analysis of variance was conducted on the first swim escape latencies using the same variables as the previous analysis. There was a significant main effect of Group ($F[2,15] = 6.04$, $p = .012$), and a significant interaction between Group and Test Time ($F[2,15] = 3.80$, $p = .046$). Pairwise comparisons showed that, after surgery, rats with HPC lesions had significantly higher first-swim escape latencies than PRh and Sham lesioned rats (all $ps < .05$, see Figure 11). PRh and Sham lesioned rats did not differ significantly after surgery ($p > .05$). There were no significant differences between the groups before surgery (p

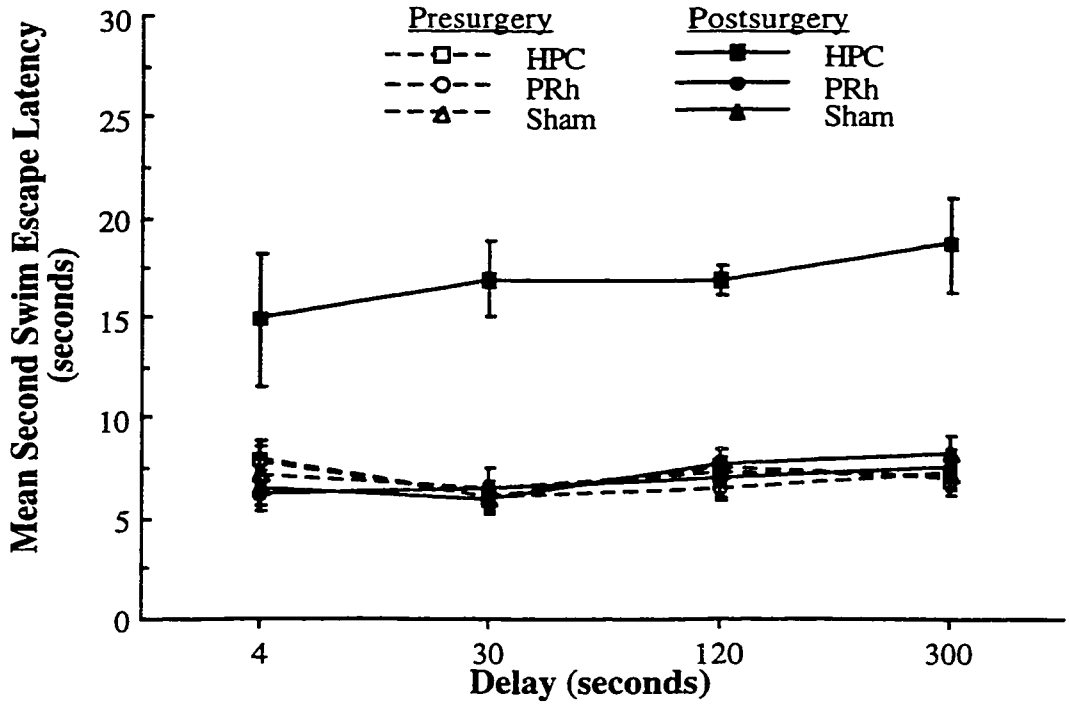


Figure 10. Mean second swim escape latency during pre- and postsurgery mixed-delay testing. Error bars represent standard errors of means.

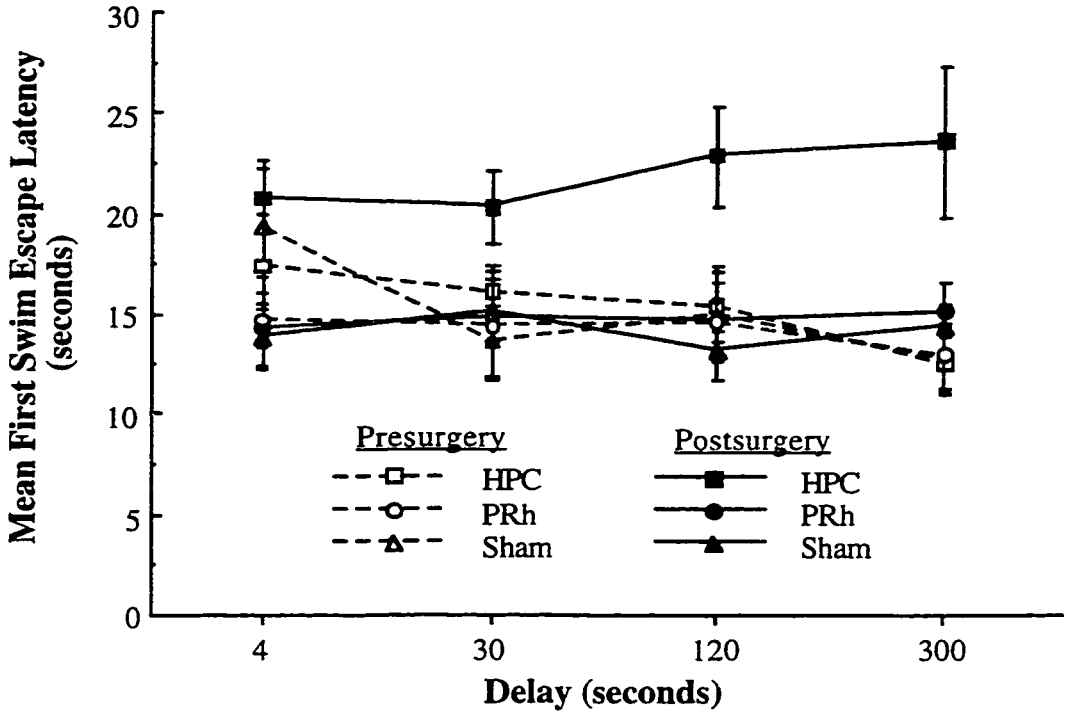


Figure 11. Mean first swim escape latency during pre- and postsurgery mixed-delay testing. Error bars represent standard errors of means.

>.05).

The differences in second-swim escape latencies between the HPC lesioned rats and the PRh and Sham lesioned rats is not clearly interpretable when there are similar differences in latency existing on the first swims of trials. To further explore the relation between the two swims and the amount of savings from first to second swims, a "savings ratio" was computed for each rat. This savings ratio was calculated by dividing the total swim time by the second swim escape latency:

$$\frac{\text{second swim escape latency}}{\text{first swim escape latency} + \text{second swim escape latency}}$$

The amount of savings should be evident in the magnitude of the decrement in escape latency from first swims to second swims, and the savings ratio would approach 0.0 as savings increased. Little to no savings should be evident by savings ratios that approached or exceeded 0.5.

An analysis of variance conducted on the mean savings ratio for each group at each delay revealed a significant main effect of Group ($F[2,15] = 12.42$, $p = .001$, see Figure 12). Pairwise comparisons revealed that HPC lesioned rats had significantly higher ratio values than rats with PRh or Sham lesions ($ps < .05$). PRh and Sham lesioned rats did not differ ($p > .05$). There was not a main effect of Delay, nor was there an interaction between Group and Delay ($ps > .05$).

Figure 13 shows the mean path length of each group on first and second swims during postsurgery mixed-delay testing. The total distance swam by the rats during postsurgery mixed-delay testing was analyzed using a mixed factorial analysis of variance with Group, Delay, and Swim as variables. There was a significant main effect of Group ($F[2,15] = 26.37$, $p = .001$). Pairwise comparisons showed that HPC lesioned rats had significantly longer path lengths on first and second swims than PRh and Sham lesioned rats ($ps < .05$). The was also a significant main effect of Swim ($F[1,15] = 100.16$, $p = .001$), but the interaction between Group and Swim was not significant ($F[2,15] = 2.553$, $p = .111$). Planned comparisons revealed that the PRh and Sham lesioned rats swam

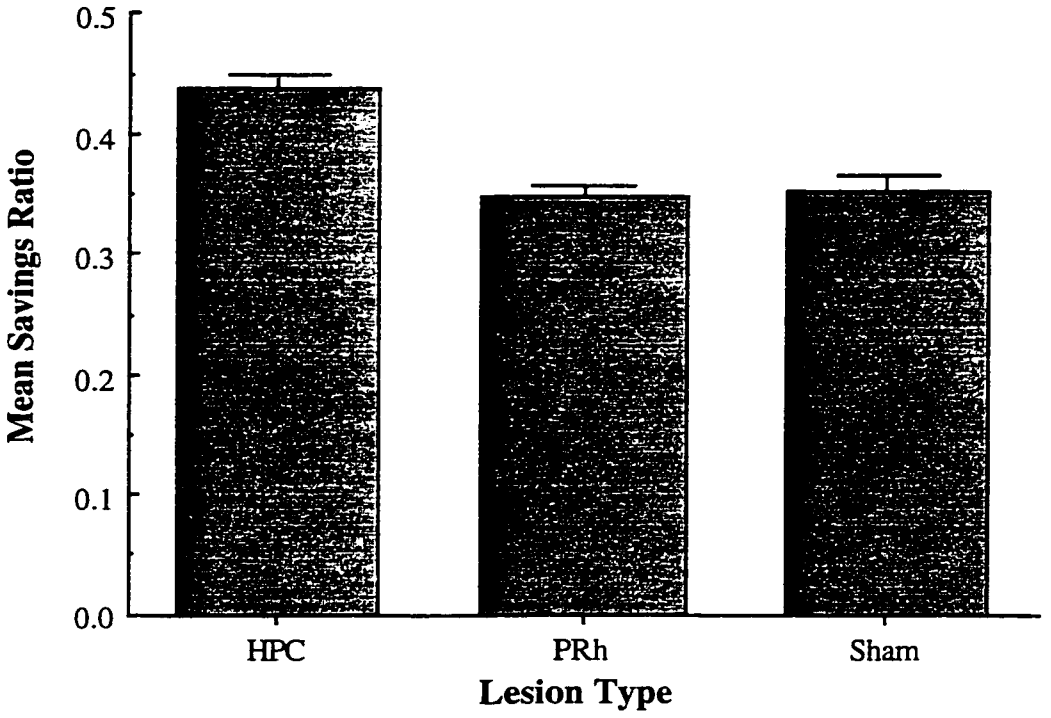


Figure 12. Mean savings ratio for each group during postsurgery mixed-delay testing. Error bars represent standard errors of means.

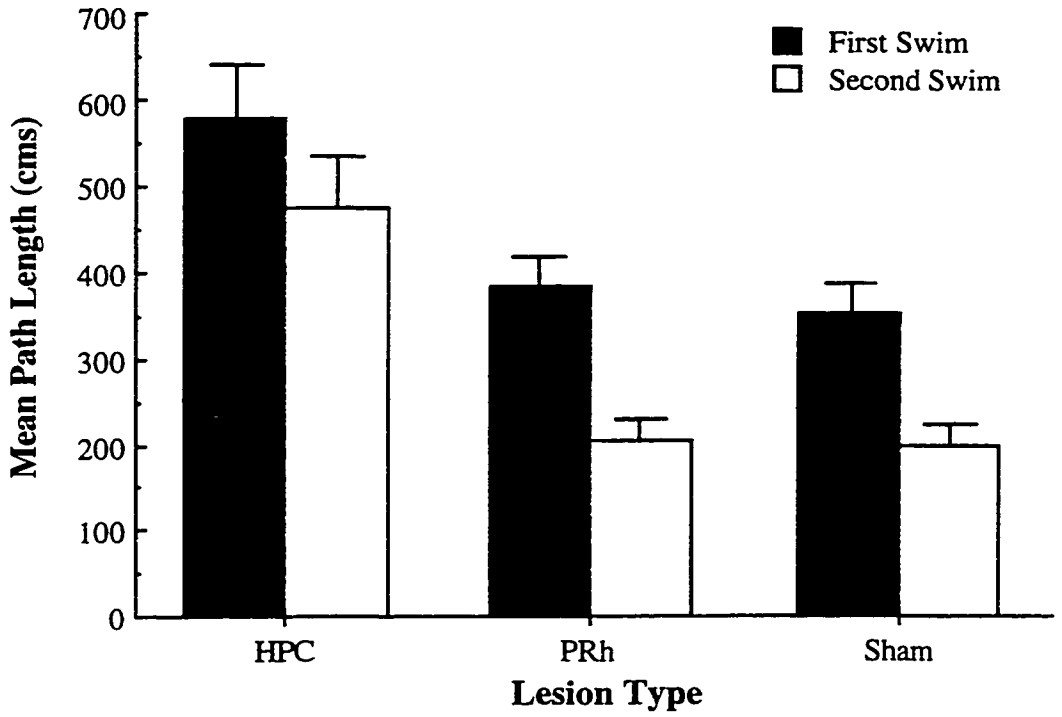


Figure 13. Mean path length for each group on the first and second swim during postsurgery mixed delay testing. Error bars represent standard errors of means.

significantly shorter distances on second swims than on first swims (ps < .05). The HPC lesioned rats also tended to swim shorter distances on second swims than on first swims (p = .06). The main effect of Delay, and the interactions between Group and Delay, Delay and Swim, and Group, Delay, and Swim were not significant (ps > .05).

Figure 14 shows the mean swim speed during postsurgery mixed delay testing for each group on first and second swims. An analysis of variance using the same variables described for the path analysis was conducted on swim speed. There was a significant increase in swimming speed from first swims to second swims ($F[1,12] = 107.262$, $p = .001$). HPC lesioned rats tended to swim faster overall, but this effect was not significant (p >.05). There was a significant main effect of Delay ($F[3,33] = 11.998$, $p = .001$), but there were no significant interactions between Group and Delay, or Group, Delay, and Swim (ps > .05).

DMTP with a visible platform. When the platform was visible during a single session of 4 trials of DMTP with a 4 second delay all rats performed similarly. A mixed factorial analysis of variance conducted with Group and Swim as variables revealed a significant effect of Swim ($F[1,15] = 5.333$, $p = .036$; Swim 1--M = 5.181, SE = .563, Swim 2--M = 4.222, SE = .377). There was not a significant effect of Group, nor was there a significant interaction between Group and Swim (ps > .05). The escape latencies for HPC lesioned rats was not significantly different from those of the PRh and Sham lesioned rats (ps > .05, see Figure 15).

DISCUSSION

The results from this experiment indicate a clear and marked impairment in allocentric spatial memory in rats with HPC lesions, but not in those with PRh lesions. The HPC lesioned rats displayed a significant reacquisition deficit, and they continued to show severe deficits on DMTP during postsurgery mixed-delay testing. The first and second swim escape latencies of HPC lesioned rats were significantly higher than those of the PRh and Sham lesioned rats. In addition, the rats with HPC lesions were observed to swim longer distances on the second swim than PRh and Sham lesioned rats. There was

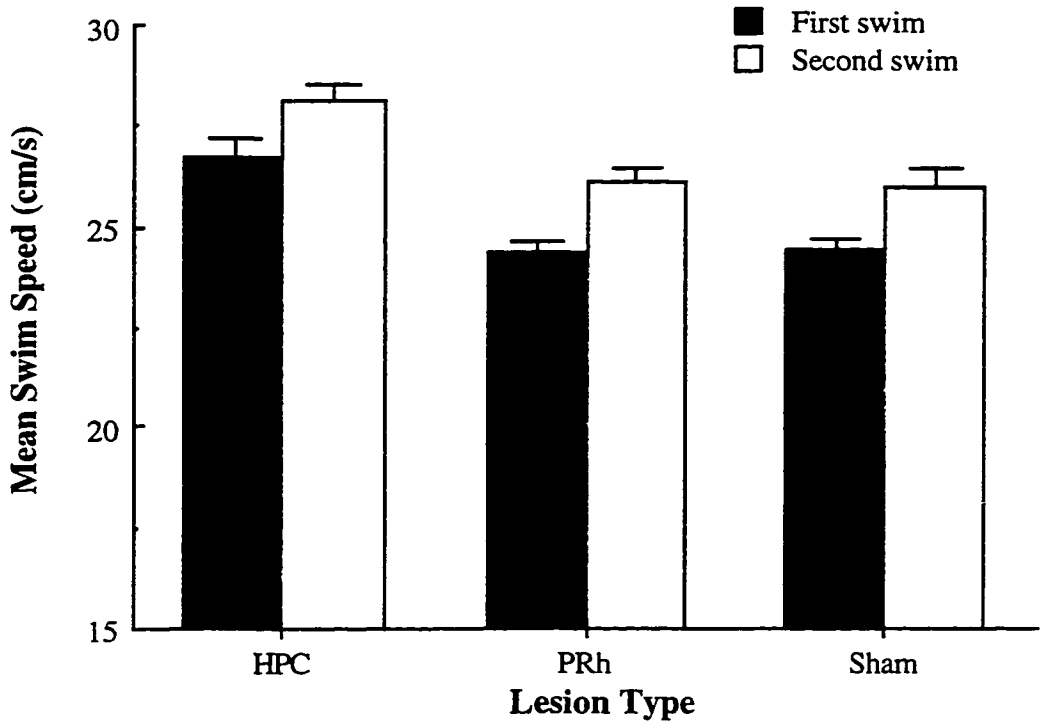


Figure 14. Mean swim speed on the first and second swim during postsurgery mixed-delay testing. Error bars represent standard errors of means.

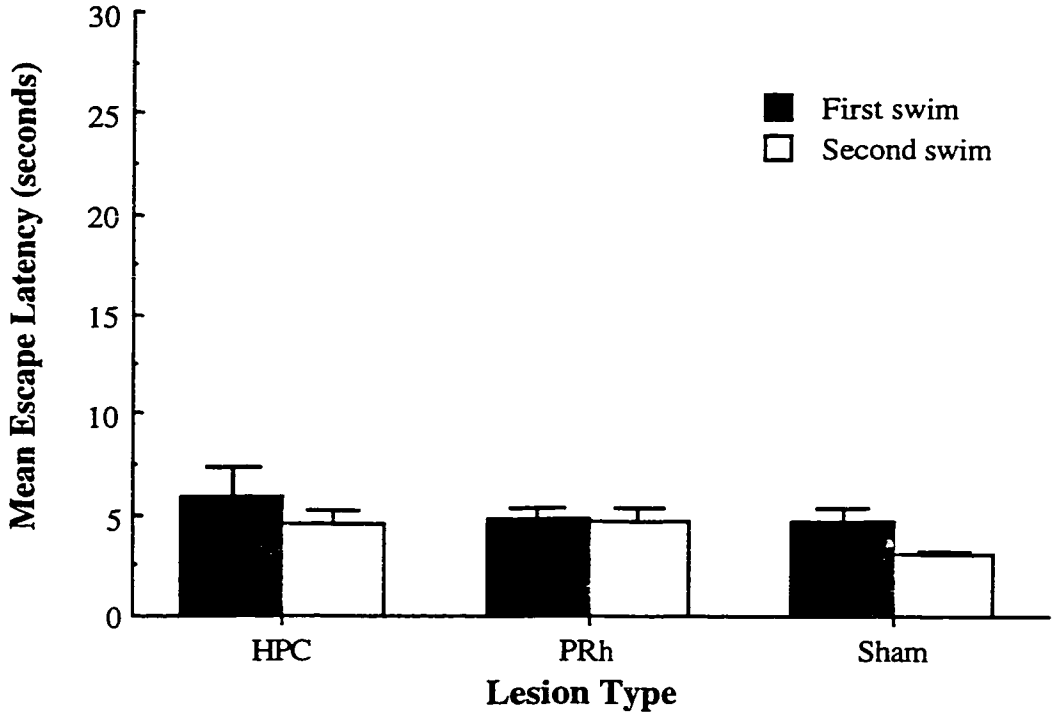


Figure 15. Mean escape latency on the first and second swim during the postsurgery visible platform task. Error bars represent standard errors of means.

also a tendency for HPC lesioned rats to swim longer distances on the first swim.

On the first swim the rats do not know the platform's location within the pool and as a result escape latencies on that swim should be similar for all groups. The differences observed in escape latency and path length on the first swim between the HPC lesioned rats and the PRh and Sham lesioned rats might reflect a navigational impairment that is not a memory impairment in the HPC lesioned rats. The HPC lesioned rats may be unable to swim well, or may not be able to reach a desired location. However, a number of findings obtained from this study suggest that the differences in first swims were not the result of non-mnemonic impairments. First, it was observed that the groups did not swim at differenct speeds, and the HPC lesioned rats even tended to swim faster than PRh and Sham lesioned rats. Second, when the platform was made visible to the rats the differences in escape latencies on first and second swims were no longer evident between the groups. It is possible that the PRh and Sham lesioned rats could recall the 10 hidden platform locations used throughout training, thereby enabling them to efficiently search each of the locations on first swims.

The interpretation that the higher escape latency and path length on second swims of trials reflects impaired allocentric spatial memory in the HPC lesioned rats, despite similar differences in escape latencies on first swims, is further supported by the analysis of savings ratios. The findings were that HPC lesioned rats displayed less savings from first swims to second swims, as demonstrated by higher savings ratios. The HPC lesioned rats had higher escape latencies and path lengths on first and second swims, but they also showed less savings from first swims to second swims. Rats with PRh lesions did not differ from Sham lesioned rats on either first or second swims, and their savings ratios were also comparable and indicative of substantial savings.

The finding that HPC lesions produce spatial memory impairments is consistent with other reports using rats (Morris et al., 1982; Sutherland et al., 1983) and monkeys (Mahut and Cordeau, 1963). Rats with PRh lesions did not show any impairment on the DMTP task. Their escape latencies during reacquisition were much lower than those of the HPC lesioned rats, and their pre- and postsurgery performance during mixed-delay testing

did not differ. These findings are in agreement with the findings of Aggleton et al. (1996) and Ennaceur et al. (1996) that PRh lesions do not disrupt spatial memory, but are inconsistent with the findings of Nagahara et al. (1995) and Wiig and Bilkey (1994b) that PRh lesions disrupt spatial memory.

Nagahara et al. (1995) employed a delayed matching-to-place task that was similar to the one used in the present experiment. One difference between the study by Nagahara et al. and the present study was the location and extent of the PRh lesions. In the Nagahara et al. study the lesions included large portions of the entorhinal cortex, a major source of input to the hippocampus, and spared substantial portions of PRh bilaterally. Also, unlike the rats in the present experiment, the rats in the Nagahara et al. study were not trained prior to surgery.

It is possible that the PRh may be involved in spatial memory during acquisition, and spatial memory deficits would be observed in rats that are not presurgically trained. Glenn and Mumby (1997) examined the effect of PRh lesions on the acquisition of the same DMTP procedure used in the present study. We found that rats with PRh lesions were not impaired during any stage of training. These findings provide further, convincing evidence that the functions of the PRh are not critical for normal spatial memory, even in the absence of presurgery training.

Wiig and Bilkey (1994b) trained rats to learn the location of a fixed and hidden platform in the water maze over multiple trials. This procedure differs substantially from the DMTP task used in this experiment which requires the learning of a platform location from a single trial. Therefore, it is possible that PRh lesions produce deficits on spatial tasks like that used by Wiig and Bilkey, but do not produce deficits on spatial working memory tasks, like the one used in the present experiment. Francis, Glenn, and Mumby (1997) looked at the effect of PRh lesions on rats' ability to remember the location of a fixed and hidden platform learned prior to surgery. They found that rats with PRh lesions were not impaired. Thus, the lack of presurgery training in the Wiig and Bilkey study is not likely to have contributed to the mild impairment they observed in rats with PRh lesions.

The findings from this experiment suggest that the functions of the PRh and HPC

are dissociable. HPC lesions produced severe DMTP deficits, whereas PRh lesions had no effect on performance. According to the unitary-system model of Eichenbaum et al. (1994) it is possible for the PRh to be functionally independent from the HPC, however, if the HPC requires input from the parahippocampal region (which includes the PRh, entorhinal and parahippocampal cortices) to form relational representations between items of spatial information, then more complete lesions of the parahippocampal region should also disrupt spatial memory. Further research would be necessary to adequately assess the validity of this aspect of Eichenbaum et al.'s model of a medial temporal lobe memory system. The findings from this experiment are consistent with the view that multiple memory systems exist within the medial temporal lobe. However, to adequately assess the validity of this model it is necessary to demonstrate that the HPC and PRh are independently involved in supporting spatial memory and object-recognition memory, respectively. Experiment 2 examined this possibility.

EXPERIMENT 2

Experiment 2 of this thesis was designed to assess the possibility that the PRh and HPC make separate contributions to object-recognition memory and spatial memory. Experiment 1 demonstrated that PRh lesions do not disrupt spatial memory, and other findings demonstrated that PRh lesions disrupt object-recognition memory (Mumby et al., 1994; Murray et al., 1996). In addition, Experiment 1, and other reports (Morris et al., 1982; Sutherland et al., 1983), demonstrated that HPC lesions disrupt spatial memory, and other findings have demonstrated that HPC lesions do not disrupt object-recognition memory (Aggleton et al., 1986; Rothblat and Kromer, 1991; Mumby et al., 1992; Mumby et al., 1995; O'Boyle et al., 1995).

Experiment 2 was designed to replicate the above findings in a single experiment by concurrently training and testing rats, before and after surgery, on a spatial memory task and an object-recognition task. Rats were trained on a DNMS task, using objects as stimuli. This task has previously been shown to adequately assess object-recognition in rats (Mumby, 1990). Rats were also trained on DMTP using procedures similar to that of

Experiment 1. In this experiment the delays were extended to 10 minutes to further examine the possibility that increasing the difficultly of the task by increasing the retention demands might reveal an involvement of the PRh at very long delays. HPC lesions were observed to produce DNMS deficits when the delay period was 10 minutes long (Squire, 1982).

Based on the view that the HPC and PRh are components in functionally independent memory systems, it is expected that the rats with lesions of the PRh will be impaired on DNMS, but will not be impaired on DMTP. The HPC lesioned rats are expected to be impaired on the DMTP task, but not on the DNMS task.

METHOD

Subjects

The subjects were fourteen adult, male Long-Evans rats (Charles River, Quebec), weighing between 300-350 g at the start of the experiment. Housing and feeding conditions were the same as in Experiment 1. Training and testing and surgeries were conducted during the light cycle.

Surgery

All rats received extensive presurgery training on two behavioral tasks concurrently (see below for details) before undergoing surgery. Between 24 and 72 hours following the completion of presurgery testing rats received either 1) bilateral aspiration of the PRh (n=6), 2) bilateral NMDA lesions of the HPC (n=4), or Sham lesions (n=4). Two of the Sham lesioned rats underwent a second surgery following the completion of postsurgery testing on both tasks. One rat received a PRh lesion, and the other received a HPC lesion. Therefore, the total number of PRh lesioned rats was increased to n=7, and the total number of HPC lesioned rats was increased to n=5.

All surgical procedures were the same as in Experiment 1, with the exception of the use of NMDA to lesion the HPC. NMDA (Sigma Chem. Co., St. Louis, MO; 5.1 M

dissolved in 0.1 M phosphate buffered saline) was infused into the same sites as in Experiment 1 (see Appendix A) at a rate of .15 µl/m for a total injection volume of .4 µl per site. As in Experiment 1, the cannulae remained lowered for 2 minutes following the injection before being raised. Rats in this experiment were also permitted to recover for two weeks before testing began.

Object-recognition memory testing: DNMS

Apparatus and Materials

The object testing apparatus (see Figure 16) was constructed from sheet aluminum (thickness = .127). It was an elevated runway consisting of two identical end areas and a central start area. The apparatus had dimensions 60 x 20 x 40 cm and stood 90 cm from the floor. Each end area (15 x 20 cm) contained two recessed wells (diameter 3.5 cm) separated by a divider wall (9 x 9 cm). Food pellets (45 mg, Precision Pellets, Bioserv, Frenchtown, N.J., USA) were delivered to the food wells by the experimenter through tubing attached to funnels on the outside of the apparatus. The end areas were separated from the central start area (30 x 20 cm) by opaque guillotine doors (40 x 20 cm) which were operated externally by the experimenter via a pulley system. The walls of the apparatus were open at the end areas to permit easy placement and removal of the objects.

The stimuli were 150 objects that varied in size, shape, colour, and sometimes texture. The objects were sorted into 3 sets of 50 objects and each set was used once before any were used again. All of the objects were washed regularly in a dilute bleach solution to remove odours.

Procedure

Presurgery training: Habituation and shaping. Rats were habituated to the apparatus in two 30 minute sessions. The guillotine doors were kept raised during habituation. Food pellets were placed in each of the recessed wells and rats were permitted to freely explore the apparatus. When they found and ate the food, the wells were baited again with several food pellets.

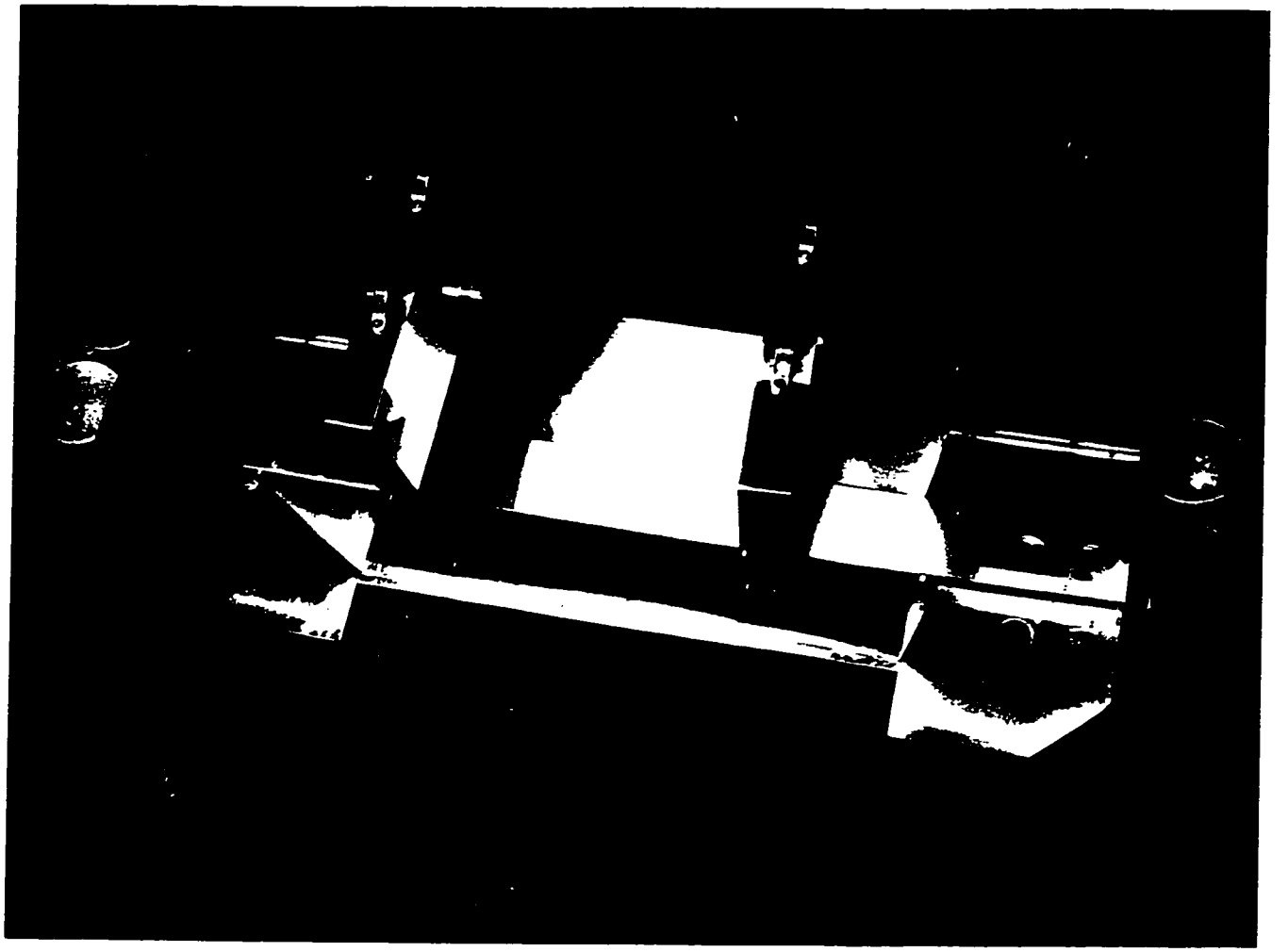


Figure 16. The object-recognition testing apparatus.

Following habituation rats were shaped to move readily from one end area to the other for a single food pellet. These sessions lasted 15 to 30 minutes. The number of sessions required to complete the shaping procedure varied for individual rats, and depended on the progress of each rat.

A rat was first trained to shuttle from one end area to the other by baiting only the wells at one side of the apparatus at a time. The rat eventually learned to run back and forth between the end areas to retrieve food from the wells. The number of pellets were gradually reduced until the rat was shuttling back and forth for one pellet in one food well. Once the rat was successfully shaped to shuttle within the apparatus it was habituated to the guillotine doors. While the rat was retrieving a food pellet from a well in one end area the opposite door was quietly lowered. When the rat approached the door it was raised and the rat could go through and retrieve the food pellet from the opposite end area. This procedure was repeated until the rat was readily approaching the doors to gain access to the end areas.

Presurgery training: Simple object discrimination. Rats were trained on a simple object discrimination task. This procedure served to shape a rat to displace the objects from over the food well to obtain a food reward, and to ensure that it could easily discriminate between objects. Two objects were selected as stimuli and one object of the pair was assigned to be correct for a rat. The rat received a food pellet as reward when the correct object was displaced.

In the first training session the food wells were pre-baited with a food pellet. The objects were first placed adjacent to the food wells and were gradually, over trials, moved until they completely covered the recessed wells. The rat learned to move the correct object and retrieve the hidden food pellet. Once this behavior was established the wells were no longer baited with food. The rat was trained to first move the correct object and then wait for the food pellet to be dropped through the tubing to the well. The object pairs were presented 20 times in each session and correction trials were given on the first two sessions. On a correction trial the rat was permitted to displace the correct object after initially displacing the incorrect object. Object discrimination training was continued until all rats were selecting the correct object 85% of the time on two consecutive sessions.

Presurgery training: Delayed nonmatching-to-sample (DNMS) at a 4-second delay. After attaining criterion performance on the object discrimination problem rats were trained on DNMS with a brief, 4 second, retention delay. Each DNMS session consisted of 20 trials. At the start of a trial the rat was enclosed in the central start area with both doors lowered. Two objects were randomly selected from an object set and placed over wells in opposite end areas. A food pellet was placed under one object, the sample. The trial began when one door was raised and the rat was able to approach and displace the sample object to retrieve the food pellet. The object was removed from the end area and placed over the remaining well in the opposite end area. The other door was then raised and the rat was permitted to approach the two objects and displace one of them. If the rat chose the novel object a food reward was delivered to the well after the object was displaced and both objects were removed. If the rat selected the sample object both objects were removed and no food pellet was delivered. During the first two sessions rats were permitted to correct their mistakes. During these sessions, if the rat displaced the sample object, that object was removed and the rat was then allowed to displace the novel object and received a food reward.

During this training phase the delay period between the presentation of the sample object and the choice phase was approximately 4 seconds, and the intertrial interval was approximately 30 seconds. Training continued until rats attained a criterion of 85% correct responses on two consecutive sessions.

Presurgery training: DNMS at successively longer delays. Following training at the 4 second delay, the delay periods were successively lengthened to 15, 30, 60, and 120 seconds. Rats received 8 sessions of 20 trials at each delay before training at the next longest delay was initiated.

Presurgery testing: Mixed-delay sessions. Rats received 10 sessions of 25 trials in which each of the 5 delays were presented 5 times. The order of the delays was arranged in an ascending-descending manner (eg. 4, 15, 30, 60, 120, 120, 60, etc).

Post-surgery testing: Reacquisition of DNMS at the 4 second delay and mixed-delay sessions. After the two week recovery period rats were retrained on DNMS at the

brief, 4 second, delay. Reacquisition performance was assessed by the number of trials required to reattain the presurgery training criterion. Once the rats had reattained criterion performance on DNMS at the 4 second delay their performance at all the delays was assessed in mixed sessions. Rats received 10 mixed-delay sessions. These sessions were conducted in the same manner as before surgery.

Spatial memory testing: DMTP

Apparatus and Materials

The testing apparatus was the water maze described in Experiment 1. All general testing conditions, including transport, extramaze cues, and equipment were the same.

Procedure

Presurgery training: Delayed matching-to-place (DMTP) at a 4 seconds delay. The procedures used during this phase of training were the same as those in Experiment 1, except that rats received only 7 days of training with a different platform location on each trial (compared with 10 training days in Experiment 1).

Presurgery training: Delayed matching-to-place (DMTP) training at successively longer delays. After training at the 4 second delay, the delay period was successively increased to 60, 300, and 600 seconds. Each rat received 3 days (i.e., 12 trials) at each delay before being trained on the next longest delay.

Presurgery testing: Mixed-delay sessions. The procedures for this phase of testing were the same as those in Experiment 1, except that rats received 12 sessions of mixed delay testing (compared with 15 sessions in Experiment 1).

Post-surgery testing: Reacquisition of DMTP at the 4 second delay and mixed-delay sessions. Most rats received 8 days of DMTP retraining at the 4 second delay, using the same trial-unique, presurgery procedure. Two rats--one hippocampal lesioned and one sham lesioned rat--received only 5 days of DMTP retraining at the 4 second delay. After performance reached an asymptote at the 4 second delay, each rat received 12 mixed delay sessions.

DMTP with a visible platform. When all other post-surgery testing was complete a visible platform task was conducted to determine whether all rats were equally proficient at swimming and navigating in the maze. The procedure used was the same as that for the DMTP procedure with the 4 second delay, except that the platform was visible during the entire session.

Histology

All histological procedures were the same as those in Experiment 1.

Statistical Analyses

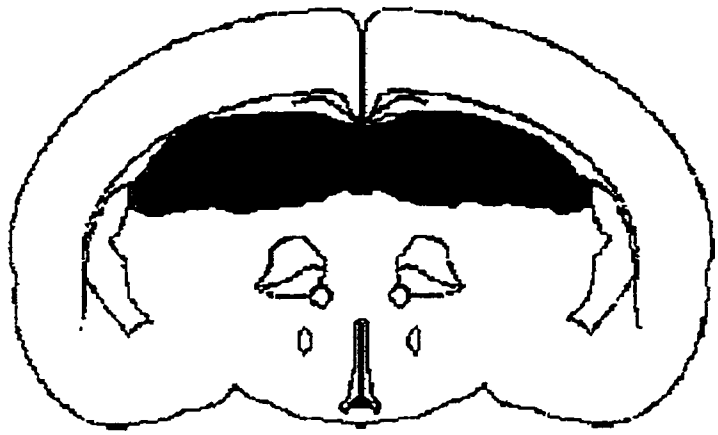
Initial acquisition of the simple object discrimination and DNMS at the 4 second delay and postsurgery reacquision of DNMS at the 4 second delay was analyzed using the number of trials to attain the performance criterion. The primary dependent measure for the analysis of DNMS performance during mixed-delay testing was the number of correct responses made in each session. Mixed factorial analyses of variance were conducted using the between factor Group (HPC, PRh, and Sham), and the within factors Test Time (pre- and postsurgery) and Delay (4, 15, 30, 60, and 120 seconds). Planned, pairwise comparisons (t-tests) were conducted to examine differences between groups and between pre- and postsurgery performance at each delay.

The analyses of the DMTP data were the same as those in Experiment 1.

RESULTS

Histological Results

Figure 17 shows the location and extent of the HPC lesions. The lesions produced by the NMDA were similar to those lesions produced by the ibotenic acid in Experiment 1. The lesions in this experiment included significant bilateral damage to the hippocampus proper, dentate gyrus, and subiculum. There was more extra-hippocampal damage evident in the lesions made in this experiment. The cannula tracts produced substantial damage to



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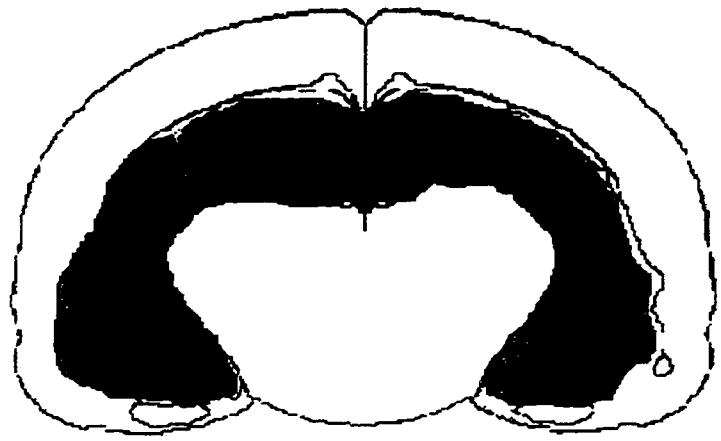

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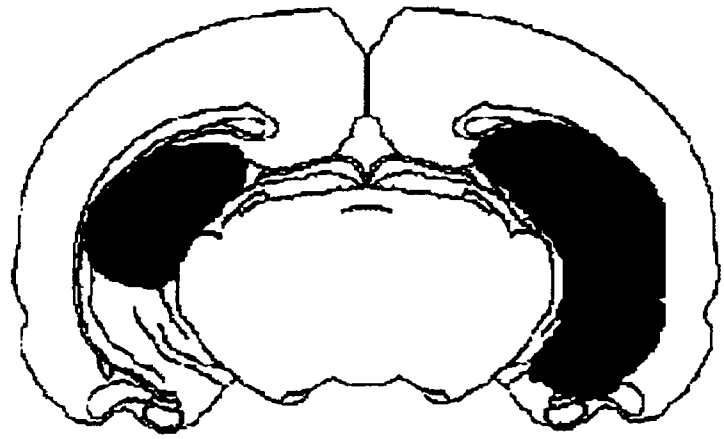

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Figure 17. A schematic representation of the coronal view of the largest and smallest HPC lesions. The largest HPC lesion is represented by the light shading and the smallest HPC lesion is represented by the dark shading. (Adapted from Paxinos and Watson, 1986).

the overlying parietal cortex. In addition, the fimbria-fornix was also frequently lesioned. The PRh and entorhinal cortex consistently remained spared. As in Experiment 1, the dorsal HPC sustained the most complete damage in all rats. The damage to the ventral HPC was more variable, and the amount of the subicular complex that was damaged bilaterally also varied. As in Experiment 1, there was no detectable damage to thalamic structures.

Figure 18 shows the location and extent of the PRh lesions on the lateral surface of the rat brain. Figure 19 shows the coronal view of the location and extent of the PRh lesions. The PRh lesions in this experiment were also quite similar to those produced in Experiment 1. All lesions included significant bilateral damage to the PRh. The posterior PRh was most consistently lesioned in all rats with the most sparing occuring in the anterior PRh. The lesions also included portions of the lateral entorhinal cortex, the postrhinal cortex, and temporal association cortex. Only the damage to the entorhinal cortex was frequently bilateral. The other structures rarely sustained bilateral damage. There was also damage to the ventral HPC in most rats. This damage was also rarely substantial or bilateral.

Behavioral Results

Object-recognition memory: DNMS

Presurgery training and testing

Habituation and Shaping. There was substantial variability between rats in the amount of time required for habituation and shaping. Rats completed this phase of testing in 5 to 14 sessions. There were no significant differences, however, between the groups in the mean number of sessions required for habituation and shaping ($F[2,10] = 1.284$, $p = .319$; PRh, M = 6.6, SE = .510; HPC, M = 9.5, SE = 1.732; Sham, M = 9.0, SE = 1.414).

Simple object discrimination. The rats readily learned to displace objects during training on the simple object discrimination. They also demonstrated that they were able to easily discriminate between the objects as all rats reached the criterion of two consecutive 20 trial sessions of 85% correct responses in 40 to 140 trials. There were no significant

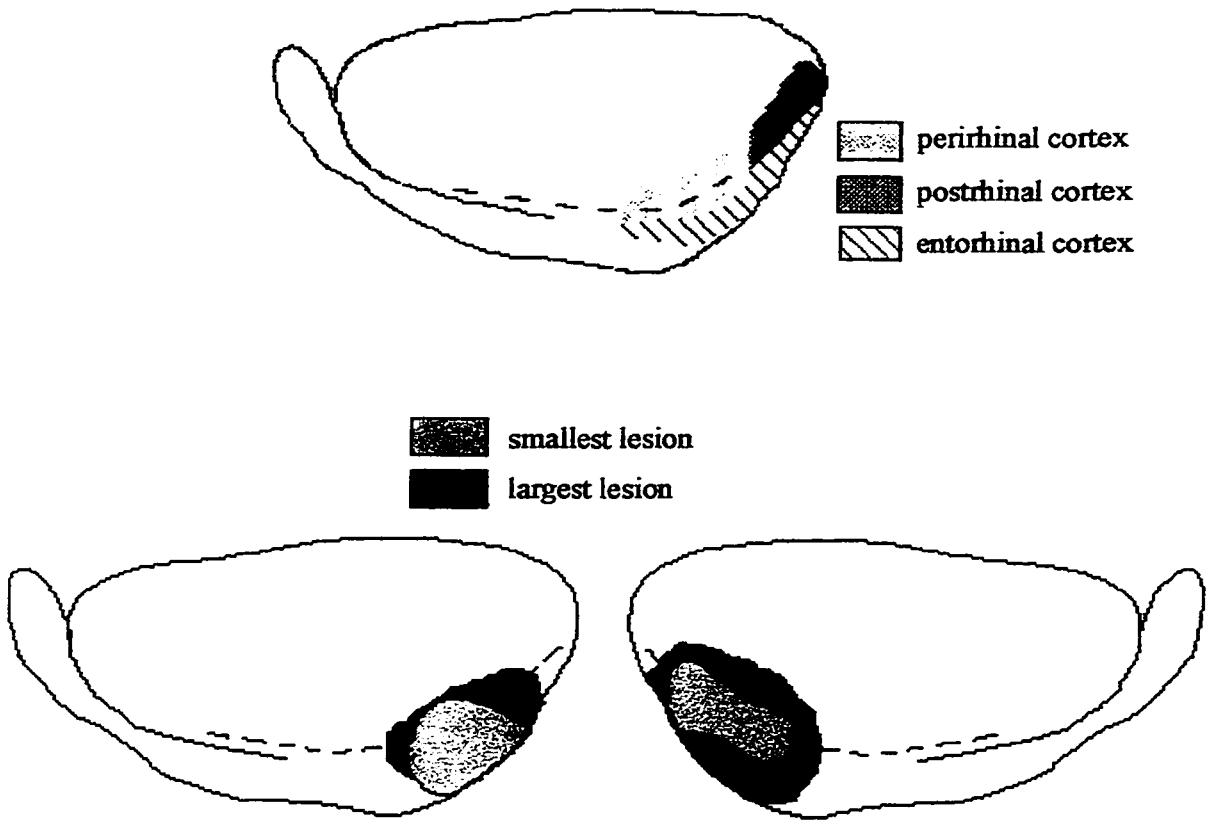

Figure 18. The lateral view of the boundaries of structures in the rhinal cortex are represented in the uppermost schematic diagram. The bottom schematic shows the lateral view of the largest and smallest PRh lesions. (Adapted from Burwell, Witter, and Amaral, 1995).

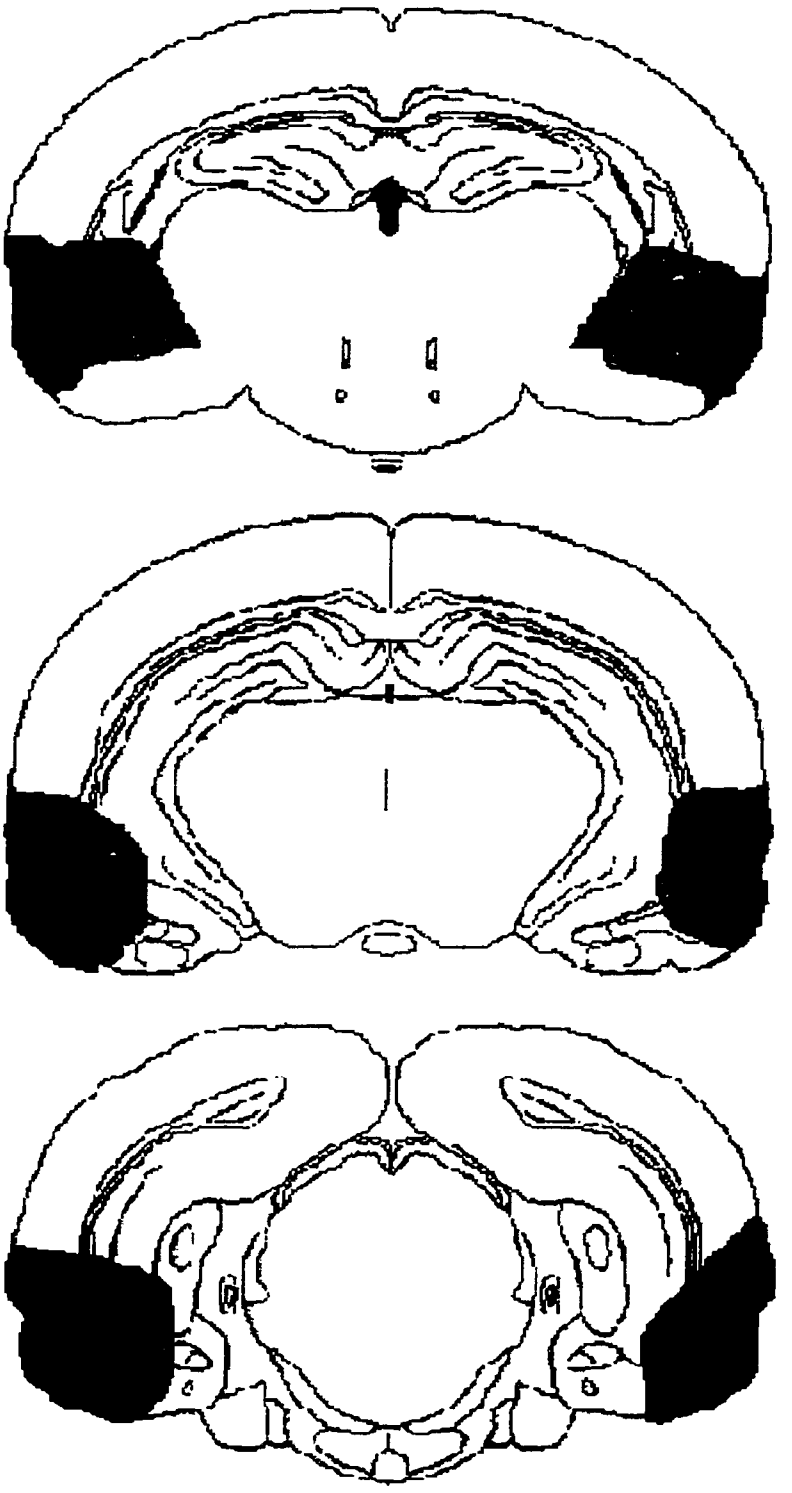

Figure 19. A schematic representation of the coronal view of the largest and smallest PRh lesions. The largest PRh lesion is represented by the light shading and the smallest PRh lesions is represented by the dark shading. (Adapted from Paxinos and Watson, 1986).

differences between the groups in the number of trials to criterion ($F < 1$, see Figure 20).

Acquisition of DNMS. A substantial amount of variability was also observed between rats in the number of trials required to reach the criterion of two consecutive 20 trial sessions of 85% correct responses on DNMS at the 4 second delay. Rats took as few as 460 trials and as many as 1300 trials to reach the criterion. There were, however, no group differences in the number of trials to criterion ($F < 1$, see Figure 21).

Mixed-delay testing. The groups were well matched on their presurgery DNMS performance during the mixed-delay sessions. A mixed factorial analysis of variance on the number of correct responses during mixed-delay testing with Group and Delay as factors showed that the groups did not differ significantly ($F < 1$). The number of correct responses did significantly decline as the retention delay was lengthened ($F[4,40] = 12.440$, $p = .001$). This was the case for all groups, as indicated by the lack of a significant interaction between Group and Delay ($F < 1$).

Postsurgery testing

Reacquisition of DNMS. Rats reattained the presurgery training criterion of two consecutive sessions of 85% correct responses in 20 to 340 trials. There were no significant group differences in the amount of trials recquired to reattain DNMS criterion performance ($F < 1$, see Figure 21). One PRh lesioned rat would not displace objects following surgery. This rat was unable to adequately complete trials and was not included in any of the object-recognition analyses and the number of rats in the PRh group was reduced to 6.

Mixed-delay testing. Figure 22 shows the mean number of correct responses for each group at each delay during mixed-delay testing, before and after surgery. An analysis of variance was conducted on the number of correct responses using the between factor Group, and the within factors Test Time and Delay. There was a significant main effect of Delay ($F[4,48] = 49.653$, $p = .001$). Pairwise comparisons showed that as the retention delay was increased, performance declined. There were no significant main effects of Group or Test Time ($Fs < 1$). The interaction between Group and Test Time approached

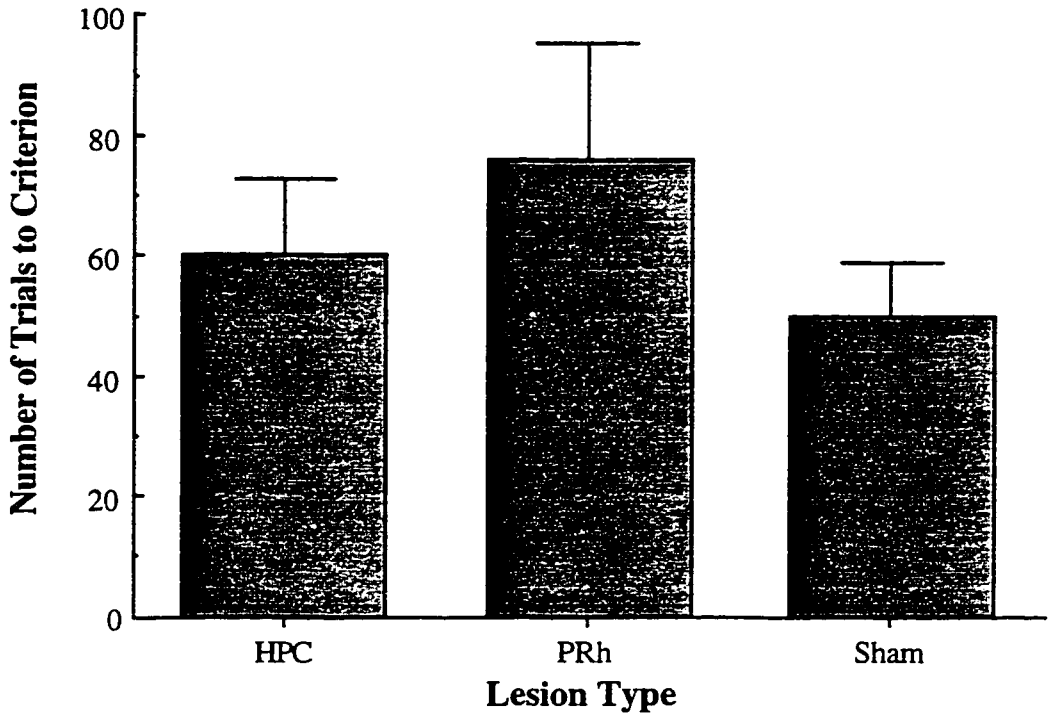

Figure 20. Mean number of trial for each group to reach the performance criterion on the presurgery simple object discrimination task. Error bars represent standard errors of means.

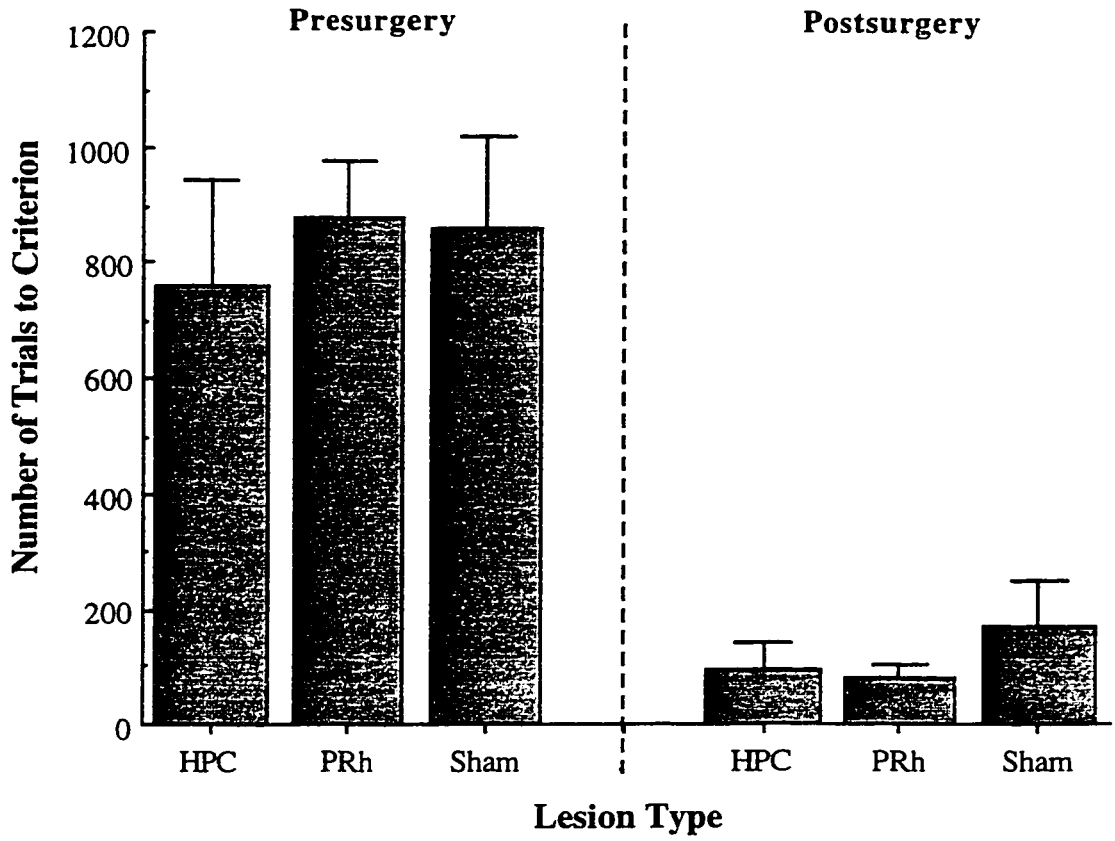

Figure 21. Mean number of trials for each group to reach the DNMS performance criterion at the 4 second delay before and after surgery. Error bars represent standard errors of means.

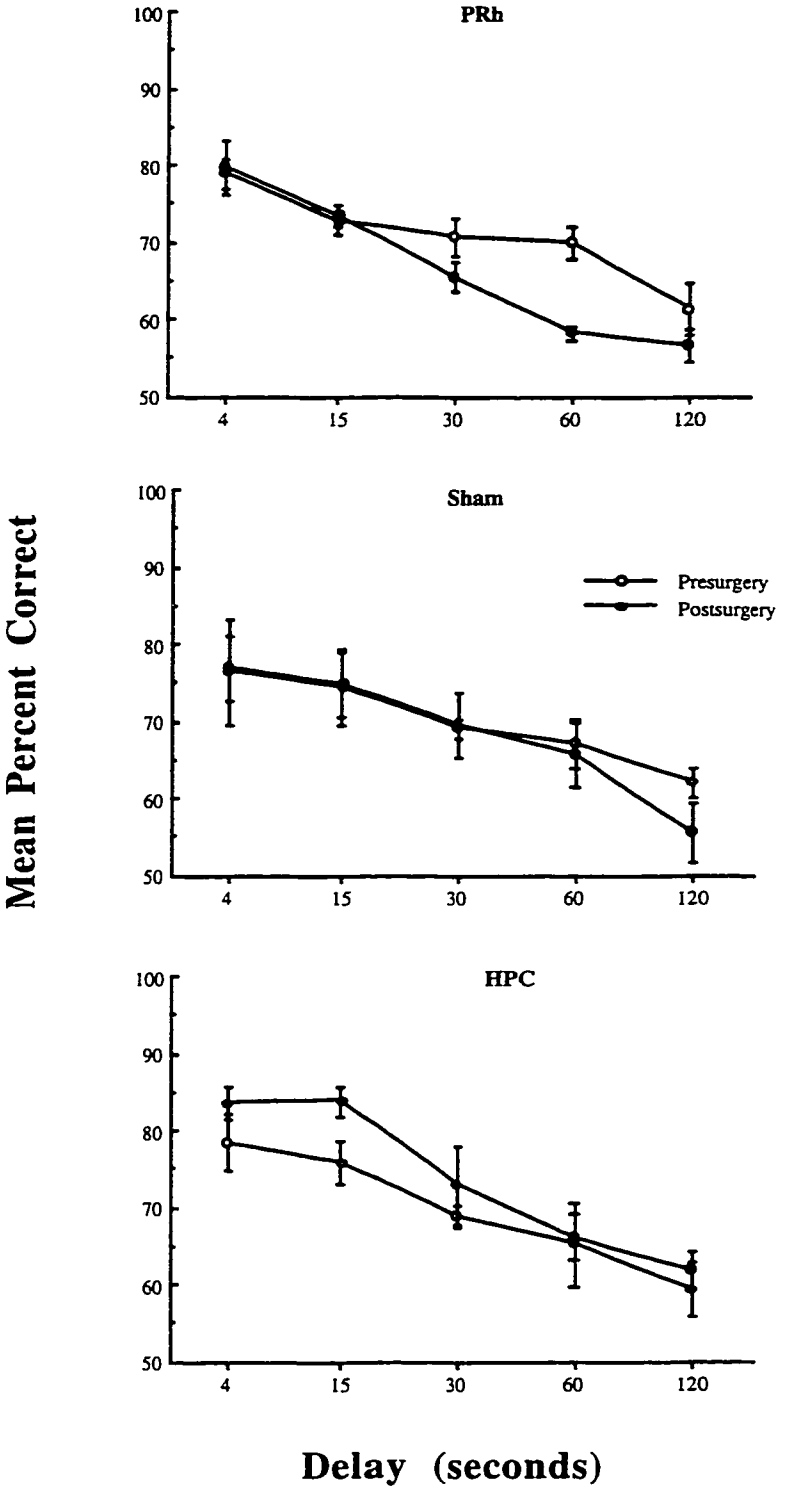

Figure 22. Mean percent of correct responses of each group at each delay during mixed-delay testing before and after surgery. Error bars represent standard errors of means.

statistical significance ($F[2,12] = 3.319$, $p = .071$). The interactions between Group and Delay, Test Time and Delay, and Group, Test Time, and Delay were also not significant ($Fs < 1$).

On average, the HPC lesioned rats made more correct responses at each delay after surgery than before surgery. Planned comparisons showed that the HPC lesioned rats made significantly more correct responses after surgery, relative to their presurgery performance, at the 15 second delay ($p < .05$), but not at the other delays ($ps > .05$). On average, the PRh lesioned rats made fewer correct responses at each delay after surgery than before surgery. Planned comparisons showed that the PRh lesioned rats made significantly fewer correct responses after surgery, relative to their presurgery performance, at the 60 second delay ($p < .05$), but not at the other delays ($ps > .05$), though the difference at the 30 second delay approached statistical significance ($p = .077$). There were no significant differences between the number of correct responses made by Sham lesioned rats before and after surgery ($ps > .05$).

An analysis of variance conducted on the number of correct responses made during postsurgery mixed-delay testing using the between factor Group and the within factor Delay revealed a significant main effect of Group ($F[2,12] = 3.824$, $p = .051$) and Delay ($F[4,48] = 31.768$, $p = .001$), but the interaction between Group and Delay was not significant ($F[8,48] = 1.263$, $p = .285$, see Figure 23). Planned comparisons showed that PRh lesioned rats differed signficantly from Sham lesioned rats at the 60 second delay ($p < .05$), but not at the other delays ($ps > .05$). HPC lesioned rats did not differ significantly from Sham lesioned rats at any of the delays ($ps > .05$), though HPC lesioned rats tended to make more correct responses at the 15 second delay ($p = .077$). PRh lesioned rats made fewer correct responses than HPC lesioned rats at the 15 second delay ($p < .05$), and the 60 second delay ($p < .05$), but not at other delays ($ps > .05$).

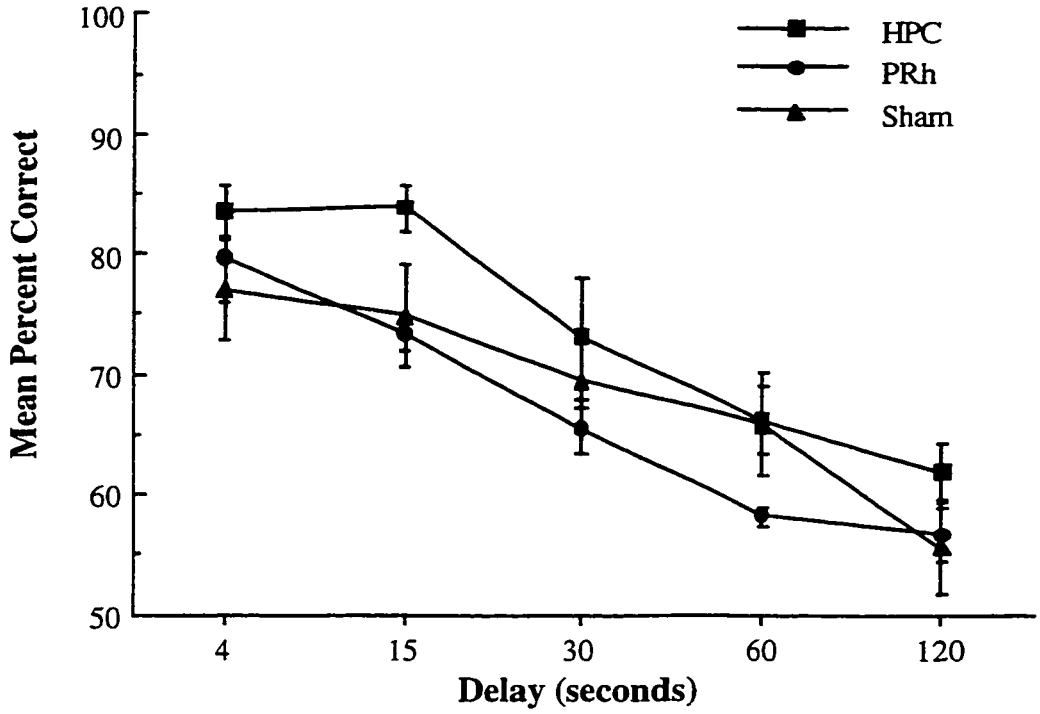

Figure 23. Mean percent of correct responses of each group during postsurgery mixed-delay testing. Error bars represent standard errors of means.

Spatial memory-DMTP

Presurgery training and testing

Acquisition of DMTP. There were no significant differences between the groups in the second swim escape latencies during training on DMTP at the 4 second retention delay ($F < 1$). There were also no substantial decrements in performance of any of the groups as the retention delay was increased ($ps > .05$).

Mixed-delay testing. The groups were adequately matched on their latencies to escape onto the hidden platform on the second swim during presurgery mixed-delay sessions. An analysis of variance on second swim escape latency with Group as a between factor and Delay as a within factor revealed that there were no significant group differences ($F < 1$). There was a significant main effect of Delay ($F[3,33] = 5.999$, $p = .002$). The interaction between Group and Delay was not significant ($F < 1$).

Postsurgery testing

In general, the results from this experiment are in agreement with the findings from Experiment 1. Rats with lesions of the HPC were impaired at reacquiring DMTP at the 4 second delay, and continued to show marked deficits during mixed-delay testing. PRh lesioned rats were not impaired during reacquisition or during mixed-delay testing.

Reacquisition of DMTP. Figure 24 shows the mean second swim escape latency for each group on each of the first 5 reacquisition sessions of DMTP at the 4 second delay. A mixed factorial analysis of variance on second swim escape latencies with Group as the between variable and Session (1 to 5) as a repeated variable revealed a significant main effect of Group ($F[2,11] = 21.916$, $p = .001$). Pairwise comparisons showed that HPC lesioned rats had significantly higher second swim escape latencies than PRh or Sham lesioned rats ($ps < .05$). Rats with PRh lesions and Sham lesioned rats did not differ significantly ($p > .05$). The main effect of Session and the interaction between Group and Session were not signficant.

Mixed-delay testing. Figure 25 shows the mean second swim escape latency during

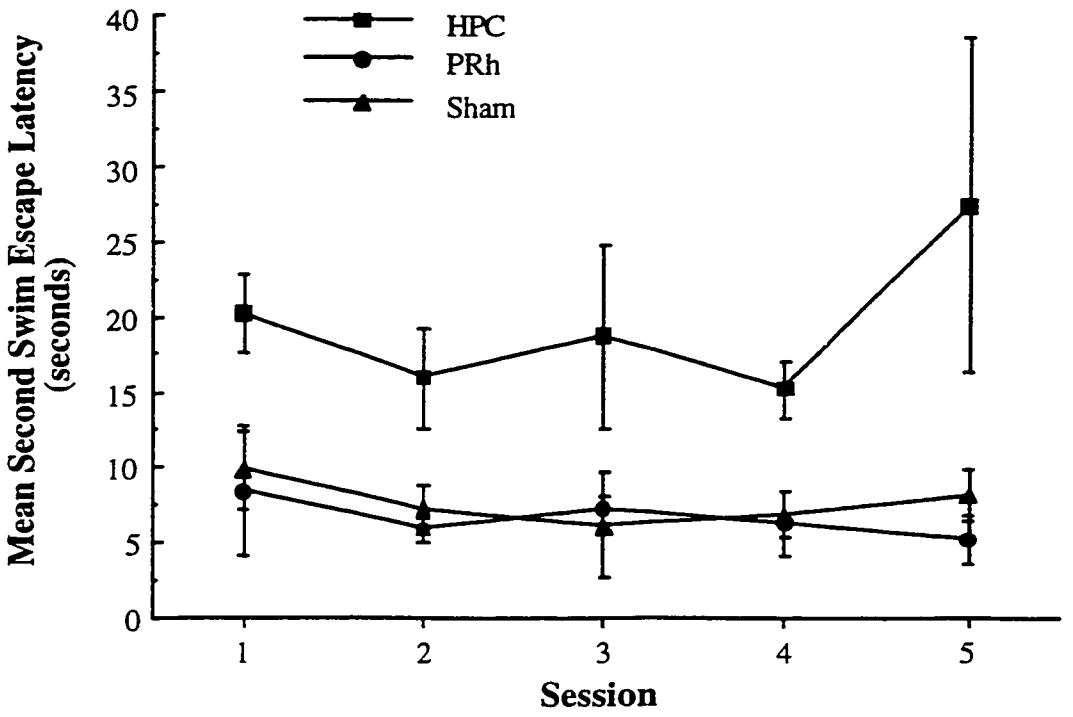

Figure 24. Mean second swim escape latency of each group during postsurgery reacquisition of DMTP at the 4 second delay. Error bars represent standard errors of means.

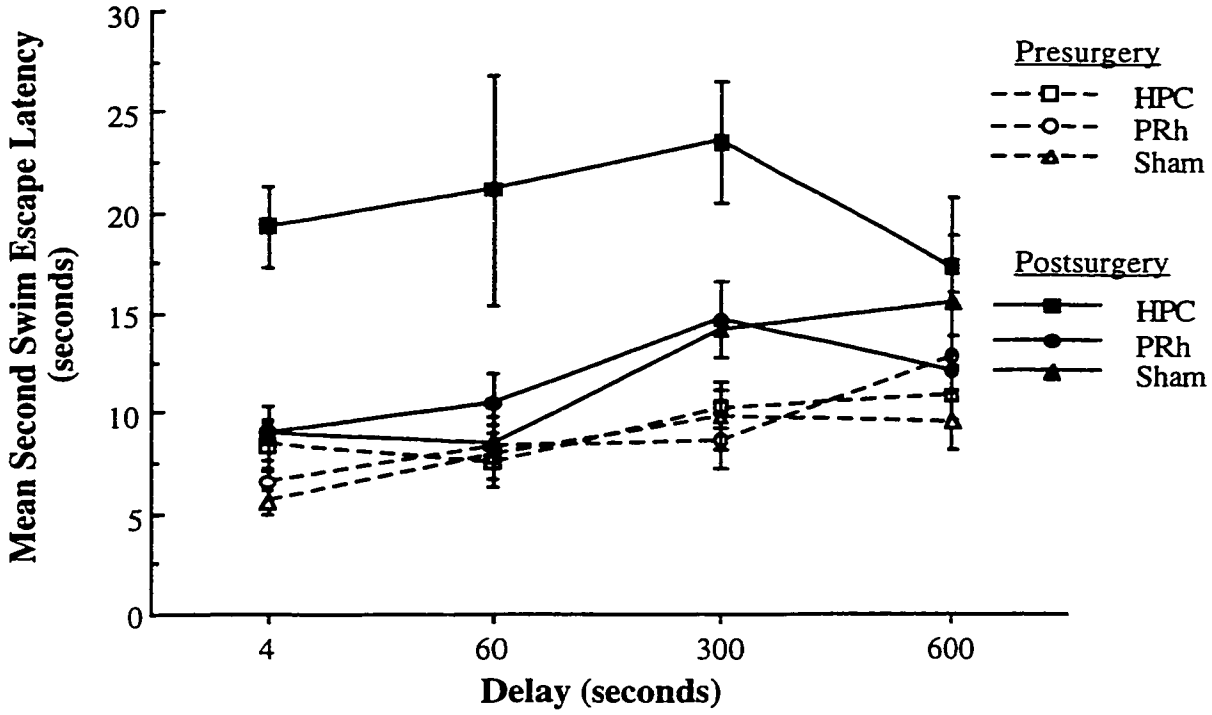

Figure 25. Mean second swim escape latencies during mixed-delay testing, before and after surgery. Error bars represent standard errors of means.

pre- and postsurgery mixed delay sessions. A mixed factorial analysis of variance was performed on second swim escape latencies with the variables Group, Test Time, and Delay. There were significant main effects of Group ($F[2,11] = 7.835$, $p = .008$), Test Time ($F[1,11] = 83.670$, $p = .001$) and Delay ($F[3,33] = 5.343$, $p = .004$), and a significant interaction between Group and Test Time ($F[2,11] = 19.738$, $p = .001$). A simple effect analysis revealed a significant effect of Group after surgery ($F[2,11] = 17.183$, $p = .001$), but not before surgery ($F < 1$). Also HPC lesioned rats had significantly higher second swim escape latencies after surgery, relative to their presurgery ($F[1,11] = 23.931$, $p = .001$). The pre- and postsurgery performance of PRh and Sham lesioned rats did not differ signficantly ($p > .05$). Pairwise comparisons showed that HPC lesioned rats had significantly higher second swim escape latencies after surgery than PRh or Sham lesioned rats at the 4, 60, and 300 second delays ($ps < .05$). Rats with PRh or Sham lesions did not differ significantly at these delays ($p > .05$). There were no significant differences between the groups at the 600 second delay ($p > .05$). The interactions between Group and Delay, Test Time and Delay, and Group, Test Time, and Delay were not significant ($ps > .05$).

Figure 26 shows the mean first swim escape latencies of each group at each delay, before and after surgery. An analysis of variance was conducted on first swim escape latencies with the same variables used in the above analysis. There were no significant main effects of Group ($F[2,11] = 1.088$, $p = .3704$), Test Time ($F[2,11] = 3.403$, $p = .092$), or Delay ($F < 1$). The interactions betw`een Group and Test Time, Group and Delay, Delay and Test Time, and Group, Test Time, and Delay were not significant ($ps > .05$).

As in Experiment 1, the relation between latency on the first and second swims was examined using a savings ratio (see formula on page 38). An analysis of variance was conducted on the savings ratio values for postsurgery mixed-delay escape latencies with the factors Group and Delay. The main effect of Group was not statistically significanct ($F[2,11] = 3.250$, $p = .078$, see Figure 27), but planned comparisons did show that rats with HPC lesions had higher savings ratios than PRh lesioned rats ($p < .05$), but HPC and Sham lesioned rats did not differ significantly ($p > .05$). There was a significant main effect

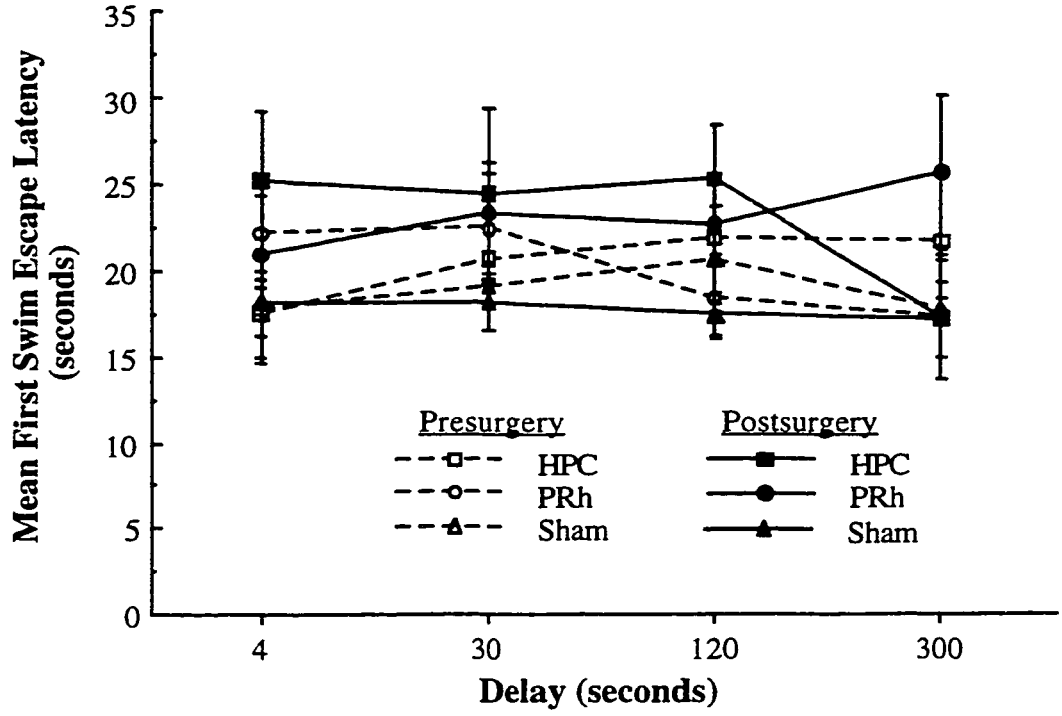

Figure 26. Mean escape latency on first swim during mixed-delay testing before and after surgery. Error bars represent standard errors of means.

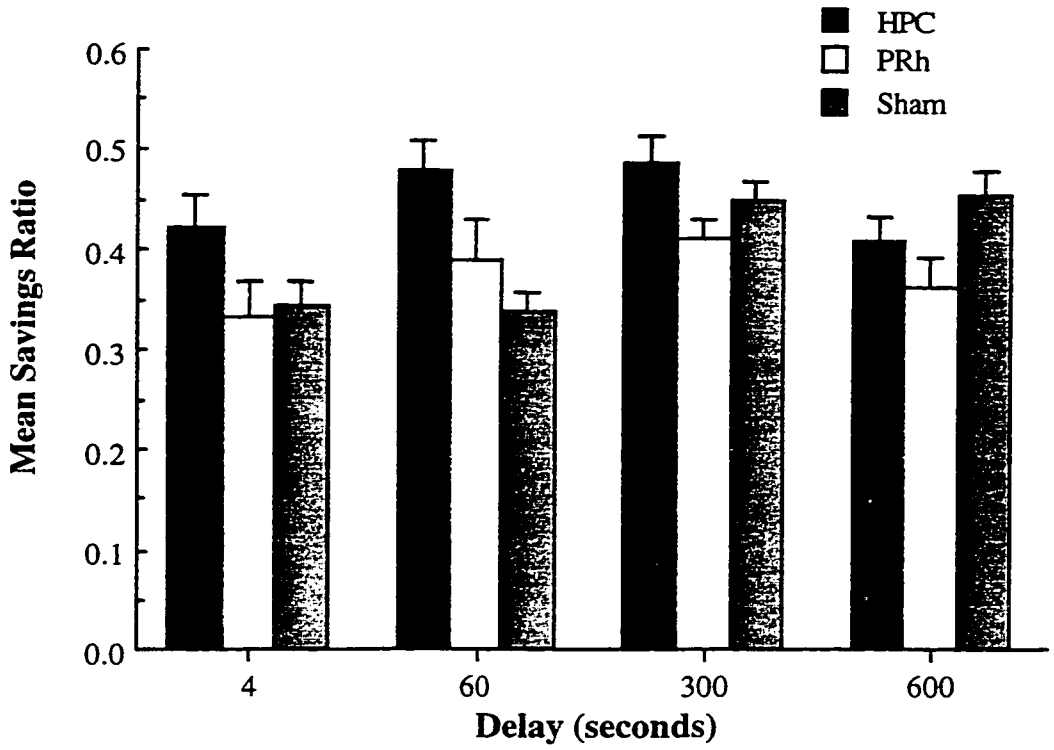

Figure 27. Mean savings ratio for each group during postsurgery mixed-delay testing. Error bars represent standard errors of means.

of Delay ($F[3,33] = 5.928$, $p = .002$) and a significant interaction between Group and Delay ($F[6,33] = 2.396$, $p = .049$). A simple effect analysis revealed a significant effect of Group at the 60 second delay ($F[2,11] = 4.492$, $p = .037$) and pairwise comparisons showed that both the Prh and Sham lesioned rats had significantly lower savings ratios than HPC lesioned rats at this delay ($ps < .05$). No significant differences were evident at the 4, 300, and 600 second delays ($ps > .05$).

Figure 28 shows the mean path length for each group on first and second swims during postsurgery mixed-delay testing. An analysis of variance conducted on the postsurgery path lengths for first and second swims with the variables Group, Delay, and Swim indicated significant main effects of Group ($F[2,11] = 15.580$, $p = .001$), and Swim ($F[1,11] = 28.023$, $p = .001$). Pairwise comparisons showed that, overall, the HPC lesioned rats had longer path lengths than PRh and Sham lesioned rats ($ps < .05$). PRh and Sham lesioned rats did not differ significantly ($p > .05$). The interaction between Group and Swim was not significant ($F < 1$), but planned comparisons revealed that HPC rats swam signficantly farther than PRh and Sham lesioned rats on second swims ($ps < .05$), but not on first swims ($ps > .05$). The main effect of Delay was not significant ($F < 1$), nor were the interactions between Group and Delay, Delay and Swim, and Group, Delay, and Swim ($Fs < 1$).

An analysis of variance performed on swim speed with the variables Group, Delay, and Swim revealed that swim speed increased significantly from first swims to second swims ($F[1,11] = 8.564$, $p = .014$), but there were no significant differences between the groups ($F < 1$, see Figure 29). There was also a significant main effect of Delay ($F[3,33] = 11.998$, $p = .001$). Pairwise comparisons showed that swim speed was significantly faster at the 4 second retention delay than at all the other delays ($ps < .05$), which did not differ significantly ($ps > .05$). The interaction between Delay and Swim was also signifcant ($F[3,33] = 11.804$, $p = .001$). A simple effect analysis revealed that the effect of Delay on swim speed was only significant for second swims ($F[3,33] = 21.445$, $p = .001$), and not for first swims ($F < 1$).

DMTP with a visible platform. When the platform was made visible (as in

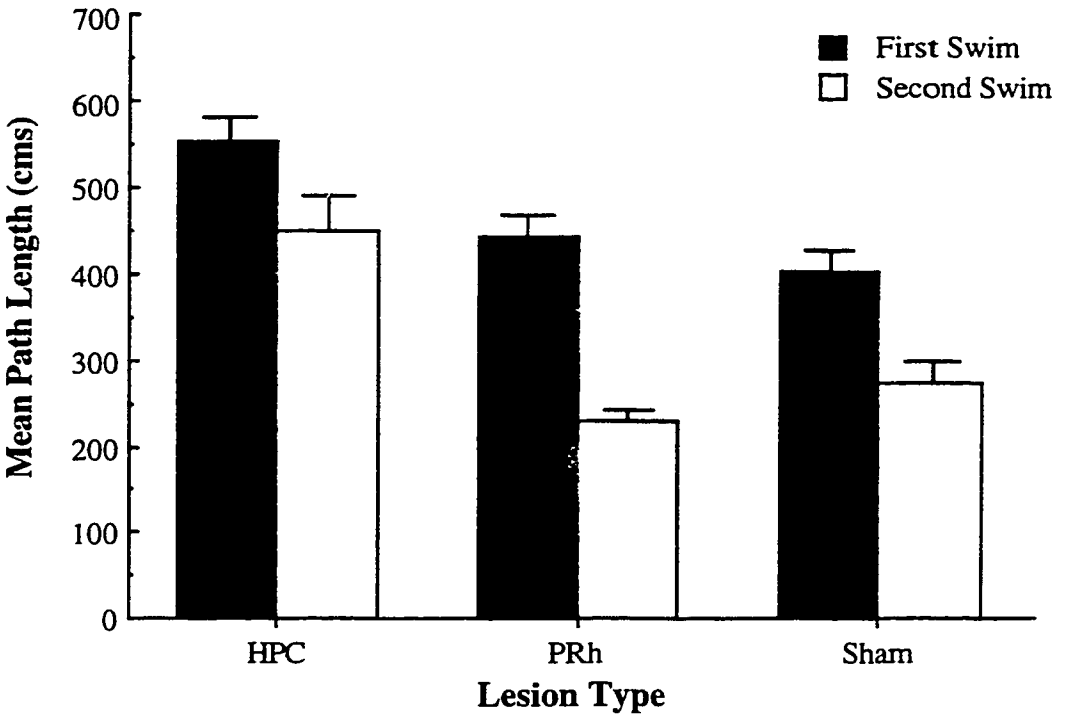

Figure 28. Mean path length of each group on first and second swims during postsurgery mixed-delay testing. Error bars represent standard errors of means.

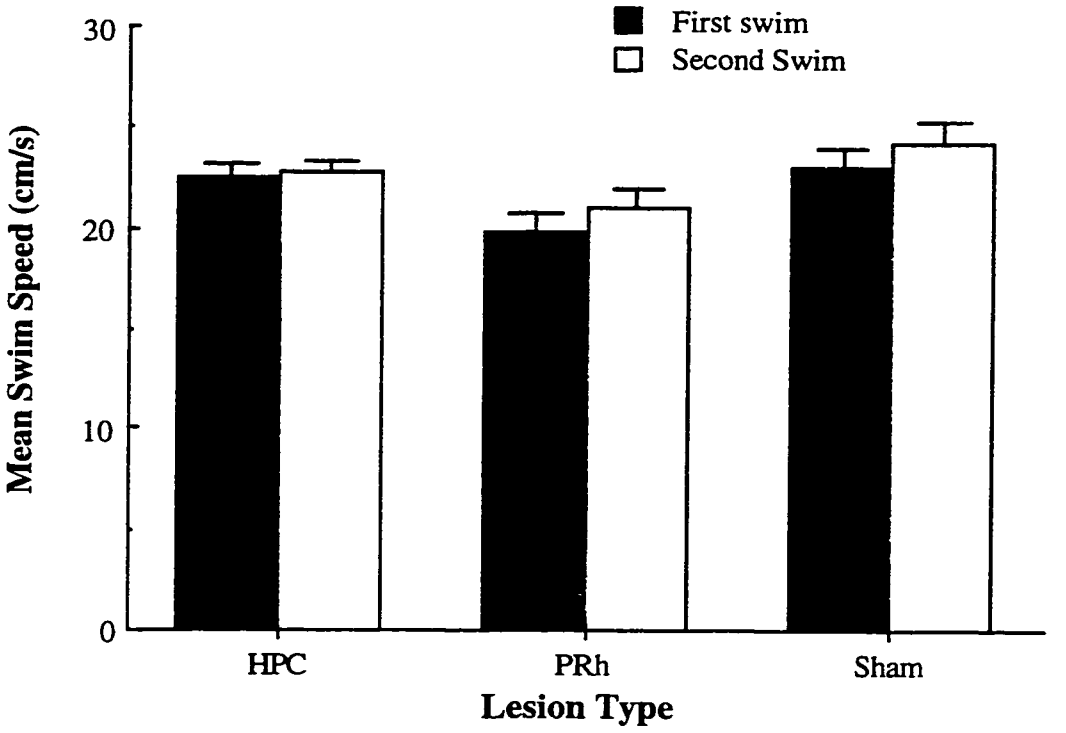

Figure 29. Mean swim speed for each group on first and second swims during postsurgery mixed-delay testing. Error bars represent standard errors of means.

Experiment 1) for a 4 trial session of DMTP with a 4 second delay the effect of the HPC lesions on performance was no longer evident. An analysis of variance was conducted on escape latencies from the visible platform session with the variables Group and Swim. Overall, the rats had shorter escape latencies on the second swim relative to first swim escape latencies ($F[1,10] = 26.502$, $p = .001$), but there were no signficant differences between the groups ($F[2,10] = 1.659$, $p = .238$, see Figure 30). The interaction between Group and Swim was not significant ($F < 1$).

DISCUSSION

The main findings of this experiment were that rats with lesions of the PRh were impaired on DNMS, but performed normally on DMTP, and that rats with lesions of the HPC were impaired on DMTP, but performed normally on DNMS.

The rats with PRh lesions showed mild DNMS impairments. The number of trials required for PRh lesioned rats to reacquire DNMS at the 4 second delay after surgery did not differ significantly from the number of trials required for the HPC and Sham lesioned rats. Other studies have observed DNMS reacquisition deficits with PRh lesions in rats (Mumby et al., 1994) and monkeys (Meunier et al., 1993; Buckley, Gaffan, and Murray, 1997). A significant impairment in the DNMS performance of the PRh lesioned rats in the present study was most evident at the 60 second retention delay. At this delay the PRh lesioned rats were observed to make fewer correct responses than HPC and Sham lesioned rats. Also, the postsurgery performance of PRh lesioned rats was significantly worse than their presurgery performance at the 60 delay. The HPC lesioned rats were not only unimpaired at DNMS relative to their presurgery performance, they also tended to improve slightly at some delays and substantially at others. The rats with PRh lesions did not show improvement at any of the delays, in fact, their postsurgery scores were lower than their presurgery scores at all delays.

Consistent with the results of Experiment 1, the HPC lesioned rats, but not the PRh lesioned rats, were impaired on the DMTP task. HPC lesioned rats showed reacquisition deficits on DMTP during postsurgery retraining at the 4 second delay. They also displayed

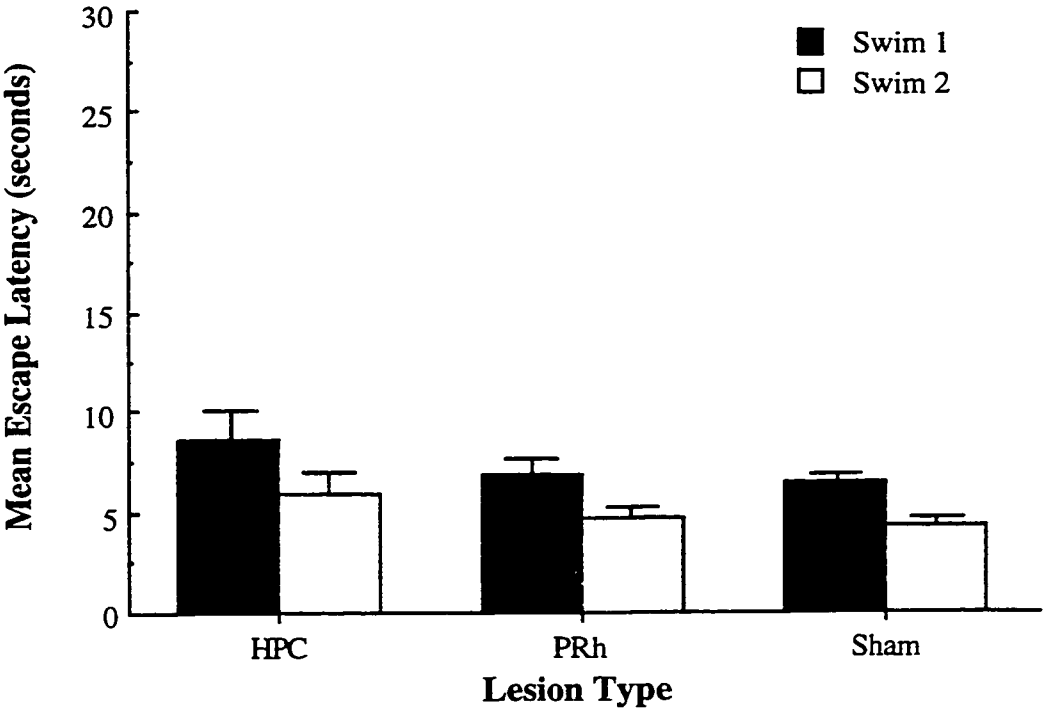

Figure 30. Mean escape latency on the first and second swim during the postsurgery DMTP session with the visible platform. Error bars represent standard errors of means.

higher second swim escape latencies during postsurgery mixed-delay sessions compared to presurgery mixed-delay sessions. The HPC lesioned rats also displayed higher second swim escape latencies than PRh and Sham lesioned rats during postsurgery mixed-delay sessions. During postsurgery mixed-delay testing, the HPC lesioned rats showed a delay-dependent increase in second swim escape latency; their performance declined as the delay was lengthened from 4 seconds to 60 seconds and then to 300 seconds. PRh lesioned rats did not display any DMTP deficits. Their pre- and postsurgery performance was comparable, and their postsurgery performance did not differ significantly from that of Sham lesioned rats.

The finding that HPC lesioned rats had higher second swim escape latencies than PRh and Sham lesioned rats was consistent with the finding that the HPC lesioned rats tended to swim further on second swims during postsurgery mixed-delay testing. Unlike in Experiment 1, there were no group differences in escape latency or path length on first swims. The degree of savings in escape latency from first swims to second swims suggested that the HPC lesioned rats, but not the PRh or Sham lesioned rats, had difficulty remembering the platform's location.

The deficits observed in HPC lesioned rats was likely not due to impaired swimming ability or other non-specific effects of the lesions. There were no significant differences in swim speed between the groups, and there was a slight tendency for the HPC lesioned rats to swim faster than the PRh and Sham lesioned rats. Also, when the platform was visible the escape latencies of the groups on first and second swims were not significantly different.

The findings that PRh lesions, and not HPC lesions, impair DNMS performance is consistent with other reports in rats (Mumby et al., 1994; Aggleton et al., 1996) and monkeys (Eacott, et al., 1994; Meunier et al., 1996; Murray et al., 1996). The spatial memory deficits observed in the HPC lesioned rats is consistent with the widely held belief that this structure is critically involved in processing spatial information (O'Keefe and Nadel, 1978; Olton et al., 1982; Morris et al., 1984; Sutherland et al., 1983). The lack of a spatial memory deficit in the rats with PRh lesions is consistent with the findings from

Experiment 1 of this thesis. These results are consistent with the view that at least two memory systems exist within the medial temporal lobe: The PRh is part of a system that underlies object-recognition memory (Mumby et al., 1994; Meunier et al., 1996; Murray, 1996), and the HPC is part of a system that underlies spatial memory (Mumby et al., 1994; Aggleton et al., 1996).

GENERAL DISCUSSION

The results presented here from two experiments provide evidence that there is a dissocation between the functions of the PRh and HPC. The results from Experiment 1 demonstrated that the HPC, but not the PRh is important for spatial memory. The results from Experiment 2 also demonstrated that the HPC, but not the PRh is important for spatial memory. In addition, Experiment 2 also demonstrated that the PRh, but not the HPC is important for object-recognition memory.

There were minor differences between the DMTP results of Experiment 1 and Experiment 2. In Experiment 2 HPC lesioned rats displayed a delay-dependent impairment. In Experiment 1 HPC lesioned rats were impaired at all delays, and there was not a corresponding decrement in performance as the delay periods were lengthened. Differences in the location and extent of the HPC lesions, and the amount of damage to structures adjacent to the HPC may account for these differences. For instance, the HPC lesions in Experiment 2 included more damage to the overlying pariatel cortex. This extra-HPC damage may have contributed to the delay-dependent impairment observed in Experiment 2.

Another minor difference between the DMTP results of Experiment 1 and Experiment 2 was the effect of HPC lesions on first swims. In Experiment 1 rats with HPC lesions had higher escape latencies on first and second swims, compared to rats with PRh and Sham lesions. In Experiment 2 rats with HPC lesions had higher escape latencies on second swims, but not on first swims, compared to rats with PRh and Sham lesions. The rats in Experiment 2 were trained concurrently on DMTP and DNMS, which may have influenced the results.

The findings from the present experiments suggest a functional dissociation between the PRh and HPC. This is consistent with a multiple-systems view of memory in the medial temporal lobe, in which the PRh is a critical component in an object-recogntion memory system and the HPC is a critical component in a spatial memory system. The HPC and PRh may both contribute to memory task performance under certain circumstances, such as when the task require both recognition of an object and memory for its spatial location. Gaffan and Parker (1996) found that a unilateral lesion of the PRh, in combination with a unilateral transection of the fimbria-fornix in the opposite hemisphere, impaired the ability of monkeys to remember the spatial organization of different objects. They interpreted this finding as evidence that two memory systems, namely an object-recognition system and a spatial memory system, may function interdependently if memories for both types of information are required for successful performance on a task.

Studies that examined the firing patterns of neurons in different medial temporal lobe structures during the presentation of novel and familiar stimuli provide further evidence that the PRh, and not the HPC, is involved in object-recognition. Riches, Wilson and Brown (1991) demonstrated that neurons in the rhinal and temporal cortices of monkeys discriminate between the relative familiarity of presented stimuli. Neurons in these areas were observed to decrease firing in response to repeated presentation of a visual stimulus. This suggests that there are neurons in these cortices that differentiate between stimuli on the basis of how frequently they have been viewed. Riches et al. also reported that this type of preferential firing pattern to familiar and novel stimuli was rarely observed in HPC neurons. Zhu et al. (1995) observed that neurons in the rhinal and temporal cortices of rats also responded preferentially to stimuli that were repeatedly presented. They viewed the similarities of the neuronal activity in these cortical areas in the rat and monkeys and the concordance between recording and lesion studies as compelling evidence that these structures are importantly involved in visual recognition memory.

In addition to the consensus between lesion and recording studies, Zhu, McCabe, Aggleton, and Brown (1996) recently examined the expression of the immediate early gene, c-fos, in the PRh and HPC of rats in response to the presentation of a novel or a

familiar stimulus. The objects were presented simultaneously so that a familiar object was presented to one eye, and one monocular field, and a novel object was presented to the other eye and field. Consistent with the evidence that neurons in the PRh will decrease their rate of firing when familiar stimuli are presented, Zhu et al. observed significantly less expression of c-fos in the PRh in the hemisphere associated with the presentation of a familiar stimulus than in the hemisphere associated with the presentation of a novel stimulus. Zhu et al. did not observe any hemispheric differences in c-fos expression in the HPC.

The findings presented in this thesis can be assessed with reference to the two types of memory systems discussed previously, namely the unitary medial temporal lobe memory system and the multiple medial temporal lobe memory systems. According to Squire and Zola-Morgan (1991) and Eichenbaum et al. (1994) structures in the medial temporal lobe, including the HPC and PRh, are components of a unitary memory system. Squire and Zola-Morgan proposed that both and the HPC are involved in declarative memory. Eichenbaum et al. proposed that the PRh, and the entorhinal and parahippocampal cortices, support intermediate-term representations of individual items of information, and the HPC represents the relations among these items.

The results of the experiments presented in this thesis do not support the views of Squire and Zola-Morgan (1991). If the functions of the HPC and PRh were interdependent and critical for the formation of declarative memories then lesions of either of these structures should result in a similar pattern of deficits on DMTP and DNMS. However, it was demonstrated by the present experiments that lesions of the HPC produced DMTP deficits, but not DNMS deficits, and lesions of the PRh produced DNMS deficits, but not DMTP deficits.

The results of the experiments presented in this thesis do not directly refute the predictions made by Eichenbaum et al.'s model of a unitary medial temporal lobe memory system. According to their model the PRh is part of a region that includes other cortical areas. This thesis focused solely on lesions limited to the PRh, therefore, it is not possible to fully evaluate their model in relation to the present findings. However, Eichenbaum et al.

argue that DNMS does not require relational processing because HPC lesions do not produce deficits on DNMS. It is true that DNMS can be solved in at least two ways. The animal could make a judgement of familiarity, and always chose the object that seems least familiar. This strategy would support successful DNMS performance, and it would not require relational processing. Therefore, in this case, lesions of the HPC would not produce DNMS deficits, as predicted by Eichenbaum et al. On the other hand, animals could solve DNMS by matching a memory for the sample object with the perceptual features of the objects presented during the choice phase. This strategy would also support successful DNMS performance, and it would require relational processing. It is presently not clear how animals solve DNMS. Therefore, it possible that the PRh forms relations between individual representations of objects, and the HPC forms relations between individual representations of places.

A more parsimonious explanation for the pattern of results presented in the experiments of this thesis is that the HPC and PRh have independent functions. Meunier et al. (1996) and Murray (1996) proposed that the PRh is part of a memory system for object-recogntion that does not require the integrity of the HPC. Mumby et al. (1994) and Aggleton et al. (1996) proposed that the PRh and HPC are components in separate systems that play distinct roles in processing object and spatial information, respectively. The results of the present experiments are consistent with these views.

The results from this thesis and the many experiments discussed above clearly show that the PRh is critically involved in object-recognition memory. There is little evidence to indicate that the HPC plays any more than a minor role in supporting this type of memory. Evidence that this is the case is derived from experiments in which 1) lesions of the PRh, and not HPC, produce object-recognition deficits (Gaffan and Murray, 1992; Suzuki et al., 1993; Meunier et al., 1993; Eacott et al., 1994; Mumby et al., 1994; Aggleton et al., 1996; Ennaceur et al., 1996 ; Meunier et al., 1996; Murray et al., 1996), 2) neurons in the PRh, and not the HPC, encode information about the familiarity of objects (Riches et al., 1991; Zhu et al., 1995), and 3) the expression of the immediate early gene, c-fos, is negatively correlated with the degree of familiarity of an object in the PRh, but not

in the HPC (Zhu et al., 1996). Furthermore, in the present experiments the PRh did not impair spatial memory in rats with presurgery training. The HPC, on the other hand, impaired spatial memory performance. Based on these findings, the most appropriate view of the organization of memory in the medial temporal lobe is that there are multiple, functionally dissociable and independent systems. At least two systems exist: The PRh is a critical component in a system that supports object-recognition abilities, and the HPC is a critical component in a system that supports spatial memory abilities.

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APPENDIX A

Stereotaxic coordinates for the HPC lesions

Table 1

The cannulae coordinates, in mm relative to bregma, for the neurotoxic lesions of the HPC.

Anteroposterior (AP)	Mediolateral (ML)	Dorsoventricular (DV)
3.1	1.0	3.6
3.1	2.0	3.6
4.1	2.0	4.0
4.1	3.5	4.0
5.0	3.0	4.1
5.0	5.2	5.0
5.0	5.2	7.3
5.8	4.4	4.4
5.8	5.1	6.2
5.8	5.1	7.5