

Research report

Anterograde and retrograde memory for object discriminations and places in rats with perirhinal cortex lesions

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Abstract

Three experiments examined the effects of perirhinal cortex lesions on rats' retrograde and anterograde memory for object-discriminations and water-maze place-memory problems. In Experiment 1, rats learned two object-discriminations — the first was learned 2 weeks before surgery and the second 24 h before surgery. Rats with perirhinal cortex lesions displayed mildly impaired retention of both object discriminations, with no evidence of a temporal gradient. They also learned a new discrimination at a normal rate, but were impaired on a retention test 24 h later. In Experiment 2, rats learned two water-maze place problems, conducted in different rooms — the first was learned 4 weeks before surgery and the second during the week immediately before surgery. Rats with perirhinal cortex lesions displayed deficits on the early retention trials of both place problems, but they quickly relearned both problems. In Experiment 3, rats with perirhinal cortex lesions learned a new place problem at a normal rate and performed as well as control rats on a retention test 3 weeks later. Although some of the results are consistent with the conclusion that perirhinal damage disrupts storage or retrieval of place information acquired before surgery, additional considerations suggest instead a role for perirhinal cortex in the representation of nonspatial information that makes a useful but nonessential contribution to water-maze performance. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Studies in humans and laboratory animals indicate that damage to medial-temporal-lobe structures can produce retrograde amnesia in which information that was acquired recently prior to the injury is more severely affected than information acquired long before the injury (see Ref. [32] for a review). It has been widely supposed for decades that damage to the hippocampal formation is responsible for such temporally-graded retrograde amnesia, and the most widely adopted interpretation is that hippocampal damage interrupts the consolidation of long-term memories. According to one type of account, information about an event is encoded and temporarily stored within the hippocampal forma-

tion and over time a more permanent representation is gradually established in some other brain area [20]. By another account, information is stored as numerous distributed neocortical traces, each representing a different aspect of the to-be-remembered event, and the consolidation function of the hippocampal formation is to bind together the distributed traces that together represent the entire event [39,48]. According to both accounts, eventually the hippocampus is no longer needed for storage or retrieval of the information.

The penchant for attributing retrograde amnesia to hippocampal damage has been enduring, and investigators have only recently started to assess the contributions of damage in other temporal-lobe structures, such as the rhinal cortex (entorhinal and perirhinal cortices) or the parahippocampal gyrus (postrhinal cortex in the rat). These areas share reciprocal connections with the hippocampal formation and are usually damaged along with the hippocampal formation in patients with tem-

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poral-lobe amnesia. Findings in humans, monkeys, and rats suggest that some aspects of anterograde amnesia previously attributed to hippocampal damage actually reflect damage to the rhinal cortex. For example, damage to the perirhinal cortex impairs object-recognition memory in rats [1,11,27,46] and monkeys [10,21,49], whereas hippocampal damage does not [29–31,37]. It seems reasonable to suspect that perirhinal cortex damage may also underlie some aspects of retrograde amnesia in patients with temporal-lobe damage.

This study assessed the effects of perirhinal cortex lesions on retrograde and anterograde memory for spatial and nonspatial information. Perirhinal cortex receives input from temporal, parietal, occipital, cingulate, and insular cortices, and shares reciprocal connections with the subiculum and the CA1 subfield of the hippocampus [6,17,41], and with the adjacent entorhinal cortex, which in turn provides a major input to the hippocampal formation through the perforant path [47]. The perirhinal cortex is thus considered an important link in the pathway through which information from polymodal association cortices reaches the hippocampal formation.

Despite compelling anatomical reasons to expect hippocampal memory functions should require inputs from perirhinal cortex, recent studies of anterograde memory in animals with lesions restricted to the hippocampal formation or perirhinal cortex suggest there are, at least, some important exceptions. For example, hippocampal lesions impair rats' ability to learn and perform allocentric-spatial memory (i.e. place) tasks in a water maze, but perirhinal cortex lesions generally do not [5,12,15,44]. In the few studies that found impaired place-memory following perirhinal cortex lesions the deficits were much milder than those typically seen after hippocampal damage [18,45], or else there was also substantial damage to the entorhinal cortex [34].

In addition to their anterograde place-memory impairments there is evidence that rats with hippocampal lesions also display retrograde amnesia for places [25]. The effects of perirhinal cortex damage on retrograde memory for places are not known, so one goal of this study was to determine what, if anything, those effects are. The answer has important implications for the question of whether anterograde and retrograde amnesia reflect disruption of the same processes. If anterograde and retrograde amnesia reflect the same underlying functional impairment, amnesic subjects should display anterograde and retrograde amnesia for the same kinds of information, and because perirhinal lesions fail to produce anterograde amnesia for places they should also fail to produce retrograde amnesia for places.

Perirhinal cortex lesions impair anterograde object recognition [11,21,27], but little has been firmly estab-

lished about the effects of perirhinal damage on retrograde memory for objects. Anterograde object-recognition tasks such as delayed matching- or nonmatching-to-sample are not suited for the study of brain-damage produced retrograde amnesia because normal rats and monkeys perform poorly on these tasks when the retention delay is longer than a few minutes. Instead, several investigators have used the two-choice object discrimination task to study retrograde memory for objects. Rats and monkeys easily learn object-discrimination problems and can remember them for several weeks.

Monkeys with bilateral lesions of the hippocampal formation, rhinal cortex, and temporal-lobe white matter, displayed retrograde amnesia for object discriminations [38,48], but it is not clear what aspect of the brain damage was responsible. Rats with bilateral lesions of the hippocampal formation (cornu Ammonis, dentate gyrus, and subiculum) displayed normal retrograde memory for object discriminations [25], suggesting that extrahippocampal damage contributed to the retrograde amnesia in the abovementioned monkey studies. The first experiment of this study assessed retrograde and anterograde memory for object discriminations in rats with perirhinal cortex lesions.

2. Experiment 1: anterograde and retrograde memory for object discriminations

Monkeys with large lesions of the medial temporal lobes have displayed both temporally-graded [48] and nongraded [38] retrograde amnesia for object discriminations learned between 2 and 16 weeks prior to surgery. In both studies the lesions included most of the hippocampal formation, and also the rhinal cortex and parahippocampal gyrus, the temporal stem and other white matter, and in the Salmon et al. [38] study, the amygdala. A more recent study found that rats with large excitotoxic lesions restricted to the hippocampal formation displayed normal retention of five object-discrimination problems they had learned between 13 and 1 week before surgery [25]. This finding suggests that the hippocampal formation is not required for long-term consolidation of information underlying accurate performance of an object-discrimination task, and that the retrograde amnesia for object discriminations observed in monkeys with large medial-temporal-lobe lesions [38,48] may have been caused by damage to white matter or to cortical areas overlying the hippocampal formation and amygdala, including the rhinal cortex and parahippocampal gyrus.

Findings from the few studies that have assessed retrograde memory for object discriminations following perirhinal cortex damage are, so far, inconclusive. Monkeys with rhinal cortex lesions (combined damage

to perirhinal and entorhinal cortices) displayed retrograde amnesia with a flat gradient for object discriminations learned up to 16 weeks before surgery [10,42]. However, damage to entorhinal cortex may have been a critical factor, and it is possible that more restrictive lesions of perirhinal cortex would not impair retrograde memory of object discriminations. A recent study found that perirhinal cortex lesions in rats, in which there was only slight damage to the lateral entorhinal cortex, had no effect on retrograde memory for object discriminations learned between 13 and 1 week before surgery [2]. It is possible, however, that the perirhinal lesions in the latter study were ineffective only because the shortest interval between learning and lesion — 1 week — was long enough that consolidation of relevant information was complete by the time of surgery. This hypothesis was addressed in the present experiment by training rats on two object-discrimination problems — one of them 2 weeks before surgery and the other one just 24 h before surgery. After a 2-week recovery period, their retention of those problems and their ability to learn a new object-discrimination problem was assessed.

2.1. Method

2.1.1. Subjects

The subjects were ten experimentally naive, male, Long–Evans rats (Charles River, St. Constant, Quebec) that were between 8 and 10 weeks old at the beginning of the experiment. They were housed individually with continuous access to water under a 12:12 light–dark cycle, with light onset at 07:00 h. Their body weights were reduced to approximately 85% of free-feeding levels by giving them daily rations of rat chow. They received approximately 25 g of rat chow/day throughout the remainder of the experiment. Training began after the rats had been on the restricted feeding regimen for 10 days.

2.1.2. Apparatus

The apparatus for object-discrimination training has been described in detail elsewhere [28]. Briefly, it consisted of an elevated runway, which was separated from identical goal areas at each end by opaque guillotine doors. Each goal area contained two food wells into which food pellets (45 mg Bio-Serv, Frenchtown, NJ) could be delivered by hand through plastic tubes that were mounted on the outside of the apparatus. A short divider wall protruded from the center of the end wall to separate the two food wells.

The test stimuli for the object-discrimination problems were six objects of various shapes, sizes, textures, and colours, but all were made of a similar plastic material. Each object was large enough to cover a food well but small enough and light enough to be easily displaced by a rat. The objects were washed with a

solution of diluted chlorine bleach at the end of each session.

2.1.3. Procedure

2.1.3.1. Presurgery Training. All training and testing was done during the light phase of the light–dark cycle, between 14 and 24 h after the rats' most recent meal. The rats were first habituated to the apparatus and shaped to retrieve food pellets from the food wells (see Ref. [28]). The six objects were divided into three pairs, which served as the discriminanda for the three object-discrimination problems. One of the objects in each pair was designated S+ (rewarded) and the other one was designated S– (not rewarded), counterbalanced as well as possible within groups.

Each discrimination problem was learned in a single training session. One was learned 14 days before surgery (the REMOTE problem) and another was learned on the day before surgery (the RECENT problem). Training on each problem continued until a rat reached a criterion of ten consecutive correct trials; however, each rat received a minimum of 40 trials per problem.

To begin a session, the rat was placed into the center of the apparatus and allowed to explore for approximately 1 min. To begin the first trial, one of the guillotine doors was closed, and the experimenter positioned S+ and S– over the food wells on the other side of the door from the rat. The experimenter opened the door, and the rat approached and displaced one of the objects. If it displaced S+, a food pellet was delivered to that food well; if it displaced S–, no food pellet was delivered. A rat was considered to have made a choice if the object was displaced enough to expose the food well. The experimenter then closed the far door and positioned S+ and S– over the food wells on the other side, in preparation for the next trial. The location of S+ (i.e. left or right well) varied pseudorandomly across trials. The intertrial interval was approximately 15 s.

2.1.3.2. Surgery. Surgery was performed under pentobarbital anaesthesia (65 mg/kg), approximately 24 h after the final training session on the RECENT discrimination problem. Rats in group PRH ($n = 5$) received bilateral electrolytic lesions centered on the perirhinal cortex. The lesions were made bilaterally at five sites (1.5 mA for 10 s) with a bipolar stainless steel electrode that was insulated with Teflon except for approximately 1 mm at its tip. The electrode coordinates are shown in Table 1.

Rats in group SHAM ($n = 5$) received identical treatment with the exception that the electrode was not lowered beneath the skull and thus they sustained no brain damage. All rats were allowed to recover for 2

weeks before behavioral testing recommenced. The experimenter who collected the behavioral data was unaware of the group assignment of individual rats.

2.1.3.3. Postsurgery training and retention testing. Two weeks after surgery, the rats were trained on a third object discrimination (the NEW problem) using procedures identical to those used during training on the REMOTE and RECENT discriminations. Training on the NEW problem continued for each rat until it reached the criterion of ten consecutive correct trials, but each rat received a minimum of 40 trials.

Retention of all three object-discrimination problems was assessed in a single session on the following day. Each problem was administered in blocks of five consecutive trials — the first block of trials involved the NEW discrimination problem, and was followed by a block of trials on the REMOTE problem, and then the RECENT problem. This cycle was repeated three times so there were a total of 15 trials of each problem.

Retrograde memory for object discriminations is usually assessed by administering trials in the same manner as during presurgery training and calculating the percentage of postsurgery reacquisition trials on which S+ is selected or the number of trials required to reach some criterion of accuracy. One potential problem is that giving the subject a reward for selecting S+ during retention testing could lead to anterograde learning that could then obscure a retrograde memory deficit. To circumvent this problem an extinction procedure on retention trials was employed for the REMOTE and RECENT discrimination problems. No food reward was given for responses on those trials. However, reward was still delivered when rats selected S+ on the NEW discrimination trials. It was hoped that the intermittent availability of rewards would maintain responding on the extinction trials of the REMOTE and RECENT problems.

Table 1
Electrode coordinates (in mm) for electrolytic lesions of perirhinal cortex^a

Anteroposterior	Mediolateral	Dorsoventral
−3.3	±5.5	6.5
−4.3	±5.5	6.5
−5.3	±5.5	6.5
−5.8	±5.5	6.5
−6.5	±5.5	6.2

^a Anteroposterior and mediolateral coordinates are relative to bregma; dorsoventral level is relative to brain surface beneath bregma. The electrode was angled 10° from vertical. Current (1.5 mA) was passed for 10 s at each site.

2.2. Results

2.2.1. Histological findings

Fig. 1 shows the location and extent of the lesions. The perirhinal cortex was nearly completely destroyed bilaterally in each PRH rat, and each also had minor bilateral damage to portions of lateral entorhinal cortex. Most of the lesions included slight damage to ventro-posterior portions of area Te2 — unilateral in two rats and bilateral in two others. Each PRH rat sustained minor bilateral damage to anterior portions of the postrhinal cortex, and in two rats there was unilateral damage to the ventral subiculum and temporal CA1 field.

2.2.2. Behavioral results

There was no significant difference between PRH and SHAM rats in the number of trials required to reach criterion on the NEW discrimination (PRH $M = 31.20$, S.E. = 12.08; SHAM $M = 58.00$, S.E. = 14.56). Fig. 2 shows the results of the retention tests conducted the next day for all three problems. All rats continued to readily displace objects on the REMOTE and RECENT discrimination trials despite the extinction procedure used on those trials. The PRH rats were mildly but significantly impaired on the object-discrimination problems they had learned before surgery. Analysis of variance with scores on the RECENT and REMOTE problems as repeated measures yielded a significant group effect ($F[1,8] = 11.85$, $P < 0.01$), but the group effects were not significant when results from the two problems are considered separately ($P_s > 0.05$).

The PRH rats also made significantly more errors than SHAM rats on retention trials for the NEW problem ($t[8] = 3.58$, $P < 0.01$). Although the latter effect was not large, it may have been attenuated by ceiling effects because most of the SHAM rats obtained perfect scores on the retention test for this problem.

2.3. Discussion

Rats with perirhinal cortex lesions displayed evidence of mild retrograde amnesia with a flat gradient for object discrimination problems learned 2 weeks or 1 day before surgery. They showed a strong tendency to select S+ on retention trials for the REMOTE and RECENT problems, but they did so less often than control rats. The results on those trials were unaffected by anterograde learning, at least anterograde learning of object-reward associations, because responses were not rewarded.

The lesions also had no discernible effect on acquisition of the NEW discrimination problem learned after surgery — perirhinal rats and control rats did not differ significantly in the number of trials they required to master this problem. These results are consistent

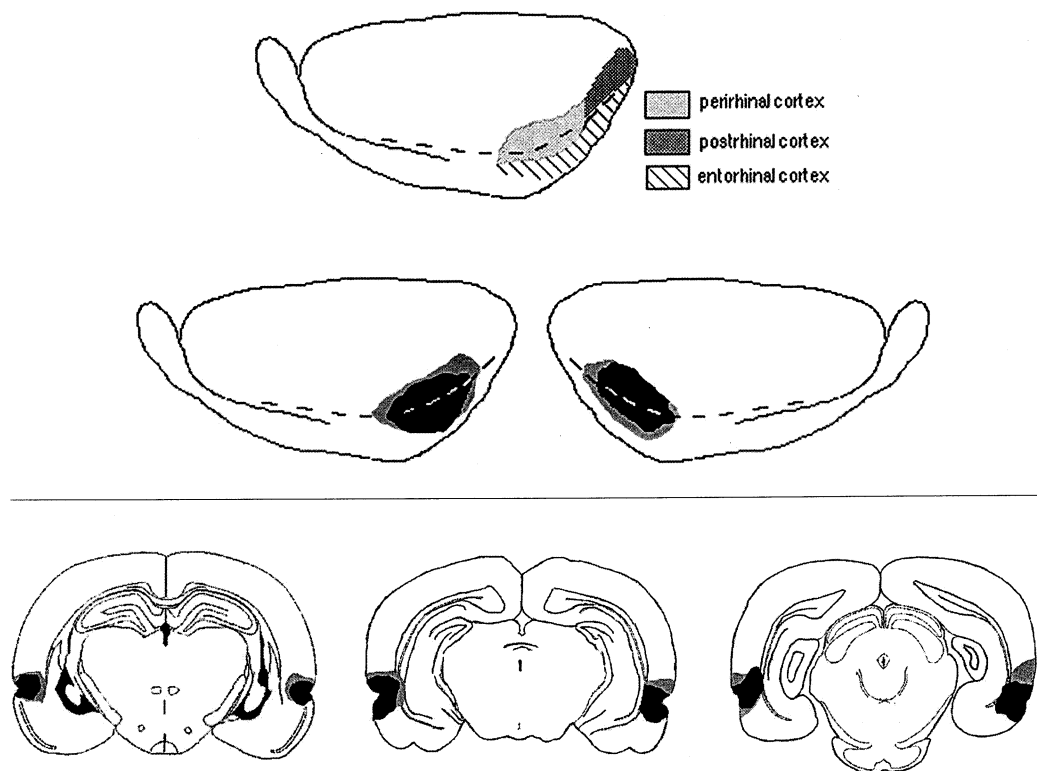


Fig. 1. Top shows the approximate boundaries of perirhinal, postrhinal, and entorhinal cortex on lateral surface of rat brain, according to Burwell et al. [4] and the location and extent of the largest (grey) and smallest (black) PRh lesions in Experiment 1. Bottom shows the depth of largest (grey) and smallest (black) PRh lesions at three coronal planes. Coronal drawings are based on the rat brain atlas of Paxinos and Watson [35].

with those of previous studies in rats [2] and monkeys [10], and they suggest that the perirhinal cortex plays, at most, a noncritical role in encoding the information that underlies accurate object-discrimination performance. Although others have found impairments in new object-discrimination learning after perirhinal cortex lesions [16,42], the lesions in those studies included the entorhinal cortex and this may have been responsible, in whole or in part, for the impairment. The PRH rats sustained considerably less collateral damage to the entorhinal cortex.

The rats with perirhinal cortex lesions were significantly impaired on the 24-h retention test for the discrimination problem they learned after surgery (the NEW problem). Although they made significantly more errors than control rats on retention trials for the NEW problem, as a group the rats with perirhinal cortex lesions still chose correctly on approximately 86% of the trials ($M = 21.4$ correct trials out of 25; S.E. = 0.93). It is not likely that new learning during the test session obscured a more severe retention deficit because the PRH rats scored higher on the first five retention trials for the NEW problem than they did over the entire session ($M = 4.4$ correct trials out of the first five trials, or 88%, S.E. = 0.24). However, the severity of the 24-h retention deficit may have been obscured by ceiling effects, because most control rats made no errors at

all on the NEW problem ($M = 5$ correct trials out of the first five trials; $M = 24.8$ correct trials out of all 25 trials).

The present experiment included certain design features that were intended to facilitate interpretation of the results. In most previous studies, retrograde mem-

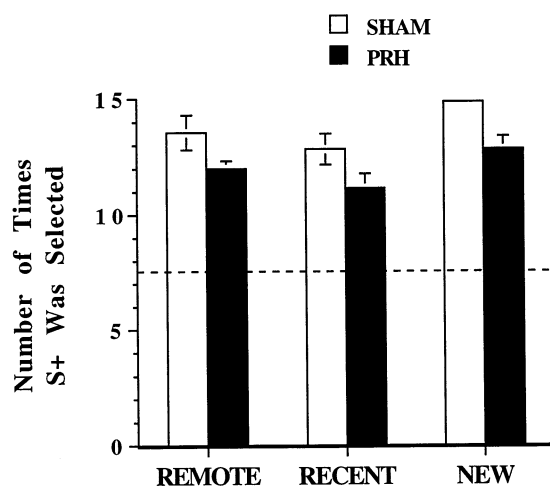


Fig. 2. Mean number of retention trials on which S+ was selected for each of the three object-discrimination problems. The dashed line shows the level of chance performance (i.e. 7.5 correct trials out of 15). Error bars represent S.E.M.

ory for object discriminations has been assessed by administering retention trials in the same manner as learning trials, and determining either the percentage of postsurgery trials on which S+ is selected or by the number of postsurgery trials required to reach some criterion of accuracy. A problem with these methods is that giving the subject a reward for selecting S+ during retention testing introduces the possibility that anterograde learning of object-reward associations could obscure a retrograde memory deficit. Some investigators analyse separately the data from the first retention trial because performance on that trial cannot be influenced by anterograde learning. But this solution introduces another potential problem: It is reasonable to assume that most subjects experience some degree of stress, arousal, or disorientation upon returning to a test situation for the first time following a long postsurgery recovery period and these responses are likely to be greatest on the initial trials, before the subject habituates once again to the test situation. This could influence performance on the first retention trial, and perhaps interact with lesion effects, thereby obscuring the true status of retrograde memory. A solution to this second problem is to assess retention of preoperatively learned problems on multiple trials, but this must be done without introducing the problem of contamination by anterograde learning. The solution to both problems was to employ an extinction procedure during retention testing for the problems learned before surgery. This made it possible to assess retention over several trials, and while *something* may have been learned on the extinction trials, this would not include object-reward associations. It is interesting to note that the performance of most rats was quite stable over the 15 retention trials of each problem.

Another important feature of the procedure was the restriction of original learning of each problem to a single session. This was done for several reasons: first, it ensured an accurate estimation of the interval between learning and surgery. In experiments where subjects are trained on discrimination problems over several days and sessions until they reach some level of consistently high accuracy [2,10,25,26] it can be assumed that something is learned on each session, so the interval between learning and surgery cannot be estimated to the accuracy of 1 day. This may not be a major problem in studies where retrograde memory is assessed for information acquired over presurgery intervals spanning several weeks, but it does mean that multi-session training should not be used when comparing retrograde memory for information acquired at different presurgery time points that span only a few days. Second, the single-session training procedure ensured that the rats were not overtrained on the discrimination problems to same extent as rats in previous experiments using multi-session training. The rats did not receive the mnemonic

benefits of distributed learning, and they received significantly fewer learning trials on each problem than rats in previous retrograde-memory experiments using multi-session training [2,25]. It was reasoned that if perirhinal lesions disrupt retrograde memory of object-discrimination problems, one would have a better chance of detecting this in rats that had not overlearned the problems. Third, in most studies of retrograde memory for object-discriminations in monkeys, original learning of each problem occurred in a single session, and therefore, the use of a similar procedure should facilitate comparisons of findings in rats and monkeys. Fourth, it was speculated that confining the learning experience to a single session — which in most cases lasted between 20 and 40 min — might confer to subsequent performance a greater dependence on retention of episodic information about individual responses and their outcomes, relative to retention of S–R associations. Although there is no way of knowing whether this was accomplished, the objective is important because episodic memory is impaired in amnesic patients with temporal-lobe damage, whereas many forms of S–R learning are relatively spared [19].

3. Experiment 2: retrograde memory for place problems

The purpose of this experiment was to determine the effects of perirhinal cortex damage on retrograde memory for place-memory problems like those for which rats with hippocampal lesions display retrograde amnesia. Using a within-subjects design, Mumby et al. [25] assessed the effects of hippocampal lesions on two fixed-platform water-maze tasks that were run in two different rooms. One was learned during the 14th week before surgery and the other during the 2nd week before surgery. The rats with hippocampal lesions displayed impaired retention of both place problems with no evidence of a temporal gradient to their deficits.

The hypothesis that memory functions of the hippocampus depend upon inputs from the perirhinal cortex [8] predicts that perirhinal lesions should produce retrograde amnesia for place-memory problems. On the other hand, it has recently been shown that perirhinal cortex lesions do not disrupt anterograde memory on water-maze place-memory tasks [5,12], suggesting that some hippocampal functions are not dependent upon inputs from perirhinal cortex and that perirhinal cortex lesions might also spare retrograde memory for water-maze tasks.

Rats were trained on two place-memory problems — the fixed-platform water-maze task conducted in two different rooms. The first place problem was learned approximately 4 weeks before surgery and the second place problem was learned on the 3 days immediately preceding the day of surgery. After recovery retention

and reacquisition of the two place problems was assessed.

3.1. Method

3.1.1. Subjects

Sixteen adult male Long–Evans hooded rats served as subjects. They weighed between 300 and 350 g at the start of the experiment. Housing conditions were the same as those in Experiment 1.

3.1.2. Apparatus

The place problems were conducted in a water maze [23], 137 cm in diameter and 46 cm high, and filled with water (23°C) to a depth of approximately 30 cm. The water was made opaque by adding instant skim milk powder. A movable Plexiglas platform (10 cm × 10 cm × 28 cm) was hidden approximately 2 cm below the surface of the water. The rats could not see the platform, but several extramaze cues (e.g. posters, shelves, a computer, etc.) were visible from within the pool, and the rats could learn the location of the platform relative to these distal cues. Swim paths and latencies were recorded using a VP118 Super Tracker with HVSWater software (HVS Image, Hampton, UK) and these raw data were stored on computer (IBM compatible, 486 DX) for later analysis.

3.1.3. Procedure

All training, testing, and surgical procedures were conducted during the light phase. Rats were transported to the testing room in groups of five or six and were singly housed there on top of a cart inside covered wire mesh cages. A black curtain separated the cart from the rest of the room so the rats could not see the extra-maze cues that were visible from within the pool.

3.1.3.1. Presurgery place-memory training. The first (i.e. REMOTE) place problem was learned over a 3-day period, 4 weeks before surgery. The second (i.e. RECENT) place problem was learned on the 3 days immediately preceding the day of surgery. The procedures for the REMOTE and RECENT place problems were identical, but they were conducted in different rooms (room A and room B). Thus, the two problems required the rats to learn about different sets of spatial cues. The use of Rooms A and B for the REMOTE and RECENT problems was counterbalanced as well as possible within the groups.

Each rat received eight trials on each of 3 consecutive daily sessions, for a total of 24 trials. On each trial, the rat was placed into the edge of the pool, facing the wall, at one of the four cardinal compass points, N, E, S, W. Each of the four starting positions was used twice per session in a pseudorandom sequence, which was the same for all rats. The platform was located in the center

of the NW quadrant on every trial. A trial continued until the rat climbed onto the platform or until 60 s elapsed. The rat was left on the platform for 10 s; if it failed to find the platform within the 60-s maximum, it was placed onto the platform and left there for 10 s.

3.1.3.2. Surgery. Surgical procedures were identical to those in Experiment 1. One day after the final training session on the RECENT place problem, seven rats received perirhinal cortex lesions (group PRH) and nine rats received sham-surgery (group SHAM). They were allowed to recover for 14 days before postsurgery testing commenced.

3.1.3.3. Postsurgery testing. Postsurgery retention testing occurred over 2 consecutive days. On the first day the rats received 16 trials in room A and on the second day they received 16 trials in room B. Thus, roughly half of the rats in each group were tested first on the REMOTE place problem and then on the RECENT problem, and the order was reversed for the remaining rats. The general procedures were the same as during presurgery training, with the exception of the 2nd and 14th trials. The platform was removed from the pool on Trial 2 (the ‘early’ probe) and Trial 14 (the ‘late’ probe). On these probe trials the rat was placed into the pool at the South starting position and allowed to swim for 25 s. The main dependent measures on the probe trials were latency to reach the platform location, the number of times crossing that location, and the percentage of the 25-s swim that was in the NW quadrant (i.e. the platform quadrant).

3.2. Results

3.2.1. Histological findings

The perirhinal cortex lesions were very similar to those in Experiment 1 (see Fig. 2). Each rat sustained nearly complete bilateral destruction of perirhinal cortex and minor bilateral damage to lateral entorhinal cortex, anterior portions of the postrhinal cortex, and area Te2. There was slight unilateral damage to the subiculum and CA1 region in three rats.

3.2.2. Behavioral results

The groups were well-matched in terms of presurgery performance on both place problems. The mean escape latency on the final two learning trials (i.e. trials 23 and 24) of the REMOTE place problem was 5.40 s (S.E. = 0.89) for group PRH and 4.73 s (S.E. = 0.35) for group SHAM. The mean escape latency on the final two learning trials of the RECENT place problem was 4.53 s (S.E. = 0.80) for the PRH rats and 4.63 s (S.E. = 0.73) for the SHAM rats.

Fig. 3 shows the escape latencies during retention and reacquisition testing for both place problems. For

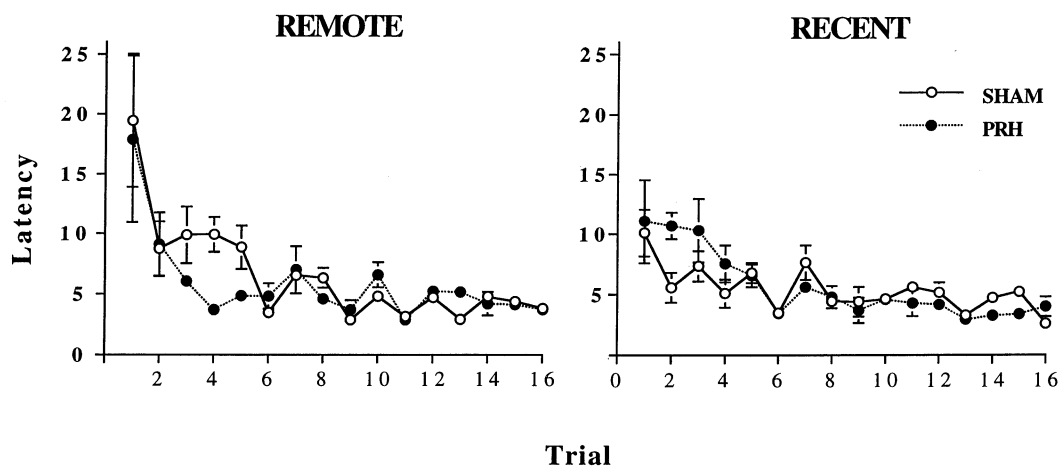


Fig. 3. Mean escape latencies during retention and reacquisition testing on the REMOTE and RECENT place problems. The platform was removed for the early probe on trial 2 and the late probe on trial 14, so the latency to the first platform-crossing was used as a corresponding measure on those trials. Error bars represent S.E.M.

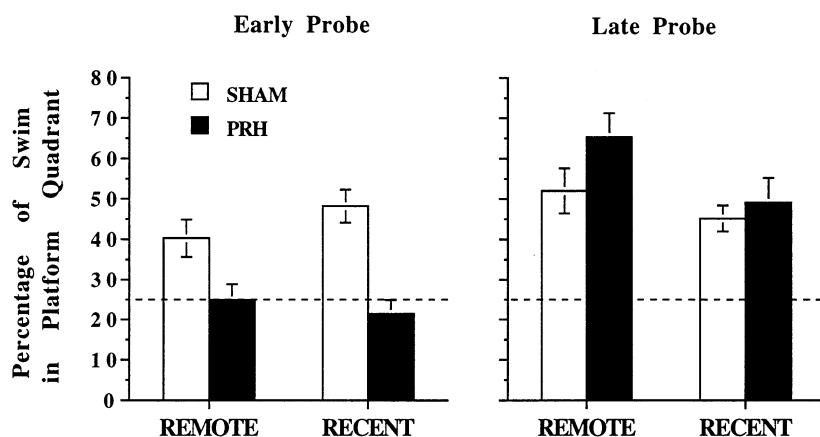


Fig. 4. Mean percentage of total swim path that was in the platform quadrant on probe trials conducted during retention testing in Experiment 2. The 'early' probe was conducted on the second retention trial, and the 'late' probe was conducted on the fourteenth trial. The dashed line shows the chance performance level (i.e. 25%). The error bars represent S.E.M.

the two probe trials with the platform removed (Trials 2 and 14) the latency to reach the platform location was used (first platform crossing) was used as a corresponding measure. Latencies on the RECENT place problem were significantly longer in group PRH than group SHAM on the early probe trial ($t[14] = 2.806$, $P < 0.02$), but the groups did not differ significantly thereafter, nor on the first retention trial that preceded the early probe. The PRH rats' escape latencies were not significantly longer than those of SHAM rats at any stage during retention testing on the REMOTE place problem; in fact, they were significantly shorter on Trials 3, 4, and 5.

Fig. 4 shows the results on the quadrant-preference measure during the probe trials. The PRH rats were impaired on the early probe trial of both place problems, as they spent significantly less of their search in the platform quadrant than did the SHAM rats (REMOTE, $t[14] = 2.43$, $P < 0.03$; RECENT $t[14] = 4.79$,

$P < 0.001$). In fact, the PRH rats showed no preference whatsoever for the platform quadrant on the early probe trials, as the mean proportion of their swim spent in that quadrant was not significantly different from chance (i.e. 25%) on either place problem. In contrast to their deficits on the early probe trials, the PRH rats displayed a strong preference for the platform quadrant on the late probe trial for both the REMOTE and RECENT problems, and they did not differ significantly from the control rats in this respect (REMOTE, $t[14] = 1.64$, $P > 0.10$; RECENT $t[14] = 0.61$, $P > 0.10$).

Fig. 5 shows the mean number of times the rats crossed the platform location during the probe trials. The pattern of results was similar to that seen on the latency measure: PRH rats made significantly fewer platform-crossings than SHAM rats on the early probe trial for the RECENT problem ($t[14] = 2.01$, $P = 0.03$, one-tailed), but the groups did not differ significantly on this measure during the early probe trial for the

REMOTE problem. There were no significant differences between the groups on the late probe for either problem (all P s > 0.05).

3.3. Discussion

Rats with perirhinal cortex lesions were mildly impaired on the initial trials of retention testing for both the REMOTE and the RECENT place problems. The clearest evidence of a deficit came on the early probe trial (Trial 2). The quadrant-preference results on the early probe trials suggest a nongraded retrograde amnesia for the place problems; the deficits on this measure were of similar magnitude on both the REMOTE and RECENT problems. These results suggest that damage to the perirhinal cortex can cause retrograde amnesia for place information, but that it does not impair reacquisition of this information.

The latency and platform-crossing data from the early probe trials, on the other hand, suggest a temporally-graded retrograde amnesia; there were significant deficits on these measures on the RECENT problem, but not on the REMOTE problem. A possible explanation for the discrepant results for quadrant-preference and the other two measures is that quadrant-preference is more sensitive to the loss of place information. Although the PRH rats' quadrant-preference deficits on the early probe trial appeared to be roughly equal for the REMOTE and RECENT problems, this may have been due to a floor effect, because the percentage of their swim that PRH rats spent in the platform quadrant on the early probe trial was not significantly different from chance on either place problem. By this view, the perirhinal rats' impairments on the early probe were more severe for the RECENT problem than for the REMOTE problem because they only displayed latency and platform-crossing deficits on the RECENT problem.

Performance on the early probe trial was presumed to be a valid index of retention because it was preceded by only one retention trial. Considerable learning may have occurred on that first retention trial, but it is also reasonable to suspect that performance on the second (i.e. probe) trial reflected to a large extent what the rats remembered from the original training experience. Indeed, the SHAM rats' performance on the early probe was not significantly different from their performance on the late probe, which suggests that they were already performing at or near their postsurgery asymptote after just one retention trial. This is more consistent with reactivation of previously formed representations than with new learning. The rats with perirhinal cortex lesions rapidly relearned both place problems after displaying deficits on the early probe trials, which suggests that they, too, remembered much about the water-maze training. Quadrant-preference and platform-crossing data on the late probes indicated no significant differences between the PRH and SHAM rats at the end of retention and reacquisition testing.

The deficits observed during early retention trials contrast with a previous report that rats with perirhinal cortex lesions performed as well as controls throughout retention testing of water-maze place problems learned either 14 or 2 weeks before surgery [2]. The presurgery training and postsurgery testing procedures used in that study were similar to those of the present experiment, with a few exceptions: one difference was that the early-probe trial occurred on the fourth retention trial in the earlier study [2], whereas it was on the second trial in the present experiment. The finding that the rats with perirhinal cortex lesions were only impaired on the early probe trials suggests the rats in the earlier study may have had transient impairments that went undetected because the probe trial was not conducted early enough and sufficient relearning occurred during the first three retention trials with the platform in place. In

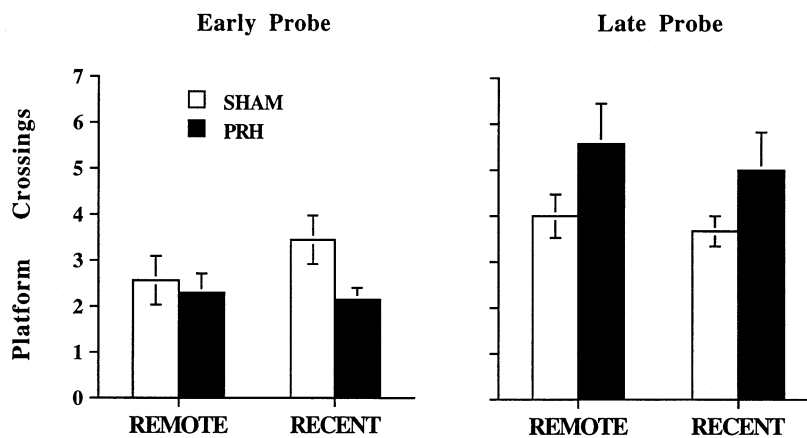


Fig. 5. Mean number of times the rats crossed the platform location (i.e. platform crossings) on the probe trials in Experiment 2. The 'early' probe was conducted on the second retention trial, and the 'late' probe was conducted on the 14th trial. The error bars represent S.E.M.

the present study only one trial was conducted with the platform in place before the early probe. It should be noted, however, that if probe-trial quadrant-preference is a more sensitive measure of place-memory than escape latency, as has been suggested, then the latency data may underestimate the number of retention and reacquisition trials over which PRH rats would have shown a deficit on another measure. Another difference between the two studies was the interval between learning and surgery. For the RECENT place problem this interval was 2 weeks in the previous study [2] and only 24 h in the present study; for the REMOTE problem it was 14 weeks in the previous study and 4 weeks in the present study. Considering that the present rats with perirhinal damage appeared to have relatively mild impairments on the early probe trial of the REMOTE problem compared to their impairments on the RECENT problem, the results suggest that whatever role the perirhinal cortex plays in memory for the place problems diminishes substantially over the first several days following learning. Thus, the ability to remember the RECENT place problem in the previous study may have become insensitive to the loss of perirhinal cortex during the 2-week interval between learning and surgery.

4. Experiment 3: acquisition and retention of a place-memory problem

Damage to the hippocampal formation causes severe and lasting deficits on the fixed-platform (i.e. reference memory) water-maze task under a variety of training and testing conditions [24,25,40]. Given the strong projections that link the perirhinal cortex and hippocampal formation, the mild and transient nature of the deficits on this task following perirhinal cortex lesions in Experiment 2 may seem surprising. But several previous studies have also found evidence of relatively normal place-learning following perirhinal cortex lesions [5,9,12,15,44]. In a study that found impairments on a working-memory water-maze task [34], the lesions included much of the entorhinal cortex, and therefore, it is not clear whether perirhinal cortex damage contributed to the results.

There is at least one report of impaired acquisition of the fixed-platform water-maze task in rats with restricted perirhinal cortex lesions [45]. This suggests that under certain conditions the perirhinal cortex may be needed for normal water-maze performance. The results in Experiment 2 fit with this general hypothesis, but the relative mildness of the deficits in the rats suggests that optimal conditions were not produced for revealing an impairment. This raises the question of just what conditions would be optimal.

One possibility stems from evidence that presurgery training can attenuate deficits on some memory tasks following temporal-lobe lesions [22]. The rats in Experiment 2 received extensive presurgery water-maze training, whereas the rats in the Wiig and Bilkey [45] study did not receive any presurgery training. However, the extant findings cannot be easily reconciled this way. Bussey et al. [5] found no evidence of acquisition deficits on the fixed-platform water-maze task in non-pretrained rats with perirhinal damage, and it was recently found that performance of an allocentric-spatial working-memory task — delayed matching-to-place — is not impaired in rats with perirhinal cortex lesions, whether or not they received presurgery training [12]. It may be that the factors which made water-maze acquisition sensitive to perirhinal damage in the Wiig and Bilkey [45] study had more to do with features of their water maze testing room than with features of their training procedures, or it may have been a combination of both.

The main purpose of the present experiment was to determine whether perirhinal damage would impair acquisition of the fixed-platform water-maze task used in our laboratory. Rats with no previous water-maze experience received either perirhinal cortex removals or sham surgery and were then trained on the water maze task. To the best of the authors' knowledge, the effects of perirhinal cortex damage on long-term retention of anterograde place learning has not previously been examined. Accordingly, retention of the place problem was assessed after a 3-week interval.

4.1. Method

4.1.1. Subjects

Ten adult male Long–Evans hooded rats served as subjects. They weighed between 300 and 350 g at the start of the experiment. Housing conditions were the same as those in Experiment 1.

4.1.2. Apparatus

The same water-maze and tracking system was used as in Experiment 2. The water maze was situated in room A throughout this experiment.

4.1.3. Procedure

4.1.3.1. Surgery. Surgery was performed under pentobarbitol anaesthesia (65 mg/kg). Rats received either aspiration lesions of the perirhinal cortex (Group PRH; $n = 5$) or sham surgery (Group SHAM; $n = 5$). In preparation for making perirhinal cortex lesions, a coronal scalp incision was made and the skull overlying the perirhinal cortex was exposed. A hole was cut into the skull with a dental drill, the dura overlying the rhinal fissure was incised, and portions of the perirhinal

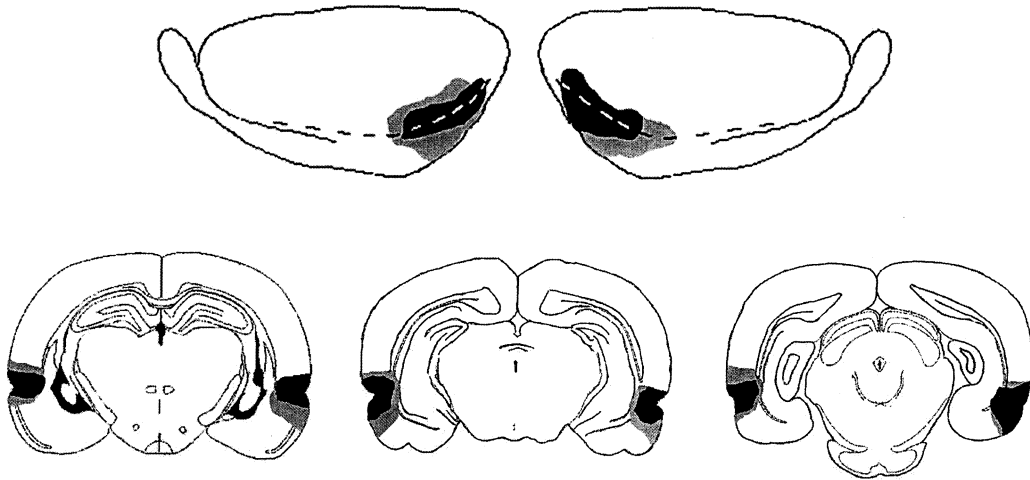


Fig. 6. Location and extent of the PRH lesions in Experiment 3.

cortex were aspirated with a vacuum pump and a glass Pasteur pipette. The cavity was filled with Gelfoam (Upjohn Company, Don Mills, Ontario, Canada), and the incision was closed with wound clips. Rats in group SHAM received the same anaesthetic dose and scalp incision as those in group PRH, but their skulls were not damaged. The rats were allowed to recover for 14 days before water-maze training commenced.

4.1.3.2. Fixed-platform acquisition and retention. The general procedures were the same as those for presurgery training in Experiment 2. Rats received 28 trials over three consecutive daily sessions, with the platform in the center of the NW quadrant on each trial. There were eight trials on Session 1 and ten trials on Sessions 2 and 3.

Three weeks after acquisition training the rats received a single 10-trial retention session with the platform in the NW quadrant. A 30-s probe with the platform removed was conducted on Trial 2 (the early probe) and on Trial 10 (the late probe).

4.2. Results

4.2.1. Histological findings

Fig. 6 shows the location and extent of the perirhinal cortex lesions. Most lesions were larger than those in Experiments 1 and 2; however, the extent of damage to the perirhinal cortex was comparable. Most of the perirhinal cortex was removed bilaterally in every rat, and each rat sustained some damage to lateral entorhinal cortex, postrhinal cortex, and area Te2. Minor damage to the subiculum and CA1 cell field occurred bilaterally in two rats, and unilaterally in one rat.

4.2.2. Behavioral results

There were no significant differences between the groups at any time during acquisition of the water-

maze place problem, nor were there any significant differences during the retention session 3 weeks later. Fig. 7 shows the mean escape latencies across the 28 acquisition trials and the ten trials of the retention session. For the probe trials latency to the first platform crossing was used as the corresponding measure. The data for each session were separately analysed and no significant group differences were found (all $P_s > 0.05$).

Fig. 8 shows the quadrant-preference scores on the probe trials conducted during the retention session. The group differences were not statistically significant on either the early probe or the late probe ($P_s > 0.10$).

4.3. Discussion

Bilateral aspiration lesions of the perirhinal cortex had no discernible effect on acquisition or long-term retention of the fixed-platform water-maze task. It should be noted that the lesions in this experiment were somewhat larger than those in Experiment 2, although most of the additional damage was in Te2 and the lateral entorhinal cortex, and the damage to perirhinal cortex was nearly complete in both experiments.

The findings are consistent with a recent study in which rats with excitotoxic lesions of perirhinal and postrhinal cortex were unimpaired in acquisition of the fixed-platform water-maze task [5]. They are inconsistent, however, with another report that rats with more restricted perirhinal cortex lesions were impaired in acquisition of this task [45].

It has been suggested that the electrolytic lesions in the study by Wiig and Bilkey [45] impaired water-maze acquisition because of damage to fibres that pass adjacent to the perirhinal cortex [5]. This now seems unlikely because the present aspiration lesions caused even more damage to these fibres without impairing water-maze acquisition, and so did the perirhinal cortex lesions in a recent study in which no impairments on a

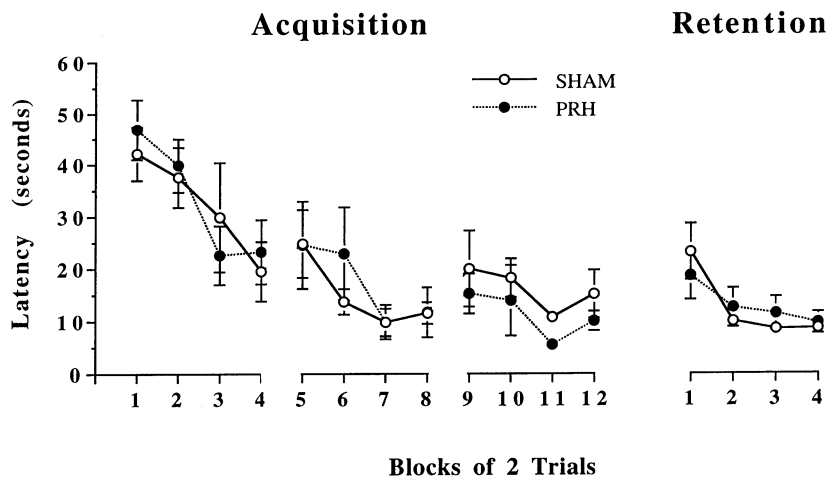


Fig. 7. Mean escape latencies on the 28 water-maze acquisition trials and the ten trials of the retention session conducted 3 weeks later. The platform was removed for the probe trials during retention testing (Trials 2 and 10) so the latency to the first platform-crossing was used as a corresponding measure on those trials. The error bars represent S.E.M.

working-memory water-maze task were found [12]. It appears, therefore, that damage to the fibres that pass medial to the perirhinal cortex is no more effective in producing allocentric spatial-memory deficits than damage to the perirhinal cortex. It is more likely that the factors which made water-maze acquisition sensitive to perirhinal damage in the Wiig and Bilkey study [45] had more to do with features of their water maze testing room or some subtle details of their training procedures, rather than merely the location and extent of their rats' lesions.

5. General discussion

Considered together, the results of the three experiments suggest that the perirhinal cortex has a significant but limited role in learning and remembering places and object discriminations. Extensive perirhinal cortex ablation failed to impair performance on either task under the majority of conditions, and the few deficits that were observed were relatively mild, with the possible exception of the 24-h retention deficit for anterograde object-discrimination learning. The lesions in all three experiments involved nearly complete removal of the perirhinal cortex bilaterally. There can be no reasonable doubt that the functions of the perirhinal cortex were severely compromised.

5.1. Perirhinal cortex and place memory

There were three main sets of results on the place-memory task: (1) in Experiment 2, rats with perirhinal cortex lesions were impaired on the early probe trial (Trial 2) during retention testing on both place problems, one of which they had learned 4 weeks before

surgery and the other only a few days before surgery. They showed no preference for swimming in the platform quadrant on the early probe trial for either problem. They differed significantly from control rats in latency to reach the platform location and the number of platform crossings during the early probe trial on the RECENT problem, but not on the REMOTE problem. (2) Despite their deficits on initial retention trials, the rats with perirhinal cortex lesions were able to quickly relearn both place problems and they performed as well as control rats on the late probe (Trial 14). (3) In Experiment 3, rats with perirhinal cortex lesions learned the location of the escape platform at a normal rate, and they performed as well as control rats on a retention test given 3 weeks later.

The first set of results can be interpreted as evidence for a temporally-graded retrograde amnesia because the deficits on the early retention trials appeared to be

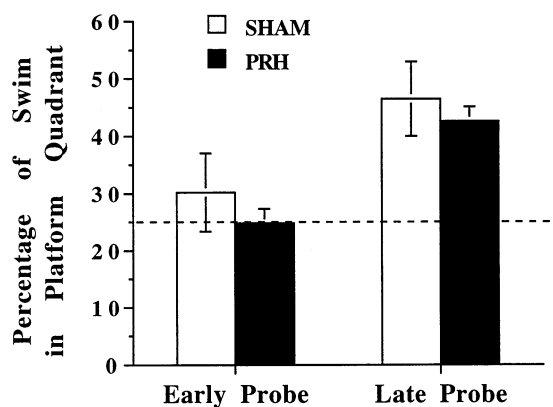


Fig. 8. Mean percentage of total swim path that was in the platform quadrant on the two 30-s probe trials during the retention session. The early probe was on Trial 2 and the late probe was on Trial 10. There were no significant group differences on any of the probe trials. The error bars represent S.E.M.

more severe for the RECENT place problem than for the REMOTE place problem. Most investigators believe that temporal gradients in retrograde amnesia reflect disruption of memory consolidation processes. The results on the retrograde place-memory tests, therefore, suggest the perirhinal cortex may play an important but time-limited role in the consolidation of place representations. However, if this is true, perirhinal cortex lesions would be expected to disrupt long-term retention of a new place problem learned after surgery. No evidence of long-term retention deficits for the place problem learned after surgery in Experiment 3 were found.

Any consolidation account for the deficits observed on the retention tests in Experiment 2 must, therefore, accommodate the finding of normal anterograde long-term retention of the place-memory problem in Experiment 3. One possibility is that the perirhinal cortex plays only an ancillary role in consolidation of place memories, representing items contained within the testing room that can be useful, but not necessary, for configuring a place representation within another part of the brain. Without the perirhinal cortex, formation of new place memories can still occur by utilizing information about the testing room that is represented in other brain areas. By this view, the perirhinal cortex normally participates in the formation of place memories, but the consolidation and long-term storage of place representations occurs elsewhere, most likely within the hippocampal formation. The PRH rats may have experienced temporally-graded retrograde amnesia because the hippocampus makes use of perirhinal inputs during the consolidation of place memories, but not after it is completed.

The relative mildness and transience of the deficits caused by perirhinal cortex lesions in Experiment 2 contrasts sharply with the severe and lasting deficits caused by hippocampal lesions in new learning of water-maze place problems [24,40], or in retention and reacquisition of place problems originally learned before surgery [25]. Water-maze deficits caused by hippocampal damage are generally attributed to impaired place-memory — the ability to represent and utilise information about the location of the platform relative to multiple extramaze cues [8,40] — although other explanations have also been proposed (e.g. Ref. [43]). It can be argued that the rats with perirhinal cortex lesions, despite showing clear deficits in quadrant-preference on the early probe trials, actually suffered little or no impairment of place memory; that is, they seemed to know where to go when they were placed into the pool. Their latencies to the first platform crossing on the early probe trial were similar to those of control rats on the REMOTE problem, and although their corresponding latencies were longer than those of control rats on the RECENT problem, they

were still significantly shorter than their own escape latencies had been on the first several trials during original learning.

Inspection of individual swim paths also indicated that most PRH rats swam somewhat directly to the platform location from the release point on the early probe trial for both problems, and they did not differ noticeably from control rats in this respect. They differed from control rats mostly in what they did *after* they arrived at the platform location: control rats had a tendency to swim only a short distance past the location before turning back to swim toward it and then past it again, sometimes repeating this pattern a few more times before the trial ended, and thus spending much of the 25-s swim near the platform location and crossing it frequently. The rats with perirhinal damage tended to swim a much greater distance past the platform location than control rats before turning to head back in a direction somewhat toward it; this resulted in fewer platform crossings and less swimming in the platform quadrant.

In sum, together with previous demonstrations of normal anterograde memory for places in rats with perirhinal cortex lesions [5,9,12,15,44], the findings in Experiments 2 and 3 suggest that the perirhinal cortex does not play an essential role in learning or remembering places. How then are the deficits on the early probe trials of Experiment 2 to be explained? The lack of a significant group difference in swim speed rules out gross motor impairments, and the transient nature of the deficits argues against motivational impairments. One can also rule out a lesion effect interacting with stress, arousal, or disorientation from being placed back into the water maze for the first time in weeks because deficits were observed on both place problems even though retention testing for the two problems was conducted sequentially. These considerations, as well as the temporal gradients in the PRH rats' deficits, strongly favour a mnemonic explanation for those deficits. One possibility is that the perirhinal cortex contributes to storage or retrieval of some aspect of the original training experience which contributes to performance in a significant, but nonessential, way. This may be to represent certain features of the training environment or aspects of the training experience, which before surgery contributed to the memory of the platform location, but which after surgery was lost. The rats with perirhinal cortex lesions may have been able to quickly overcome their initial deficits on the place problems because they could adapt to the inaccessibility of previously useful information. New learning within a brain system that operates normally without the perirhinal cortex would be involved in this adjustment. Another possibility is that the rat comes to retrieve the memory of the platform location using information retained from the original training experience and unaffected by

the perirhinal cortex damage. Reacquisition may have occurred rapidly in the rats because intact representations of certain aspects of the training environment were reactivated on the initial retention trials, and were then used to reconfigure a representation of the platform location. In other words, when remembering places, perirhinal representations might be useful, but expendable, so their loss causes only a mild and short-lasting perturbation to the remembrance of the platform location learned before surgery, and no effect on memory for the platform location learned after surgery.

5.2. Perirhinal cortex and object discrimination

The object discrimination task was one of the first tasks used to demonstrate retrograde amnesia in monkeys with large medial-temporal-lobe lesions [38,48] but there is still uncertainty about which aspect of the brain damage was responsible for the retrograde amnesia. There was some evidence in Experiment 1 that perirhinal cortex lesions caused retrograde amnesia for object-discriminations, but those deficits were quite mild and did not resemble the severe retrograde amnesia that has been produced in monkeys with large temporal lobe lesions [38,48]. In fact, when retention scores on the REMOTE and RECENT problems are analysed separately, only nonsignificant group differences are revealed. Previous findings in rats indicated that hippocampal damage is ineffective in producing retrograde amnesia for object discriminations [25]. The failure of perirhinal cortex damage to produce severe retrograde amnesia for object discriminations in the present study is consistent with some previous studies [2], and inconsistent with others [10,42]. In the studies that reported severe retrograde amnesia there was extensive damage to the entorhinal cortex, which may have been the cause of the impairment, either by itself or in combination with perirhinal cortex damage.

Another possibility is that the consequences of perirhinal cortex damage for retrograde memory of object discriminations depends upon the circumstances under which the discriminations are originally learned. In previous studies reporting retrograde amnesia for visual discrimination problems the subjects learned, and were later tested on, several discrimination problems concurrently [3,10,38,42,48]. The mildly impaired rats in the present study, and in a previous study [2], learned one discrimination problem at a time. When several discriminations are learned concurrently, later performance may benefit from recollection of past choices and outcomes involving individual discriminanda (i.e. episodic memory). This type of memory, which is impaired in amnesic patients with temporal-lobe damage, might not have been invoked by the task demands in the present study.

An alternative, but related, nonmnemonic explanation is that the perirhinal cortex plays a critical role in visual-stimulus identification [3,7]. Learning and performance of visual-discrimination tasks involving either real objects or graphic images on a computer touchscreen can be made sensitive to perirhinal cortex damage by increasing the number of distractor stimuli or by increasing the number of discriminations that must be learned concurrently [3]. Both manipulations increase the number of stimuli that must be distinguished from each other. Further evidence comes from the finding that rhinal cortex lesions impair object-recognition memory, as assessed by the delayed-nonmatching-to-sample task, only when large stimulus sets are used [7].

Overall, the results on the retrograde memory tests for object discriminations suggest that the perirhinal cortex does not play a major role in the consolidation, long-term storage, or retrieval of object-reward associations, at least not when they are learned under conditions that only lightly tax the subject's ability to identify individual objects, such as when only one discrimination problem is learned at a time. The mild retrograde deficits, with a flat gradient, may instead reflect disruption of systems involved in object identification. Even if it is true that the perirhinal cortex is needed for object identification, this fails to shed any interpretive light on the question of why retrograde amnesia for object discriminations is sometimes temporally graded in monkeys with medial-temporal-lobe ablations [48]. The results do suggest, however, that the reasons lie in damage outside the perirhinal cortex.

After surgery, the rats with perirhinal cortex lesions displayed normal acquisition rates on the single learning session for the NEW discrimination problem, but they made significantly more errors than control rats on the retention test 24 h later. During the learning session, retention had to span only the intertrial intervals, which varied slightly but averaged approximately 15 s. The results, therefore, suggest a role for the perirhinal cortex in long-term but not short-term memory for new object discrimination learning. It is tempting to suggest that the anterograde memory deficits were caused by impaired long-term consolidation mechanisms, but reasons are found in the data to doubt this conclusion. Impaired long-term consolidation of information underlying accurate object-discrimination performance would be expected to cause a retention deficit on the RECENT problem, which was learned only 24 h before surgery, but the difference between the scores of the two groups on that problem was not statistically significant. However, there is a way to reconcile the seemingly disparate findings on the anterograde and retrograde memory tests within a consolidation interpretation. This would require the additional hypothesis that long-term consolidation of memory for an object discrimination problem learned under the conditions of this study

is complete, or at least nearly so, within 24 h of learning. If this is correct, we may have failed to observe a more substantial retrograde amnesia for object discriminations because the shortest learning-surgery interval was too long.

Another possible explanation for the anterograde retention deficits is that perirhinal cortex damage somehow changed the way the rats subsequently learned the NEW object discrimination problem, in a manner that made it more difficult to remember 24 h later. What kinds of functional impairment might have produced these results? In light of the finding of relatively spared retrograde memory for object discriminations, it is not immediately clear how an impairment in visual-stimulus identification would have such consequences — not without the additional speculation that this ability facilitates the formation of some type of long-term memory that contributes in a significant way to accurate performance of an object discrimination task, that those memories are established and stored somewhere other than in the perirhinal cortex, and that the perirhinal cortex is not needed for retrieving them. One possible candidate is memory for contextual information about the training experience, which may facilitate retrieval of memories about the discrimination problems. Several experiments have demonstrated that hippocampal damage impairs memory for contextual information [13,14,33,36] and it has been proposed that this type of hippocampus-dependent memory requires inputs from the perirhinal cortex [8]. To test these hypotheses will require more studies of perirhinal cortex damage and other visual-memory tasks.

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