Anterograde and Retrograde Amnesia in Rats With Large Hippocampal Lesions

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ABSTRACT: A test of socially acquired food preferences was used to study the effects of large lesions to the hippocampal formation (HPC) on anterograde and retrograde memory in rats. In the anterograde test, rats with HPC lesions normally acquired the food preference but showed a faster rate of forgetting than control groups. When the food preference was acquired preoperatively, HPC groups exhibited a temporally graded retrograde amnesia in which memory was impaired when the preference was acquired within 2 days of surgery but not at longer delays. The results support the traditional theory that the HPC contributes to the consolidation of newly acquired information into a durable memory trace that is represented in other brain areas. Consistent with this view, the results indicate that, once a memory trace is consolidated, the HPC does not participate in its storage or retrieval. The possibility is considered that extrahippocampal areas in the medial temporal lobe are needed to maintain a memory trace throughout its existence. *Hippocampus 2001;11:18–26.* © 2001 Wiley-Liss, Inc.

KEY WORDS: hippocampal lesions; anterograde amnesia; retrograde amnesia

INTRODUCTION

The traditional view of hippocampal function is that the structure is needed to consolidate newly acquired information that is transferred into a durable representation, available for future recall (Milner, 1966; Squire, 1992). Two related predictions follow from this position. The first pertains to anterograde memory and asserts that hippocampal damage will result in impaired memory for events after long delays (long-term memory, LTM), but not after relatively short delays (short-term memory, STM). The rationale is that, in STM, information is held and recalled for a brief period of time before consolidation is initiated. The second prediction is that experiences that occur long before hippocampal damage will be remembered better than events closer to the time of damage, resulting in a temporally graded retrograde amnesia. This pattern is expected on the principle that the consolidation process will be complete for old memories, and access to them does not depend on the hippocampus. By comparison, hippocampal damage will prevent the long-term consolidation of recent experiences, leading to the obliteration of their memory traces. The time required for consolidation to occur is a matter of some uncertainty and probably depends on several factors, including species, type, and complexity of information to be recalled, and the amount of interference (see reviews by Squire, 1992; Nadel and Moscovitch, 1997).

This approach has received considerable support in the animal and human literature. With respect to anterograde memory, there are numerous studies, involving a wide range of paradigms, in which hippocampal damage severely impaired LTM, while sparing STM (Milner,

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1972; Mishkin and Delacour, 1975; Kesner and Novak, 1982; Winocur, 1985). The predicted pattern for premorbid memory has also been reported frequently (Scoville and Milner, 1957; Winocur, 1990; Kim and Fanselow, 1992; Rempel-Clower et al., 1996; Reed and Squire, 1998), but there have been conflicting results. Several investigators failed to observe time-dependent, retrograde amnesia following hippocampal damage, reporting instead a flat gradient in which memory loss was comparable over all the intervals studied (Salmon et al., 1985; Warrington and McCarthy, 1988; Gaffan, 1993; Kartsounis et al., 1995).

In a recent review, Nadel and Moscovitch (1997) concluded that the variable findings associated with retrograde amnesia are related to the extent of damage to the hippocampal complex, which includes the hippocampus itself as well as the rhinal cortex and parahippocampal gyrus. Their survey indicated that, for animals and humans, temporally graded retrograde amnesia is found most often in cases where damage to the hippocampal complex is limited, whereas large lesions to the structure reliably produce more extensive memory loss. On the basis of this evidence, Nadel and Moscovitch (1997) proposed a modification to the standard model of hippocampal function. They argued that, in addition to its involvement in the consolidation of new information, the system participates in the long-term storage of that information. This is accomplished by creating a network of memory traces that represent component features of the information within neural circuits that connect the hippocampal complex and neocortex. A key element of their model is that old memories, because they are activated often and in different ways, acquire redundant elements within the circuitry. As a result, such memories can withstand partial damage to the hippocampus and are vulnerable only when lesions are large enough to wipe out a substantial number of traces. In contrast, recently formed memories are represented in fewer traces, have a less developed circuitry, and are susceptible to smaller lesions.

The purpose of the present research was to assess the importance of lesion size in retrograde amnesia associated with damage to the hippocampus itself, and to compare predictions based on traditional consolidation theory and the model of Nadel and Moscovitch (1997). In a previous study, Winocur (1990) used a socially acquired food-preference paradigm to study anterograde and retrograde memory loss in rats with lesions restricted to the dorsal hippocampus. In this test, a naive subject rat (S) is paired with a demonstrator rat (D) that recently sampled a distinctly flavored food. Through interaction with D, S acquires a preference for that food that is retained at a declining rate over several days. The results of that study supported the consolidation theory in that, in the anterograde memory test, rats with hippocampal lesions normally acquired the food preference and retained it as well as controls at short delays. However, hippocampal groups displayed a faster forgetting rate at longer delays (see also Bunsey and Eichenbaum, 1995). In the retrograde memory test, where the food preference was learned preoperatively, hippocampal groups displayed a temporally graded retrograde amnesia in which memory for recently acquired preferences was severely impaired, whereas there was no effect of lesion at long acquisition-surgery intervals.

In the present study, a similar design was used to assess the effects of more extensive lesions to the hippocampus. Consolidation theory would predict essentially the same pattern of results in the anterograde and retrograde memory tests, although overall level of performance might be lower. Different predictions follow from Nadel and Moscovitch (1997) and consolidation theory in terms of retrograde amnesia. In contrast to the graded memory loss that is predicted by consolidation theory, with larger hippocampal lesions, Nadel and Moscovitch (1997) predicted a more severe and less graded amnesia at all delays.

METHODS

Subjects

Fifty-eight male, Long-Evans rats served as S in this experiment. An additional 10 rats served as D in the retrograde and anterograde memory tasks. The rats were obtained from the Trent University Breeding Centre and were approximately 6 months old at the beginning of the experiment. Throughout the experiment, the rats were housed in standard wire cages (225 × 18 cm) with food and water available at all times. Testing took place in larger cages (42 × 24 × 27 cm), divided into two equal compartments by a 1.25-cm wire mesh partition.

Surgery

Ten minutes before anesthesia, all rats received 20 mg/kg (i.p.) diazepam (Valium). The rats were anesthetized with sodium pentobarbital (65 mg/kg i.p.), and all lesions were stereotaxically placed with coordinates based on Paxinos and Watson (1986), measured in relation to bregma and the horizontal skull surface.

The procedure for making neurotoxic lesions of the hippocampus was slightly modified from the technique developed by Jarrard and Meldrum (1993). Using a small dental burr, six holes were drilled through the skull directly above each hippocampus. The hippocampal damage was induced by 10 intracranial microinjections of a solution containing the cellular neurotoxin, NMDA (5 mg/μl phosphate buffer per site) into each hemisphere. The coordinates for the hippocampal lesion were: anterior/posterior, 3.1, 3.1, 4.1, 4.1, 5, 5, 5, 5.8, 5.8, and 5.8; lateral, ±1, 2, 2, 3.5, 3, 5.2, 5.2, 4.4, 5.1, and 5.1; and ventral, 3.6, 3.6, 4, 4, 4.1, 5, 7.3, 4.4, 6.2, and 7.5. The solution was infused through 30-gauge stainless steel needles over a period of 2 min, using 10-μl syringes attached to a motorized infusion pump. The last sites in the ventral hippocampus (two sites) were injected for 4 min each. The needles remained in position for 2 min after the end of each injection. If any overt signs of seizure activity were observed during surgical recovery, the rats were given injections of Valium (10 mg/kg i.p.).

Histology

Following behavioral testing, the rats were deeply anesthetized with an injection of sodium pentobarbital and perfused with 0.9%

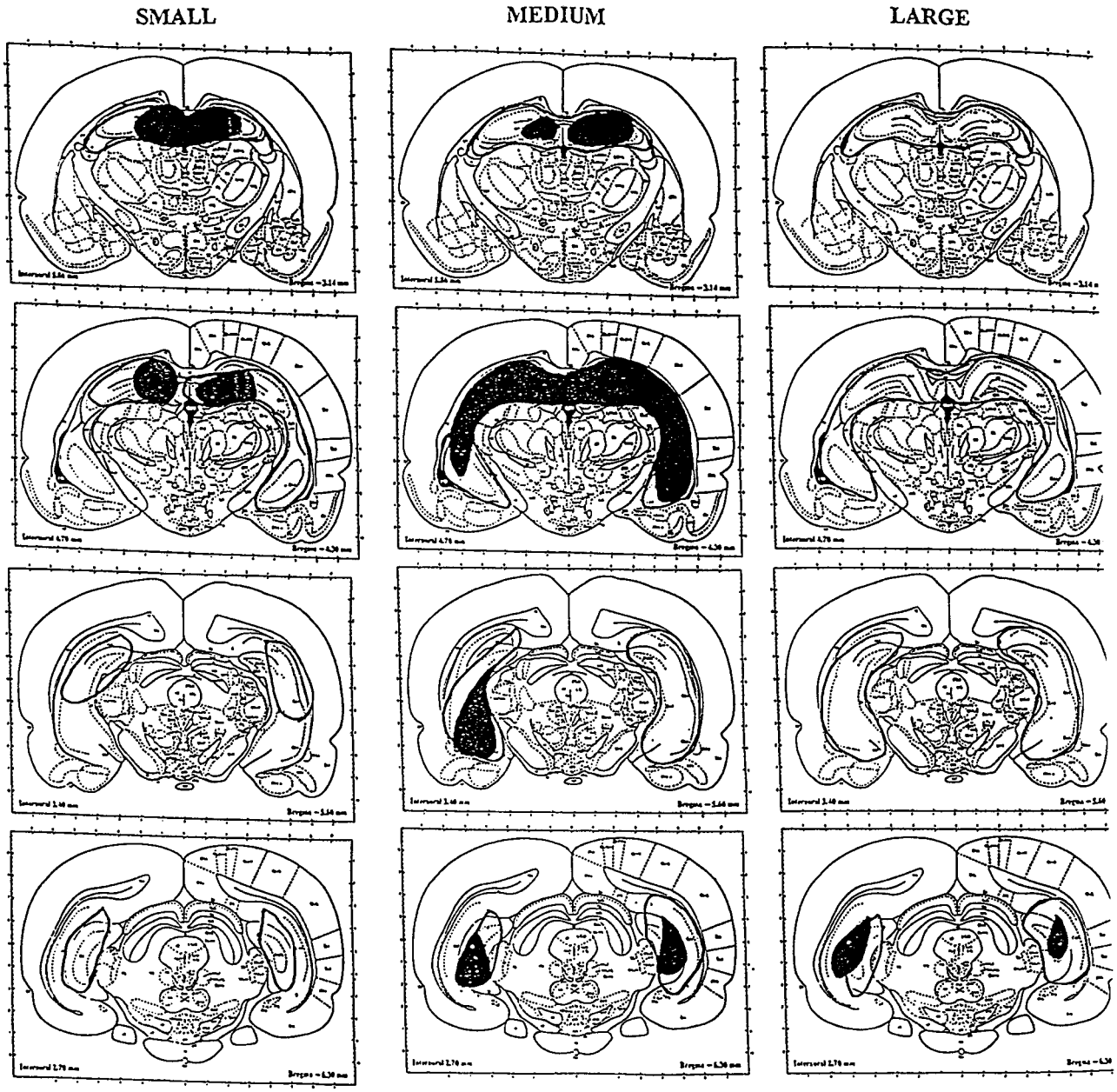

FIGURE 1. Representations of large, medium, and small HPC lesions. Shaded areas denote minimal extents of lesions; open areas denote maximal extents.

saline followed by a 10% formol-saline solution. The fixed brains were removed from the skull and stored in 10% formol saline. The brains were then frozen and sliced at 40 μm. Every fifth section was mounted on gelled glass slides and then stained with cresyl violet.

Anatomical criteria were established for deciding which animals were retained for the final data analysis in all experiments. The animals with noticeable damage to the hippocampus proper were categorized into four different groups based on the extent of the damage. The groups were: 1) large lesion; 2) medium lesion; 3) small lesion; and 4) no lesion. Figure 1 shows the maximum and minimum extent of damage to the hippocampal formation of animals that were retained for the data analysis. Animals were included in the large lesion group if there was extensive damage to all subfields of the hippocampus (CA1–CA3, dentate gyrus). Of the nine animals retained for this group, one of these animals had some unilateral ventral subiculum damage and another had some unilateral sparing of CA1 cells in the ventral portions of the hippocampus. The animals placed in this group had lesions that included damage close to 100% of the hippocampus proper. Animals were included in the medium lesion group if there was extensive damage to the hippocampus but there was some unilateral sparing in either the dorsal or ventral planes. Of the 9 animals retained in the medium lesion group, 5 of them had unilateral sparing in the dorsal hippocampus and the remaining 4 had unilateral sparing in the ventral hippocampus. The animals placed in this group had lesions that included damage to approximately 80% or more of the hip-

pocampus proper. Of the two animals retained in the small lesion group, both had bilateral damage to the hippocampus, but there was substantial sparing in both the dorsal and ventral planes. Animals that were placed in this group had approximately 50% or more of the hippocampus damaged. In four rats, initially assigned to the hippocampal group, no lesions could be detected and they were eliminated. As a result, data are reported for 20 rats in the hippocampal group and 38 rats in the control group.

Procedure

The procedure followed for testing was similar to that described in previous studies that used the food-preference paradigm to investigate memory loss in brain-damaged rats (Winocur, 1990; Winocur and Moscovitch, 1999). The same rats were used in tests of retrograde and anterograde memory.

Retrograde memory test

All D- and S-rats were placed on a 23.5-h food-deprivation schedule for 1 week before being transferred to the test cages. The experimental procedure consisted of five discrete stages: 1) D- and S-rats were placed individually in separate compartments of a test cage and left undisturbed for 2 days with unlimited access to standard rat chow and water. This allowed the rats to become familiar with each other and their new environments. 2) The next day, food was removed from both cages. 3) After 23 h of food deprivation, the D-rat was removed to another room and, for 60 min, fed a sample food of powdered rat chow mixed with commercially prepared cocoa (2% by weight) or commercially ground cinnamon (1% by weight). 4) Immediately thereafter, D was returned to its compartment and allowed to interact with S for 30 min through the wire-mesh partition.

After stage 4, S-rats were returned to their home cages for 1, 2, 5, or 10 days, during which they were fed 20 g of standard rat chow in pellet form once each day. After the appropriate interval, rats were subjected to HPC or OC surgery. Following surgery, S-rats were placed on food ad libitum for 5 days, followed by a 23.5-h food-deprivation schedule for 5 more days. The fifth, or test, stage occurred for all rats at 10 days postsurgery. This meant that S-rats were tested 11, 12, 15, or 20 days after they interacted with the D-rats and acquired the food preference. For the test, S-rats were returned individually to the test compartment, where they were offered two food cups. One cup contained 30 g of the cocoa-flavored diet, and the other, 30 g of the cinnamon-flavored diet. The S-rat was allowed 2 h to eat freely from the food cups, with water available at all times. The amount of food in the cups was weighed at 1-h and 2-h intervals. The measure of a rat's preference for the sample food was the amount of that food consumed, expressed as a percentage of the total amount of food consumed.

In the original study, Winocur (1990) included a 0-delay condition, in which surgery was performed immediately after the D-S interaction. The results of that study indicated that a general effect of invasive brain surgery, performed immediately after acquisition of the food preference, was to obliterate memory for preference, irrespective of the target site. Accordingly, a 0-delay condition was not included in this experiment.

After the retrograde memory test, S-rats were returned to their home cages and an ad libitum food and water diet.

Anterograde memory test

Approximately 5 weeks elapsed during which the S-rats participated in experiments involving other behavioral procedures. At this time, they were once again transferred individually to compartments of a test cage and allowed to interact with a new D-rat in the other compartment (stage 1). Stages 2–4 were identical to those followed in the retrograde memory test except that, in stage 3, D- and S-rats interacted for only 15 min (this was done primarily to maintain consistency with the procedures followed in our previous studies with this paradigm). For the stage 4 interaction, the sample food for each S-rat was the food that served as the distractor in the retrograde memory test, i.e., if an S-rat had acquired a preference for the cocoa-flavored food in the retrograde memory test, this time it interacted with a D-rat that was fed the cinnamon-flavored food, and vice versa. This procedure necessarily meant that, for the anterograde memory test, the rats were familiar with both foods. This was not considered a factor that would affect the results for several reasons. Memory for an acquired food preference in this paradigm is time-limited, lasting a few weeks at most, and certainly less than the time between RA and AA testing. Moreover, a rat's preference at the choice test depends on memory for the most recently sampled food, and not on general familiarity. As reported below in Results, control rats in the present study performed similarly to control rats in Winocur (1990), where different groups were used in the retrograde and anterograde memory tests.

In stage 5, the D-rat was removed from the cage and, in the 0-delay condition, each S-rat was offered two food cups, 1 containing 30 g of the cocoa-flavored food, and the other, 30 g of the cinnamon-flavored food. Water was also available. The amount of food eaten from each cup was weighed at 1-h and 2-h intervals. The measure of a rat's preference for the sample food was the amount of that food consumed, expressed as a percentage of the total amount of food consumed. Other S-rats were tested at delays of 2, 4, or 8 days. During the delays, they were returned to their home cages and fed 20 g of standard rat chow in pellet form each day. After the delay, S-rats were returned individually to the test compartment and given cinnamon- and cocoa-flavored foods in the usual manner.

S-rats, assigned to the 1- and 2-day delay conditions in the RA test, were assigned respectively to the 4 and 8 delay conditions of the AA test, whereas rats in RA 5 and 10 were respectively assigned to AA 0 and 2. Since, as reported below, a temporally graded RA was observed in HPC rats, as predicted by consolidation theory, this design was followed to determine if the same HPC rats performed as expected in the AA test on the basis of consolidation theory.

RESULTS

There was no indication that HPC and OC groups had a preference for either the cinnamon- or cocoa-flavored food. Analysis of variance (ANOVA), conducted to compare the effect of flavor on

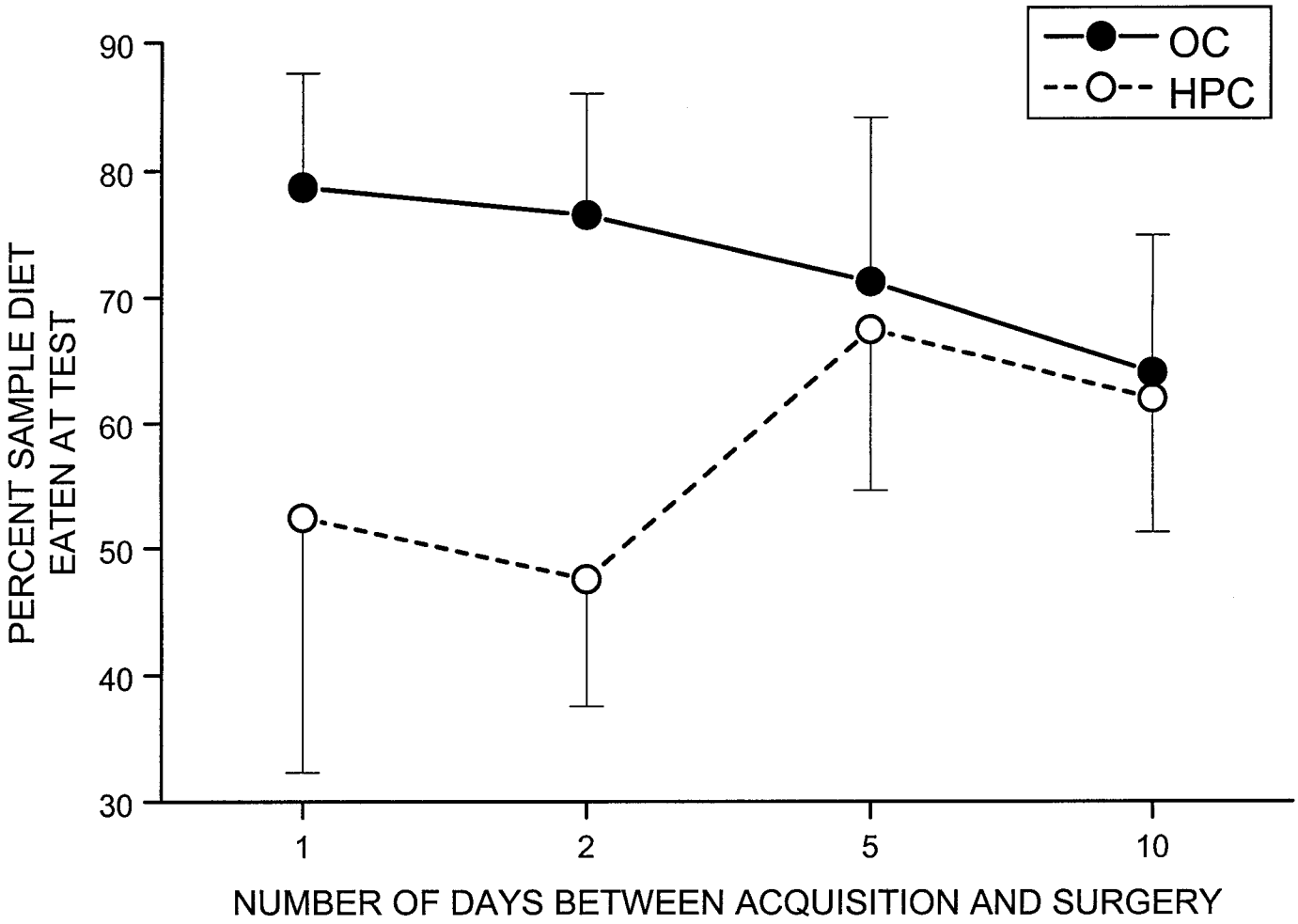

FIGURE 2. Amounts of sample diet consumed by HPC and control groups, expressed as mean percentage of total amount of food consumed, at various delays in the retrograde memory test.

food-preference, did not reveal significant effects of flavor or significant group × flavor interactions in either the retrograde or anterograde memory tests (all $P > 0.05$). Accordingly, the data for each food were combined and are presented as the sample food eaten by S-rats, as a percentage of the total amount of food consumed at each delay period.

To determine whether size of hippocampal lesion affected performance, rats with complete lesions were compared with those sustaining incomplete lesions. The incomplete subgroup included the rats with medium-sized lesions as well as the two animals that had small lesions. With respect to this variable, the meaningful comparisons involved scores at AA 4 and 8 and RA 1 and 2, where there were clear effects of lesion. Because of the relatively small numbers, within the anterograde and retrograde tests, the scores at each delay were combined to allow *t*-test comparisons between the subgroups. At AA 4 and 8, the complete and incomplete subgroups' mean sample-food consumption scores were 49.0% and 59.4%, respectively. The difference was not statistically significant, $t(10) = 1.32$, $P = 0.22$. At RA 1 and 2, the corresponding scores were 51.3% and 48.1%, $t < 1$. Since there were no differences related to lesion size, the lesioned rats were combined into single groups for purposes of statistical and analysis and reporting.

Retrograde Memory Test

The results for the retrograde memory test, expressed as percentage of sample food eaten at test, are presented in Figure 2. As can be seen, there was a clear difference between the forgetting patterns of the HPC and OC groups. The OC group's preference for the sample diet was strongest at the 1-day delay and declined progressively with longer delays. By comparison, the HPC group's performance was near chance at the 1- and 2-day delays before recovering to normal levels at the 5- and 10-day delays. These observations were confirmed by ANOVA that revealed a significant effect of group, $F(1,45) = 17.95$, $P < 0.0001$, and a significant group × delay interaction, $F(3,45) = 3.92$, $P = 0.014$.

Within-group analyses confirmed the pattern of temporally graded RA in rats with HPC lesions. For these comparisons, scores for the 1- and 2- and 5- and 10-day delays were combined into short- and long-delay conditions. *t*-tests performed on these scores showed that, for the HPC group, memory for the acquired prefer-

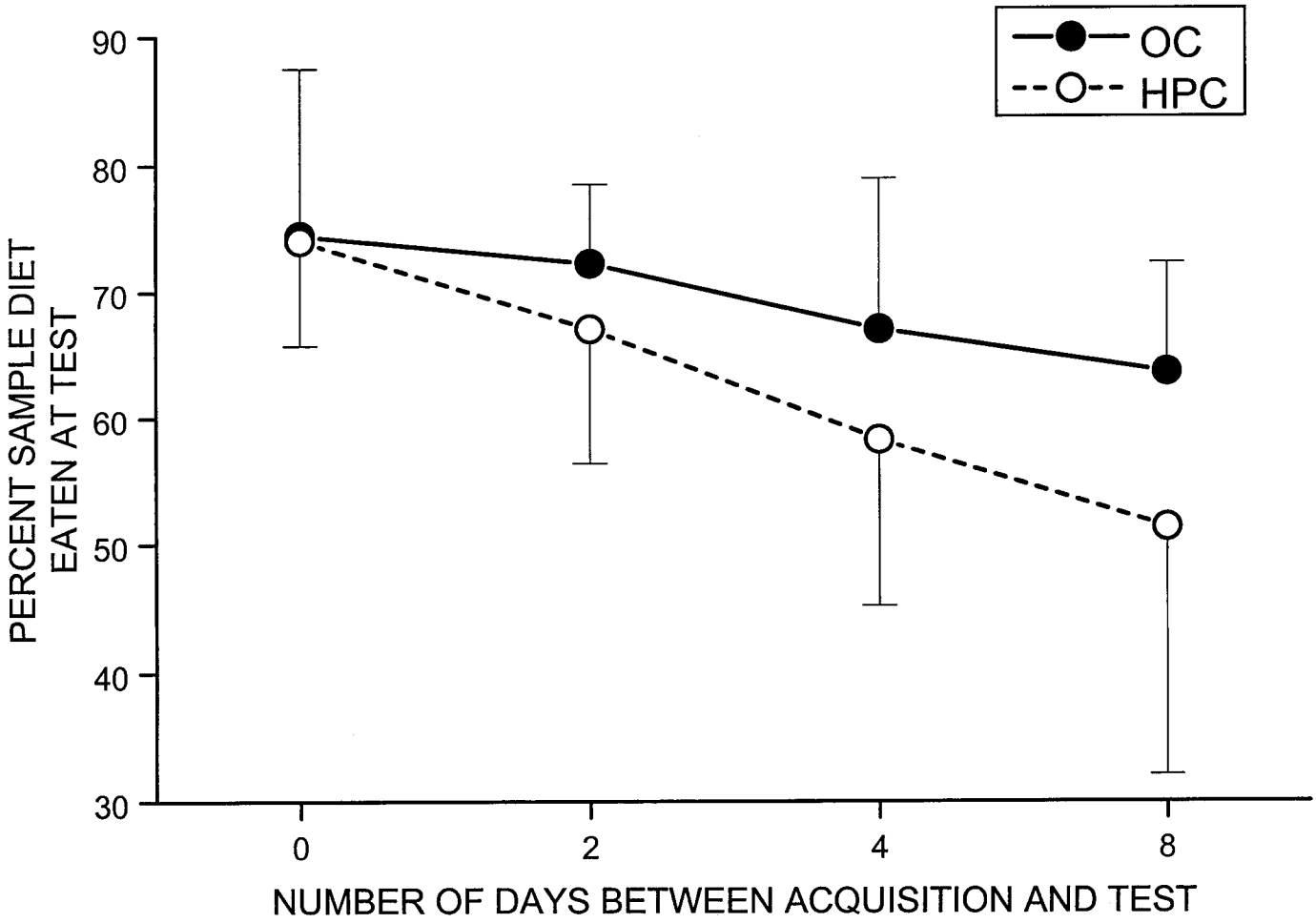

FIGURE 3. Amount of sample diet consumed by HPC and control groups, expressed as mean percentage of total amount of food consumed, at various delays of the anterograde memory test.

ence was better at the long delays ($t(18) = 2.17$, $P = 0.044$). The opposite pattern was observed in the OC groups, whose preference scores for the sample food were significantly higher at the shorter delays ($t(31) = 2.49$, $P = 0.018$).

Anterograde Memory Test

The results of the anterograde memory test, presented in Figure 3, reveal a time-dependent decline in memory for the acquired food preference. Beyond AA 0, the preference scores of the HPC groups were consistently lower than for the OC groups, resulting in an effect of lesion that was very close to the conventional level of significance, $F(1,45) = 3.78$, $P = 0.058$. When the respective groups' scores at the 0- and 2-day and 4- and 8-day delays were combined into short and long delay conditions, *t*-test comparisons yielded significant differences for the HPC ($t(18) = 2.46$, $P = 0.024$) and the OC ($t(31) = 2.27$, $P = 0.030$). The group × delay interaction was not statistically significant ($F < 1$), although, in Figure 2, it does appears that the HPC groups' memory for the acquired preference declined at a faster rate.

Relationship Between AA and RA

The experiment was designed so that rats, tested at short delays in the retrograde memory test, were subsequently assigned to long delay conditions in the anterograde memory test. In the respective tests, rats with HPC lesions displayed the greatest memory loss at these delays. Thus, a comparison of each rat's performance in the two tests, at these delays, permitted an examination of the relationship between AA and RA. Although the HPC groups were impaired at these delays, relative to controls, the extent of one type of memory loss did not reliably predict the extent of memory loss in the other (Pearson product correlation, $P =$ ns).

DISCUSSION

The major finding of this study is that virtually complete lesions of the hippocampus produced a temporally graded retrograde amnesia for a socially acquired food preference. The extent of the

deficit was comparable to that obtained in a similar study involving lesions restricted to the dorsal hippocampus under identical testing conditions. These results indicate that large lesions, confined to the hippocampus, do not necessarily produce a flat RA gradient and, as such, are consistent with other reports of the effects that large hippocampal lesions have on retrograde memory tested in a variety of paradigms. Together, the evidence supports traditional consolidation theory and indicates that, on the food-preference test, even very large lesions, that include the ventral hippocampus, will not produce severe, nongraded RA. It appears that, in the rat, dorsal hippocampal lesions are sufficient to produce the effects observed. These data invite a reconsideration of the hypothesis of Nadel and Moscovitch (1997) that multiple traces within the hippocampal complex account for the graded RA observed after partial destruction of the hippocampus.

Having established that the hippocampal formation itself is not needed for recovering remote memories in the food-preference task, two points must be considered: 1) that other structures within the hippocampal complex may be crucial, and 2) that the hippocampal formation may be important for other tasks. With respect to the first point, it is noteworthy that recent work implicates extrahippocampal structures, such as the perirhinal cortex, in recovering long-lasting, previously acquired memories. For example, Thornton et al. (1997) and Gaffan (1993) found that lesions of the perirhinal cortex produced severe loss of both recent and remote memories for objects. In related research, Mumby and Pinel (1994) used a delayed-nonmatching-to-sample (DNMS) paradigm to test anterograde object memory in rats with lesions to the hippocampal formation or adjacent rhinal cortex. They found that neither region was necessary for learning the DNMS rule, but that damage to rhinal cortex produced a severe deficit on object memory at longer delays.

Our food-preference task is a nonspatial test of recognition memory and may be sensitive to rhinal cortex lesions in a comparable way. We know that the hippocampal formation is not necessary for acquiring the preference but is required for retaining it beyond several days. It may be that lesions to the rhinal cortex will produce a more severe memory loss that is reflected in even faster forgetting in the anterograde memory test and a flat RA in the retrograde memory test. A crucial next step is to asses the effects of rhinal cortex lesions, alone and in combination with hippocampal formation lesions, on anterograde or retrograde memory in the food-preference task.

The importance of type of memory in determining the effects of hippocampal and extrahippocampal lesions on RA relates to our second point. A flat gradient following lesions restricted to the hippocampal formation may be evident only for certain types of memory, in particular those that are predominately spatial in nature. Rats with hippocampal lesions are severely impaired in processing spatial information and often exhibit long-lasting RA with a flat gradient on spatial tests of memory (Bolhuis et al., 1994; Bohbot et al., 1996; but see Cho et al., 1995). For tasks that involve nonspatial, relational learning, the evidence, on balance, points to a pattern of temporally graded RA following damage to the hippocampal formation. In a test of contextual conditioning, Kim and Fanselow (1992) found a temporally graded RA that lasted only 4 weeks. Weisend et al. (1996), using a similar task, found that rats with large hippocampal lesions displayed an RA of over 30 weeks with a flat gradient. Weisend et al. (1996) found comparable RA in a test of configural, negative patterning. However, Knowlton and Fanselow (1998) speculated that extrahippocampal damage may have affected performance in the study of Weisand et al. (1996). In addition, Kim et al. (1995) tested rabbits with large hippocampal lesions on a trace, eyeblink conditioning task that appeared to have a relational component, and reported a temporally limited RA. The food-preference test, which also yielded a temporally graded RA, may also qualify as a relational-learning task. Galef and Wigmore (1983), who first developed the test, noted that acquiring the food preference is not simply a matter of exposing the rat to the odor of the sample diet but depends critically on allowing the S-rat to form an association between that odor and carbon disulfide, a constituent of the D-rats' breath, imparted in a social context (Galef et al., 1988).

There is conflicting evidence about RA effects in nonspatial tasks that do not have a relational component. Salmon et al. (1985) reported an extensive RA with a flat gradient for object discrimination learning in monkeys, but Zola-Morgan and Squire (1990), using a similar task, found a time-limited, temporally graded amnesia. On the other hand, temporally graded RA was reported by Vnek and Rothblat (1993) in monkeys and by Wiig et al. (1996) in rats. Adding to the difficulty of interpreting these results is the reliable finding that object and visual discriminations are acquired normally in rats and monkeys with hippocampal lesions, and retained for prolonged periods. In the absence of AA following lesions restricted to the hippocampus, it is surprising that RA is observed at all. Conceivably, in an intact animal, the hippocampus is not needed for such discrimination learning but participates temporarily either in the retention, consolidation, or retrieval of recently acquired information. If this interpretation is correct, it remains to be determined which of these processes would be implicated.

The object discrimination tasks contrast with our food-preference task in that, in the latter, the hippocampus is needed for retention of postoperatively acquired preferences. The anterograde amnesia produced by bilateral hippocampal lesions, however, was found to be uncorrelated with the retrograde amnesia. This result contradicts one of the predictions of the traditional consolidation theory, although the absence of a statistical relationship may reflect the power of the analysis or the sensitivity of the procedure. On the other hand, the possibility that anterograde and retrograde memory processes differ from one another is consistent with the human literature, in which the severity of anterograde and retrograde amnesia also was found to be uncorrelated with one another.

The pattern observed following hippocampal lesions on the food-preference task is different from that observed in rats with lesions to other structures (Winocur, 1990; Winocur and Moscovitch, 1999). In the case of dorsomedial thalamic lesions, there was no observable effect on versions of the task that tested anterograde and retrograde memory. On the other hand, lesions to the frontal cortex produced severe anterograde amnesia and a retrograde amnesia that extended equally to all intervals tested when the choice was increased from two to three alternatives. The latter finding was

consistent with the interpretation that the frontal cortex is necessary for the process of working with recovered memories to select an appropriate response (Moscovitch and Winocur, 1992, 1995).

The pattern of results observed in our studies of retrograde memory may be related to that observed in humans with lesions to corresponding brain regions. When damage is restricted to the hippocampus itself, a time-limited, temporally graded amnesia is typically observed, with the extent of the amnesia varying from a few days to years. In line with our speculation regarding the role of extrahippocampal structures in remote memory, when the lesion encroaches on other parts of the hippocampal complex, such as the entorhinal cortex and parahippocampal gyrus, the RA typically is very extensive, and the slope of the gradient is diminished or flat. As for the dorsomedial thalamus and frontal cortex, our findings parallel those reported in the human literature. Patients with discrete thalamic lesions typically exhibit normal remote memory for preoperatively learned information (Hodges and McCarthy, 1993; Winocur et al., 1984; Parkin et al., 1994). As in rats, frontal cortex lesions in humans are associated with an RA of similar severity across all time periods tested (Della Sala et al., 1993; Levine et al., 1998).

The correspondence between our results and the human literature underscores the usefulness of the food-preference test for studying anterograde and retrograde memory loss following brain damage. Our finding that extensive lesions to the hippocampal formation produce a time-limited, temporally graded RA indicates that the hippocampus is not needed to recover some old memories and supports the traditional consolidation theory, at least for certain tasks. On the other hand, as the model of Nadel and Moscovitch (1997) suggested, it may be that the entire hippocampal complex is implicated in recovering old memories. It is possible that more extensive lesions affecting large portions of the complex will produce more complete RA. Alternatively, there may be a particular extrahippocampal structure that is crucial to obtaining this effect, or that the locus and extent of lesion interact with type of task to produce distinctive patterns of remote memory loss. These issues are being addressed in our laboratory as part of ongoing research aimed at developing a more comprehensive animal model of memory.

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