Retrograde Amnesia After Hippocampal Damage: Recent vs. Remote Memories in Two Tasks

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ABSTRACT: We review evidence from experiments conducted in our laboratory on retrograde amnesia in rats with damage to the hippocampal formation. In a new experiment reported here, we show that N-methyl-D-aspartate (NMDA)-induced hippocampal damage produced retrograde amnesia for both hidden platform and two-choice visible platform discriminations in the Morris water task. For both problems there was a significant trend for longer training-surgery intervals to be associated with worse retention performance. Little support is offered by our work for the concept that there is a process involving hippocampal-dependent consolidation of memories in extrahippocampal permanent storage sites. Long-term memory consolidation may take place within the hippocampus. The hippocampus may be involved permanently in storage and/or retrieval of a variety of relational and nonrelational memories if it was intact at the time of learning, even involving information which is definitely not affected in anterograde amnesia after hippocampal damage. *Hippocampus 2001;11:27–42.*

KEY WORDS: consolidation; retrograde amnesia; spatial retrieval; relational configural visual discrimination; place learning

INTRODUCTION

Nearly all investigators agree that any event which significantly alters the function of the hippocampus, either temporarily or permanently, will cause amnesia in humans and rats. Well-studied examples include drug administration (Flexner et al., 1967; Pearlman et al., 1961; Ribot, 1882; Toumane and Derkin, 1993), electroconvulsive shock (Squire et al., 1975, 1981; Zubin and Barrera, 1941), brain trauma (Markowitsch et al., 1993; Russell and Nathan, 1946; Whitty and Zangwill, 1977), brain ischemia (Zola-Morgan et al., 1986), hypoxia (Beatty et al., 1987; De Renzi and Lecchelli, 1993), encephalitis (Rose and Symonds, 1960; Yoneda et al., 1992), surgical excision of brain tissue (Corkin, 1984; Scoville and Milner, 1957), and even new learning (Keppel, 1984). These events are associated with both anterograde and retrograde amnesia, i.e., performance is disrupted in tasks which depend on either postevent learning or preevent learning.

A central feature of anterograde amnesia after damage to the hippocampus is a disruption in learning some tasks while new learning in other tasks is unaffected. Likewise, numerous studies have shown that retrograde amnesia following hippocampal disruption does not affect all memories equally. There are many reports that damage to the hippocampus has a detrimental effect on the recall of recent but not remote memories (reviewed in Squire, 1992). Experimental results supporting these general statements about anterograde and retrograde amnesia have led to the widely accepted view that there are two important properties of memories which determine their vulnerability to hippocampal damage: type and age. It is surprising then to realize that the studies on which these statements about retrograde and anterograde amnesia are based do not present a uniform picture.

In the rat, damage to the hippocampus causes deficits in the acquisition of tasks which require place navigation in the absence of local landmarks (Aggleton et al., 1986; Morris et al., 1982, 1990; Olton and Samuelson, 1976; Sutherland et al., 1982, 1983; Sutherland and McDonald, 1990), conditioning to context (Good and Honey, 1991; Kim et al., 1993; Nadel and Willner, 1980; Nadel et al., 1985; Phillips and LeDoux, 1992, 1994; Sutherland and McDonald, 1990), and responses to certain conjunctions of cues (Alvarado and Rudy, 1992, 1993; Murphy et al., 1993; Sutherland and Rudy, 1989; Sutherland and McDonald, 1990; Sutherland and Palmer, 1992; Rudy and Sutherland, 1989; but see Gallagher and Holland, 1992). In contrast, the ability to learn tasks which require navigation to a location marked by a single landmark, simple discrimination learning, and responses based on a single feature of an environment such as light, tone, or brightness are not effected by hippocampal lesions (McDonald and White, 1993; Sutherland et al., 1982; Sutherland and Rudy, 1989). Thus, the

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specificity of the anterograde amnesia produced by hippocampal damage in nonhuman animals provokes in us some optimism that there is a fundamental similarity to the properties of anterograde amnesia in humans after similar damage (see also Squire, 1992). The hippocampus is hypothesized to be important in a memory system that participates in encoding relationships among stimuli (Cohen and Eichenbaum, 1993; Sutherland and Rudy, 1989). Damage to the hippocampus causes impairment in tasks such as place learning, conditioning to context, certain discrimination learning problems, and integration of a personal or public event into a lifetime of memories, all of which require processing of the relations between multiple stimuli. The remaining mnemonic abilities after damage to the hippocampus, such as learning simple discriminations, are the result of a memory system (or systems) in which the hippocampus does not play an important role. Theories which posit multiple memory systems provide a parsimonious explanation for the ability of animals to solve only some problems after damage to the hippocampus.

The retrograde amnesia observed in human patients after medial temporal lobe lesions affects personal and public information (Beatty et al., 1987; Corkin, 1984; De Renzi and Lecchelli, 1993; Markowitsch et al., 1993; Milner, 1959, 1972; Milner and Penfield, 1955; Rose and Symonds, 1960; Russell and Nathan, 1946; Scoville and Milner, 1957; Penfield and Milner, 1958; Rempel-Clower et al., 1996; Squire et al., 1993; Whitty and Zangwill, 1977; Yoneda et al., 1992; Zola-Morgan et al., 1986), while skill memories can be spared (Milner, 1959; Penfield and Milner, 1958; Scoville and Milner, 1957; Squire et al., 1984b). For example, some patients have been able to return to their jobs, play a piano, or drive a car with minimal retraining after medial temporal lobe damage which includes the hippocampus (Kapur et al., 1992, 1994; Milner and Penfield, 1955). These reports of retrograde amnesia for the same types of information that are affected in anterograde amnesia following hippocampal damage fit nicely with the view that there are multiple, independent memory systems. However, other reports suggest that event and skill memory are impaired in the retrograde amnesia resulting from damage to temporal lobe structures (Andrews et al., 1982; Rousseaux et al., 1984). This pattern of impaired memory is called global retrograde amnesia. In addition, there are a few reports of patients with retrograde amnesia for personal and public events after temporal lobe damage who do not have anterograde amnesia for the same information (Kapur et al., 1994). There is not now a consensus on the anatomical differences which determine the variant of retrograde amnesia that will be exhibited by a given patient.

Investigations of retrograde amnesia in nonhuman animals after hippocampal lesions have resulted in conflicting reports of task specificity. Retrograde amnesia for object-based discriminations has been observed after damage to the hippocampus in nonhuman primates (Salmon et al., 1987; Zola-Morgan and Squire, 1990). In rats, retrograde amnesia is reported on tasks which require place memory (Astur et al., 1994; Bolhuis et al., 1994; Cho et al., 1993; Sutherland et al., 1987; but see Gage, 1985), conditioning to context (Good and Honey, 1991; Kim et al., 1993; Kim and Fanselow, 1992; Nadel and Willner, 1980; Nadel et al., 1985; Phillips and LeDoux, 1992, 1994), socially transmitted food preference (Winocur, 1990), and the negative patterning discrimination (Rudy and Sutherland, 1989). Fear conditioning to a single tone, object recognition, and object discrimination information has been reported to survive hippocampal damage in rats (Kim and Fanselow, 1992; Mumby et al., 1992; Astur et al., 1994).

The pattern of results in the studies of retrograde amnesia using rats is parallel to the pattern of spared and impaired tasks in anterograde amnesia. However, hippocampal lesions have been reported to disrupt the retention of tasks that are not affected by anterograde amnesia. Ross et al. (1984) reported that hippocampal damage disrupts retention of a serial feature positive discrimination. However, the same hippocampal damaged rats in this study were able to relearn the discrimination after hippocampal damage. Naive rats with hippocampal damage can also learn the serial feature positive discrimination (Jarrard and Davidson, 1991). Similarly, Sara (1981) reported that rats exhibit retrograde amnesia after hippocampal damage for a visual discrimination which is not affected in the anterograde direction. The studies by Ross et al. (1984), Sara (1981), and Jarrard and Davidson (1991) can be interpreted to mean that the anterograde and retrograde amnesia resulting from hippocampal damage may not exhibit the same specificity.

There is good correspondence between anterograde and retrograde amnesia for tasks, such as the Morris water task, that require the use of multiple cues. However, there are conflicting reports of the effect of hippocampal lesions on retention of skills and discriminations that are unaffected by anterograde amnesia. The multiple memory systems views, which postulate functionally and anatomically distinct learning and memory systems in the brain to explain anterograde amnesia, are comfortable with the prediction that the types of information affected by retrograde amnesia will parallel those affected by anterograde amnesia (Cohen and Eichenbaum, 1993; Hirsh, 1974, 1980; Mishkin, 1978, 1982; O'Keefe and Nadel, 1978; Olton et al., 1979; Squire, 1986, 1987, 1992; Squire and Zola-Morgan, 1991; Squire and Zola, 1996; Sutherland and Rudy, 1989; Tulving, 1987). However, there are some indications that this specificity may not be a consistent finding in the retrograde amnesia after lesions of the hippocampus. The paucity of the data on this issue, together with its theoretical importance, provide a strong motivation for the present experiments.

A second property of memories which determines their vulnerability to disruption by hippocampal damage is age. A commonly reported pattern of recall in retrograde amnesia following hippocampal damage is that remote events are remembered better than recent events. This pattern of recall has come to be known as temporally graded retrograde amnesia. The temporal gradient in retrograde amnesia suggests that memories become more resistant to disruption by hippocampal damage or dysfunction as time passes after the learning episode. This transformation of memories from a labile to a stable form is termed memory consolidation.

There are numerous reports of temporally graded retrograde amnesia lasting from a few months to decades as a result of damage to the hippocampus in humans (MacKinnon and Squire, 1989; Scoville and Milner, 1957; Squire et al., 1989; Walker, 1957; Penfield and Milner, 1958; Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). The well-studied patient H.M. exhibits temporally graded retrograde amnesia. He is unable to recall events which occurred during a several-year interval prior to his surgery. More remote memories are apparently unaffected (Corkin, 1984; Scoville and Milner, 1957). However, there are also many reports of retrograde amnesia which is not temporally graded (Albert et al., 1981; Barr et al., 1990; Beatty et al., 1988; Butters and Stuss, 1989; Cermak and O'Connor, 1983; Damasio et al., 1985; Graff-Radford et al., 1990; Kapur et al., 1992, 1994; Sagar et al., 1988; Sanders and Warrington, 1971; Stuss et al., 1988; Tulving et al., 1988; Warrington and McCarthy, 1988; Wilson et al., 1981). Patients with retrograde amnesia that is more or less equivalent for all past events regardless of the time that the memory was encoded prior to hippocampal damage are said to have a "flat gradient."

Reports of the length of the temporal gradient in the retrograde amnesia of nonhuman animals are just as variable as those in human patients. The length of "recent" memory loss in retrograde amnesia is reported to be days to many weeks in nonhumans. For example, memory seems to be fully consolidated after 5 days in the case of socially transmitted food preference, since hippocampal damage after this point does not affect performance (Winocur, 1990). However, hippocampal-dependent memory consolidation takes 4 weeks in classical fear conditioning (Kim and Fanselow, 1992) and several months in the case of place navigation tasks (Kubie et al., 1999; Sutherland et al., 1987). It is unclear why information dependent on the same neural architecture, the hippocampus, is consolidated over such plainly different time frames. Furthermore, amnesia is sometimes equivalent for all time periods prior to hippocampal damage. In nonhuman primates, some studies have found temporally graded retrograde amnesia (Gaffan, 1993; Zola-Morgan and Squire, 1990), but others have found flat gradients (Salmon et al., 1987). Temporally graded retrograde amnesia for the location of a hidden platform has been reported in the Morris water task (Sutherland et al., 1987). However, others have failed to replicate the finding of temporally graded retrograde amnesia in the Morris water task (Astur et al., 1994; Bolhuis et al., 1994). The factors which determine the length or presence of the temporal gradient in retrograde amnesia after hippocampal damage are currently unknown.

In spite of the variability of reported temporal dependence of retrograde amnesia, a group of theories which postulate a time limited role for the hippocampus in memory formation has been developed. There are two varieties of theories on hippocampal-dependent memory consolidation. Several theorists have suggested that the organization of the memory trace is the important factor in memory consolidation (Ribot, 1882; Burnham, 1903; Squire et al., 1984a; Wickelgren, 1979). When applied specifically to hippocampal-dependent memory consolidation, the theory suggests that the memory trace is initially stored as numerous distributed traces in the neocortex. Over the course of time, and through a process of competition among memory traces for mnemonic units in the cerebral cortex, the hippocampus binds together the distributed sites in the neocortex that together represent the memory of a whole event (Squire et al., 1984a; Squire, 1986, 1987, 1992; Squire and Zola-Morgan, 1991; Squire and Zola, 1996; Zola-Morgan and Squire, 1990). Thus, temporally graded retrograde amnesia is the result of interrupted support of the immature neocortical memory traces by damage or disruption of the hippocampus.

Another proposal about the nature of hippocampal-dependent memory consolidation is that the reorganization which occurs during consolidation is in the location of the memory trace. In this theory, memories are initially stored in the hippocampus. After some limited amount of time, which exceeds the length of short-term memory, the memory traces in the hippocampus are transferred into a neocortical long-term memory store (Marr, 1971; McClellend et al., 1995; Rawlins, 1985; Milner; 1989). In this case, temporally graded retrograde amnesia after hippocampal damage is a failure of transfer of information. Neither of the theoretical accounts of hippocampal-dependent memory consolidation provides an explanation of the variability in the length of time necessary for memory consolidation.

The significant variability in reports of the content and temporal characteristics of retrograde amnesia following damage to the hippocampus poses a problem for the current conceptions of multiple memory systems and of hippocampal-dependent memory consolidation. There are basically two problems that are likely to contribute significantly to the variability in the current body of literature on retrograde amnesia following hippocampal damage: differences in lesions and differences in task performances.

Differences among lesions are problematic across all species in which retrograde amnesia has been studied. In humans, brain damage is seldom restricted to or completely inclusive of any structure of interest within a patient and is never identical across patients. For example, extensive bilateral temporal lobe damage (Scoville and Milner, 1957), unilateral temporal lobe damage (Walker, 1957), and partial hippocampal damage (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986) yield similar temporally graded retrograde amnesia in some reports but not others (Barr et al., 1990; Kapur, 1992, 1994). In rodents, damage to the hippocampus ranges from transection of inputs (McDonald and White, 1993) to small dorsal lesions (Kim and Fanselow, 1992) to very nearly complete hippocampal lesions (Bolhuis et al., 1994). This complicates making any broad statements about the content and temporal characteristics of retrograde amnesia.

A second difficulty when trying to compare the results on retrograde amnesia associated with hippocampal damage is the variability in the tasks that are used. In humans, knowledge of previous personal life, public events, famous faces, and television shows is measured to quantify retrograde amnesia. In nonhuman primates, knowledge of previously trained discriminations with real objects or objects presented on video screens is measured. In rodents, a variety of classical conditioning, operant conditioning, and spatial tasks are used. There is no obvious way to compare results across tasks. Some rules, such as the relational/configural information

idea (Cohen and Eichenbaum, 1993; Sutherland and Rudy, 1989), have been proposed to bring together the findings from diverse studies, but these have not always been able to account for all of the data (Gallagher and Holland, 1992; Rudy and Sutherland, 1995).

The study reported below is part of a series directed toward a systematic analysis of the unresolved issues of content and temporal characteristics of the retrograde amnesia produced by hippocampal damage. The general strategy employed is to compare the effect of similar lesions across different tasks and across different intervals between training and lesion, using both within- and between-subjects designs. A previous set of experiments (Weisend et al., 1996) on rats with kainate-colchicine-induced hippocampal lesions investigated retrograde and anterograde effects on eight tasks; some relational/configural and some elemental discriminations. The results suggested that a much wider range of tasks was affected in the retrograde than in the anterograde direction, and in all cases flat gradients were observed across intervals of 1–36 weeks. However, the best evidence for sparing of remote information comes from a within-subject comparison of recall of information from different time points before the medial temporal lobe was damaged in humans. In the experiments by Weisend et al. (1996), the evaluation of recall from different training-surgery intervals involves comparisons between independent groups of subjects. In an experiment reported more fully in Mumby et al. (1999), we used a within-subject assessment of recall from different intervals before hippocampal damage in order to more closely approximate the clinical situation. Furthermore, we assessed retrograde effects on performance in a task involving multiple object discriminations (Mumby et al., 1999), which are known to be spared in the anterograde direction after hippocampal damage, in addition to the hidden platform version of the Morris water task. At several time intervals before hippocampal damage (1, 4, 7, 10, and 13 weeks), each of 30 rats was trained in several pairwise object discriminations and two place navigation problems, 2 and 14 weeks before surgery. Another issue we wished to address (Mumby et al., 1999) was the contribution of extrahippocampal damage associated with the lesion method of Weisend et al. (1996). Jarrard and Meldrum (1993) showed that far less extrahippocampal damage is produced by multiple intrahippocampal microinjections of ibotenic acid or N-methyl-D-asparte (NMDA) than by kainic acid. Mumby et al. (1999) selected ibotenate in order to reduce the extent of extrahippocampal damage. Weisend et al. (1996) may have missed seeing spared recall of remote information because of damaging extrahippocampal permanent memory storage sites in the cortex or other structures. Our ibotenate hippocampal lesion consistently involved extensive loss of cells in all principle subfields of the hippocampus and dentate gyrus. The extent of damage to the subiculum was variable, but there was some bilateral loss of subicular cells in all rats, which was incomplete in every case. There was no evidence of damage to the thalamus or rhinal cortex in any of the rats. Figure 1 shows trials to criterion before and after surgery on the five object discriminations. Figure 2 shows swim path in the correct quadrant during a no-platform probe trial early and late in postsurgery place navigation testing. Figure 3 shows mean latencies

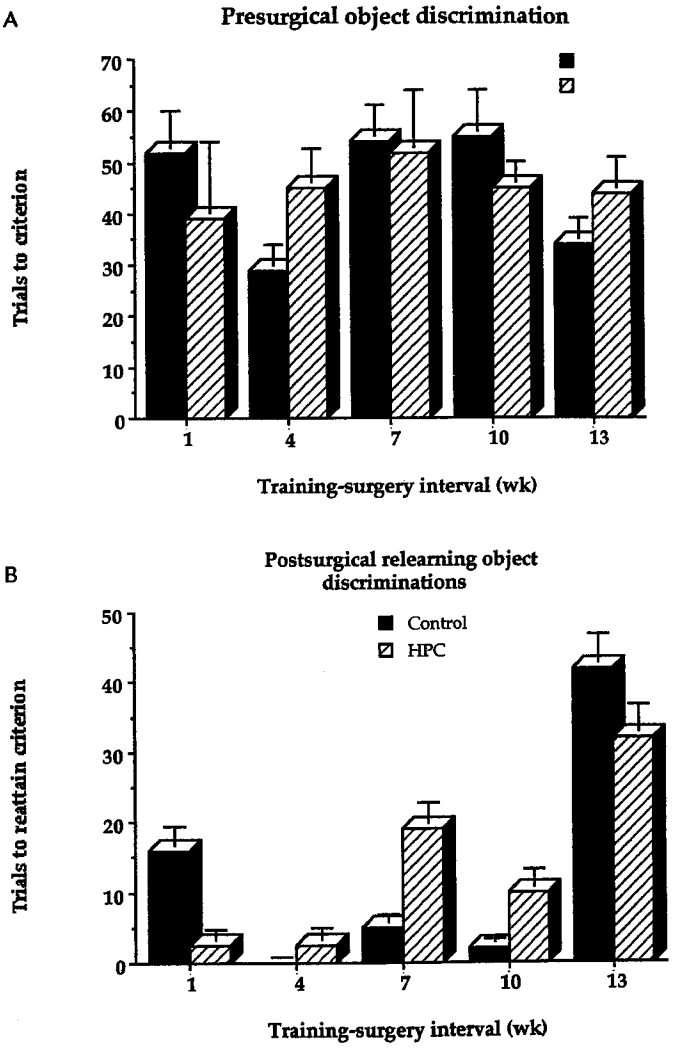

FIGURE 1. A: Number of trials to reach criterion during presurgical training of each object discrimination. B: Number of trials to reattain criterion after surgery on the original object discriminations. wk, weeks.

to find the hidden platform on the first retention trial of place navigation in the two old problems and one new one. Finally, Figure 4 shows the mean number of correct choices during the first five object discrimination retention trials. The complete methods and results are described in Mumby et al. (1999). Briefly, statistical analyses of performance in the place navigation problems revealed a significant deficit in hippocampal damaged rats which did not interact with training-surgery interval. Hippocampal damage did not affect retention of the object discriminations, and there was no interaction between group and training-surgery interval. Thus, even with a more selective ibotenate HPC lesion we found a flat retrograde gradient for place information, entirely consistent with our prior observations using kainate-colchicine lesions; the additional extrahippocampal damage associated with the latter technique may not be necessary to produce deficits in retention of even the most remote place information. An intact HPC is not necessary

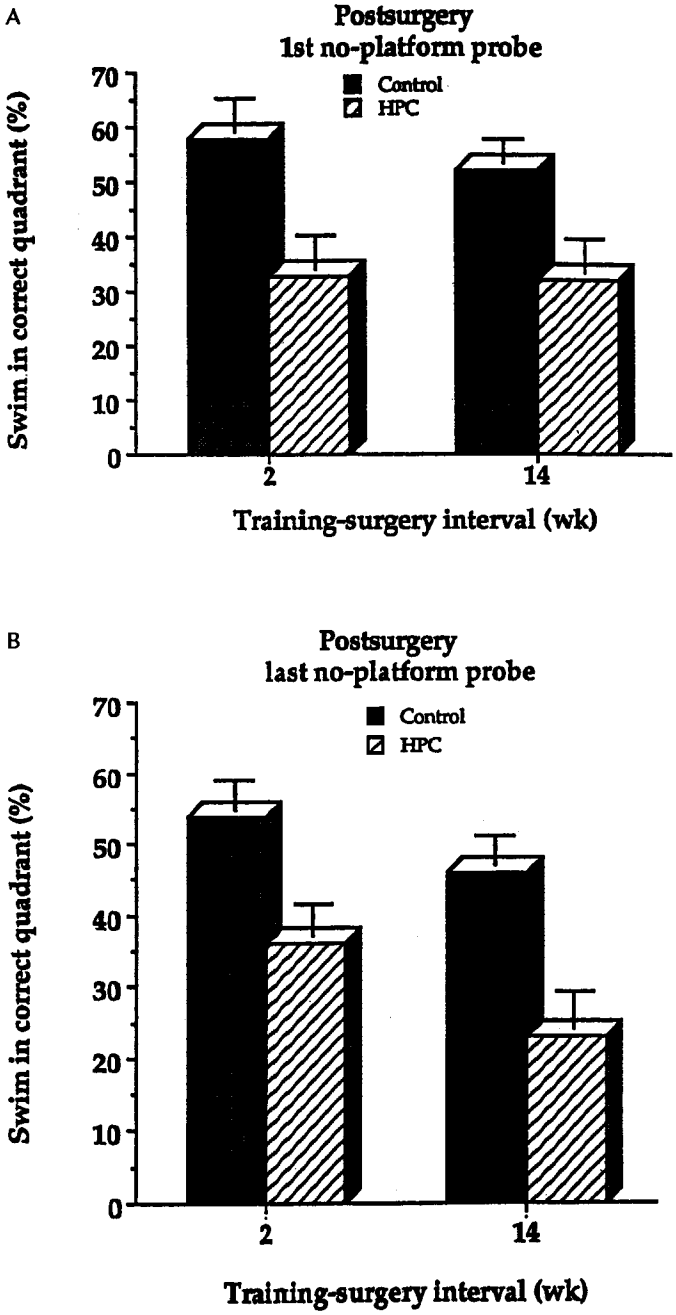

FIGURE 2. A: Percentage of swim path in correct quadrant during first postsurgical no-platform probe trial for both recent and remote place memory. B: Percentage of swim path in correct quadrant during postsurgical no-platform probe trial at end of retraining for both recent and remote place memory.

for either acquisition or retention of object discriminations of this kind.

One issue remains unresolved. Is the deficit reported by Weisend et al. (1996) in the retrograde direction, in tasks which are unaffected in the anterograde direction (such as visible platform discriminations in the Morris water task or elemental cue discriminations in the operant setting), due to the use of a lesion technique which produces substantial extrahippocampal damage? Or, is there something special about object discriminations which makes them immune in both directions from disruption by HPC damage?

In the results of Weisend et al. (1996), it was found that measures of extrahippocampal damage associated with kainate-colchicine damage did not predict the retrograde outcomes in any of the tasks. In the experiment reported below, we more directly approach this issue by using another lesion method which has been shown to be associated with less extrahippocampal damage than kainic acid and colchicine. Jarrard and Meldrum (1993) found that multiple microinjections of kainic acid into the hippocampus caused damage to hilar cells in the dentate gyrus and to CA3 pyramidal cells, and some CA1 cell loss. Importantly, damage was also demonstrated in extrahippocampal structures, to such areas as the entorhinal cortex, amygdala, various layers of the ventral neocortex, olfactory areas, and certain thalamic nuclei. In clear contrast, multiple microinjections of N-methyl-D-aspartate (NMDA) or ibotenic acid into the same loci did not produce extrahippocampal damage, despite a similar extent of intrahippocampal cell loss. Therefore, in this experiment we will repeat some of our experimental procedures, this time using multiple microinjections of NMDA. Specifically, we examine five training-surgery intervals (1 day or 1, 2, 4, and 15 weeks) using place learning and visible platforms discrimination. Performance in both of these tasks was

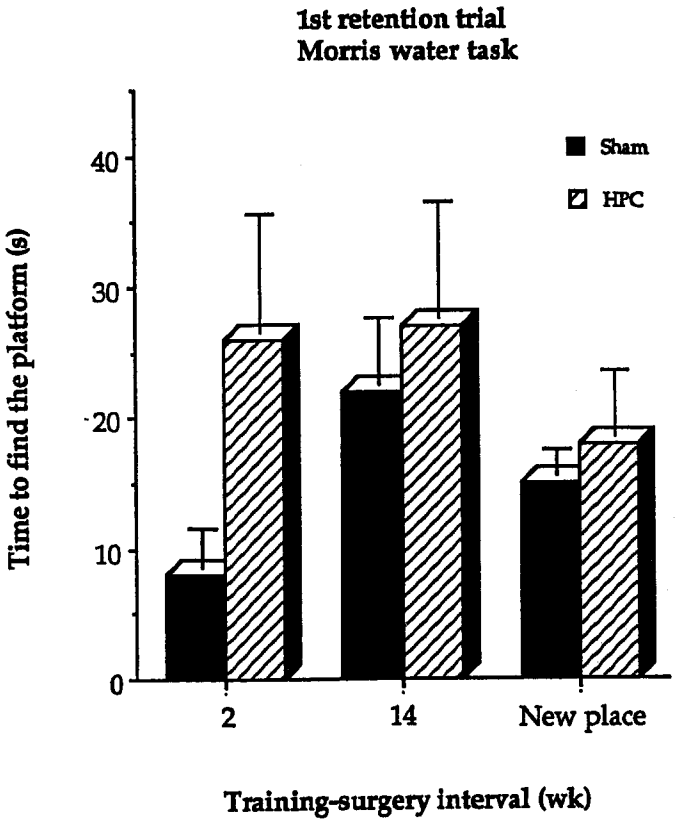

FIGURE 3. Time to find hidden platform during first postsurgical retention test in recent and remote place problems and during first training trial with a new place problem.

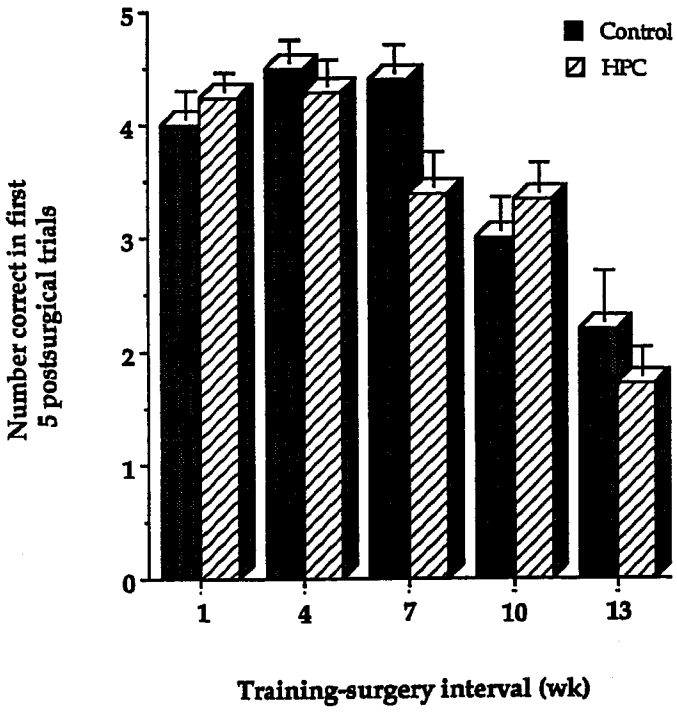

FIGURE 4. Choice accuracy during first five postsurgical retention trials with each of the object discriminations.

shown in Weisend et al. (1996) to be disrupted in the retrograde direction at each training-surgery interval tested, despite the fact that only place learning was affected in the anterograde direction by the kainate-colchicine lesion method. One possibility is that with a lesion method which reduces damage to connected extrahippocampal structures, we will find a different pattern of task or temporal specificity in retrograde amnesia. For example, if these extrahippocampal sites are involved in the permanent storage of memories, consolidated through interaction with hippocampal circuitry, we would expect to find in the NMDA lesion rats a trend for better retention with longer training-surgery intervals. Another possibility is that the range of tasks affected in the retrograde direction will be reduced, more in line with observations in the anterograde direction and the retrograde sparing of simple object discriminations seen with ibotenate-induced HPC damage.

METHODS

Subjects

The subjects were 73 experimentally naive Long-Evans hooded rats. All rats were between 250–350 g at the beginning of training. The animals were housed individually in hanging wire mesh cages and had access to food and water ad libitum. The numbers of animals assigned to each training-surgery interval were as follows: 1 day = 8 lesions, 6 control; 1 week = 7 lesions, 7 controls; 2 weeks = 9 lesions, 7 controls; 4 weeks = 8 lesions, 8 controls; and 15 weeks = 7 lesions, 6 controls.

Surgery

Rats were anesthetized with halothane (4% with 2 l per minute of oxygen and 2% after a surgical plane was established) given by face mask. A midline incision was made in the scalp and periosteum. Damage to the hippocampus was produced by stereotaxic microinjection of a solution of NMDA (3 mg/0.4 ml saline). Rats received 10 injections of neurotoxin, five in each hippocampus through 30-gauge cannulae. Rats received 0.4 μl of the excitotoxin at each of 10 sites: 3.1, 4.1, 5.0, 5.3 and 6.0 mm posterior to bregma, 1.5, 3.0, 3.0, 5.2, and 5.0 mm lateral to bregma, and 3.6, 4.0, 4.0, 7.3, and 7.3 mm ventral to the surface of the skull on both sides of the brain in respective order. The toxin was injected at 0.15 μl/min, using an infusion pump. Cannulae were left in place for 3 min after each injection. The scalp was closed with 9-mm autoclips, and the animal was returned to its home cage. Recovery was monitored for at lease 90 min before the animal was returned to the colony room. Animals were administered diazepam (20 mg/kg, i.p.) on first signs of wakefulness after surgery to suppress any seizure activity which might be associated with NMDA injection. Injections of diazepam continued every 30–60 min for 3 h after surgery. In addition, all rats received one or two injections of morphine (15 mg/kg, i.p.). Control rats received no surgical treatment. All animals were allowed to recover for 2 weeks before memory testing began.

Histology

At the conclusion of the experiment, four lesioned animals were sacrificed from each training-surgery interval group by overdose of pentobarbital (100 mg/kg, i.p.) and perfused transcardially with saline followed by 10% formalin. The brains were removed and 40-mm coronal sections were cut on a cryostat microtome. Every fifth slice of was mounted on glass slides and stained with cresyl violet. The stained sections were examined under a microscope to quantitate hippocampal and obvious extrahippocampal damage. Histological analysis was identical for all training conditions.

Behavior

Presurgical training

All rats were trained on the hidden platform and visible platform versions of the Morris water task concurrently. Training on the two versions of the task occurred on the same day, but on separate blocks of trials.

In the hidden platform version of the Morris water task, rats received 40 training trials (4 trials per day over 10 days) to learn to navigate to a hidden platform in a fixed location. On each day of training, rats were released once from each cardinal compass point around the perimeter of the pool. The sequence of these release points was determined by random draws without replacement. Latency to escape from the water by boarding the hidden platform

was recorded on each trial. On trial 41, a probe trial was conducted, during which the hidden platform was removed and rats were allowed to swim for 20 s to obtain a measure of place preference within the pool.

The second version of the Morris water task was a discrimination between two floating platforms, one uniformly gray and the other black-and-white striped. Rats received 160 training trials to learn to discriminate between the platforms (8 trials per day over 20 days). Training on this task occurred in the same apparatus where the hidden platform training was conducted. Training was broken into two 80-trial blocks. On the first 80-trial block, rats were released from each of the cardinal compass points with the platforms in the center of the quadrants directly opposite the release point. During the second block of training, rats received 8 trials per day on the same 10 days that hidden platform training was conducted. The position of the correct platform was balanced for left and right relative to the release point. Latency to escape from the water onto the correct visible platform and the number of errors committed before boarding the correct platform were recorded for each trial. An error was recorded if the rat made contact with the incorrect platform. At the conclusion of training on both versions of the Morris water task, rats were returned to their home cages for either 1 day, or 1, 2, 4, or 15 weeks. At the conclusion of this interval, rats underwent surgery to produce hippocampal damage.

Postsurgical training

In the hidden platform version of the Morris water task, retention of preoperative information was examined by returning rats to the same pool experienced prior to surgery for four trials. A 20-s no-platform probe trial was conducted on the first trial after surgery. For the next four trials, the hidden platform was positioned in the same location that the animals had learned before surgery. Rats were released once from each of the four cardinal compass points around the perimeter of the pool. The sequence of these release points was determined by random draws without replacement. Latency to escape from the water by boarding the hidden platform was recorded on each trial.

Following surgery, retention of the preoperatively trained visible platform discrimination was measured by returning rats to the pool for eight trials of visible platform discrimination during the same day of hidden platform retention testing. Rats were released from each of the cardinal compass points perimeter of the pool twice, and the platforms remained in the center of the quadrants opposite the release point. The occurrence of the correct visible platform was balanced left and right relative to the release point. Latency to escape from the water onto the correct visible platform and the errors committed before boarding the correct platform were recorded for each trial. An error was recorded if the rat made contact with the incorrect platform before the correct platform.

To examine the effect of hippocampal damage on relearning the preoperatively trained problem, rats were returned to the same Morris water task experienced prior to surgery. As before, rats received four trials per day, with one release from each of the cardinal compass points each day, in a sequence determined by random draws without replacement. Rats received a total of 40 trials of retraining. Latency to escape from the water was recorded on each trial.

Retraining also occurred on the visible platform discrimination experienced prior to surgery. Rats received 8 trials per day for 10 days. During all retraining, rats were released from each of the cardinal compass points along the perimeter of the pool twice. Platforms remained in the center of the quadrants opposite the release point. Escape latency and errors, as described above, were recorded on each trial. This training was conducted immediately before the completion of hidden platform retraining in all delay groups. Training in this phase began 2 weeks after surgery in all delay groups.

RESULTS

Histology

The damage to HPC was extensive bilaterally: 75–90% of the HPC was removed (Fig. 5). Sparing of portions of the major subfields was almost exclusively limited to the most posteroventral region. In only two rats was damage to the subicular cortex evident. The thalamus and rhinal cortices appeared to be intact in all rats. Importantly, the extent of hippocampal damage was equivalent in the groups at all three training-surgery intervals ($F < 1$). This pattern of extensive hippocampal damage with, in most cases, an absence of gross morphological evidence of extrahippocampal involvement contrasted sharply with the histological results in experiment 1 and affords us the opportunity to test our hypotheses.

Retention Testing: Visible Platform Discrimination

Presurgically, all groups acquired the visible platform discrimination to a high level of accuracy (all groups >90% by the last training day, main effect of group $F < 1$). Figure 6B shows the discrimination accuracy for all groups on the first postsurgical retention test block. The main effect of lesion was statistically significant ($F(1,63) = 12.6$, $P < 0.01$), but the main effect of training-surgery interval was not ($F < 1$). With longer training-surgery intervals the performance of the HPC lesion rats, but not the control rats, significantly declined. This is reflected in the statistically significant interaction between lesion group and training-surgery interval ($F(4.63) = 3.7$, $P < 0.01$).

Retention Testing: Place Memory

All groups achieved a similar level of proficiency at locating the hidden platform by the end of presurgery training (main effect of group on latency to find the platform, $F < 1$). Figure 6A depicts the average performance on the very first trial with the hidden platform during postsurgical retention testing. The lesion rats

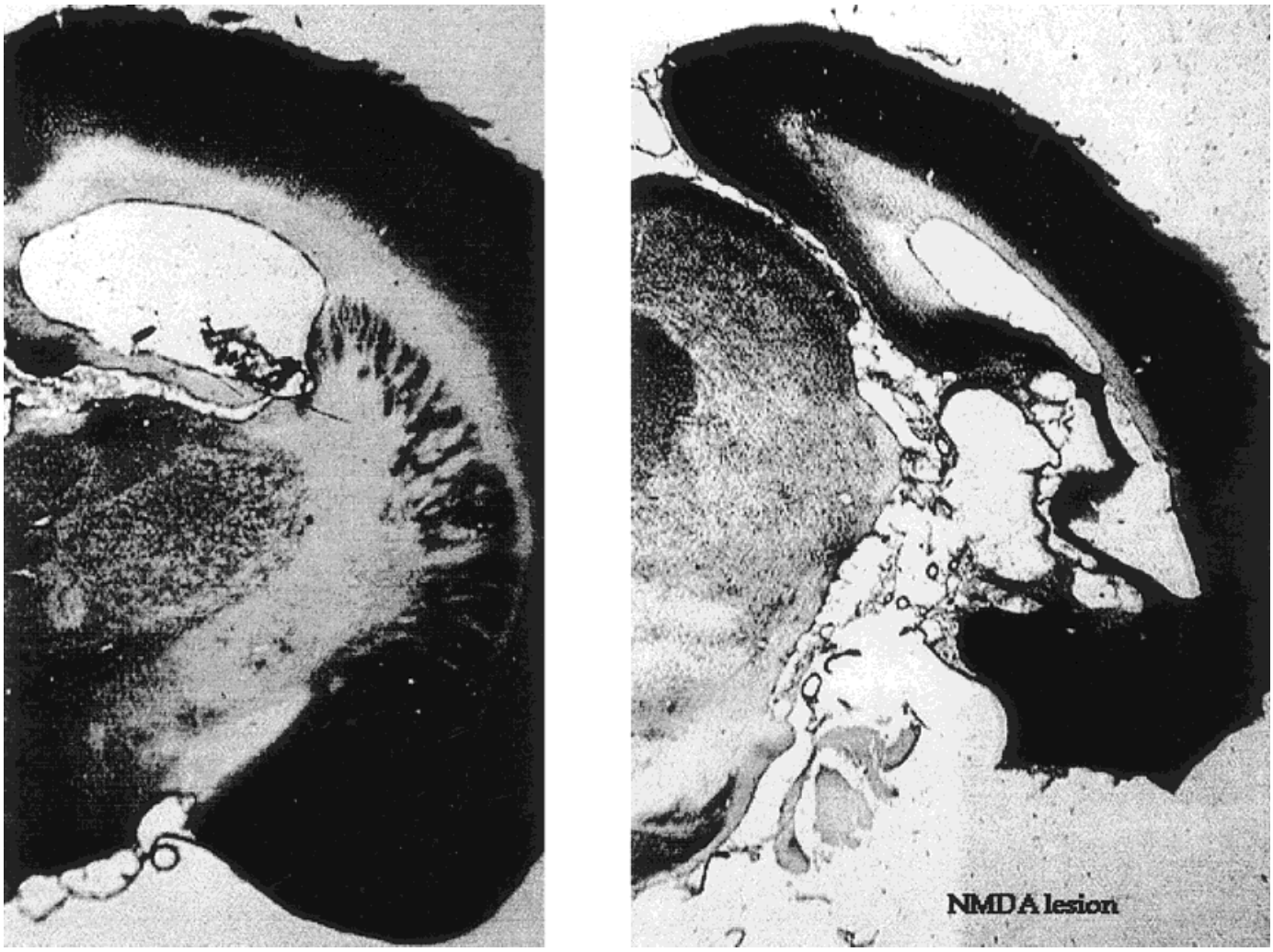

FIGURE 5. Typical NMDA lesion in coronal sections at two levels through dorsal and ventral hippocampal formation.

showed poorer initial retention performance than the control rats ($F(1,63) = 4.5$, $P = 0.037$). In addition, retention performance declined significantly with increasing training-surgery intervals ($F(4,63) = 5.7$, $P < 0.001$). The group × interval interaction did not reach significance ($F(4,63) = 0.52$, $P > 0.72$). Clearly, the difference in hidden platform performance between lesion and control rats cannot be attributed to superior relearning with a first-trial measure. Furthermore, the significant trend with training-surgery interval for both groups was worse first-trial performance, and not better for the lesion rats as would be expected if extrahippocampal consolidation occurred. The simple account of this pattern of first-trial performance is that NMDA-induced hippocampal damage causes retrograde amnesia for the hidden platform location and that forgetting of such information also occurs in both lesion and control rats. The results with quadrant preference obtained during the first postsurgical swim with no platform are also consistent with this conclusion (see Fig. 8). Control rats and not hippocampal lesion rats showed a preference for the target quadrant significantly greater than chance (25%) at all intervals but the last.

Retraining

The results of retraining in the place task and visible platform discrimination were somewhat different. We show the average performance during the first block of four retraining trials with the hidden platform (Fig. 7). The control rats at longer training-surgery intervals showed rapid relearning from their first trial level of performance (compare with Fig. 6). In contrast, the HPC rats continued to show poor performance. In a repeated measures ANOVA, we compared groups and training-surgery intervals across the first four trials of retraining. This revealed a significant effect of lesion ($F(1,63) = 22.1$, $P < 0.001$) and a significant effect of training-surgery interval ($F(4,63) = 6.4$, $P < 0.001$), but the interaction between lesion and training-surgery interval was not significant ($F < 1$). This is very similar to results when only the first

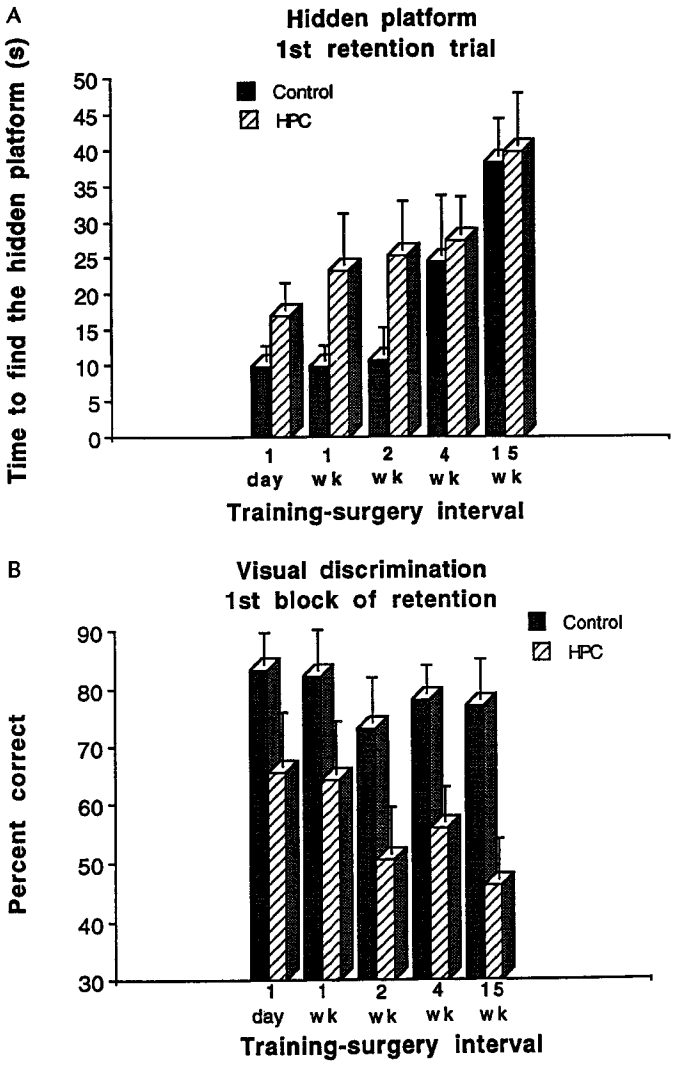

FIGURE 6. A: Time to find hidden platform on first postsurgical retention trial for both groups at each training-surgery interval. B: Choice accuracy in visible platform discrimination during first postsurgical retention block for both groups at each training-surgery interval.

retention trial is considered. The main effect of retraining trials was significant ($F(3,189) = 21.2$, $P < 0.001$), as was the interaction between retraining and training-surgery interval ($F(12,189) = 2.5$, $P = 0.004$). The interaction between lesion and retraining trials was not significant ($F < 1$), nor was the interaction between lesion, retraining, and training-surgery interval ($F(12,189) = 1.5$, $P = 0.14$). Thus, performance of both groups benefited somewhat from retraining during the first postsurgery session, particularly at long training-surgery intervals.

Next we turn to the final level of performance attained by each of the groups after 10 days of retraining. The HPC damaged rats reattained a good level of performance in the visible platform discrimination (>80% correct by the end of retraining). The main effects of lesion on discrimination accuracy on the last day of retraining ($F(1,63) = 1.02$, $P = 0.38$) and of training-surgery interval ($F < 1$) were not significant. In contrast, the HPC lesion rats remained impaired at hidden platform navigation relative to control rats even at the end of retraining, taking on average twice as long to find the hidden platform. The main effect of lesion was significant on the last trial of retraining ($F(1,63) = 12.9$, $P < 0.001$). The main effect of training-surgery interval missed significance ($F(4,63) = 2.4$, $P = 0.06$), as did the interaction between group and training-surgery interval ($F < 1$). This pattern of results best fits with clear retrograde amnesia coupled with anterograde amnesia preventing normal relearning of place navigation by HPC lesion rats.

Given that multiple intrahippocampal microinjections of NMDA are associated with less extrahippocampal damage relative to kainic acid microinjections, a comparison of the temporal and task specificity in this study to our previous ones should give an indication of the significance of extrahippocampal damage in our other experiments. Of most importance for our earlier conclusions is the finding of substantial deficits in retention of place navigation and visible platform discrimination. This supports our notion of a dissociation in the effects of hippocampal damage in the anterograde and retrograde directions, with a broader range of deficits in the retrograde direction.

Another hypothesis examined in this experiment is that extrahippocampal damage associated with the use of kainate may contribute in an important way to the deficits in retention of information from longer training-surgery intervals. This result might be predicted by the view that these extrahippocampal structures contain relevant permanent memory storage sites. In contrast to this prediction, we found that the deficit after selective NMDA-induced hippocampal damage was large and reliable across training-surgery intervals. This same pattern was evident in both place and visible discrimination tasks. The hy-

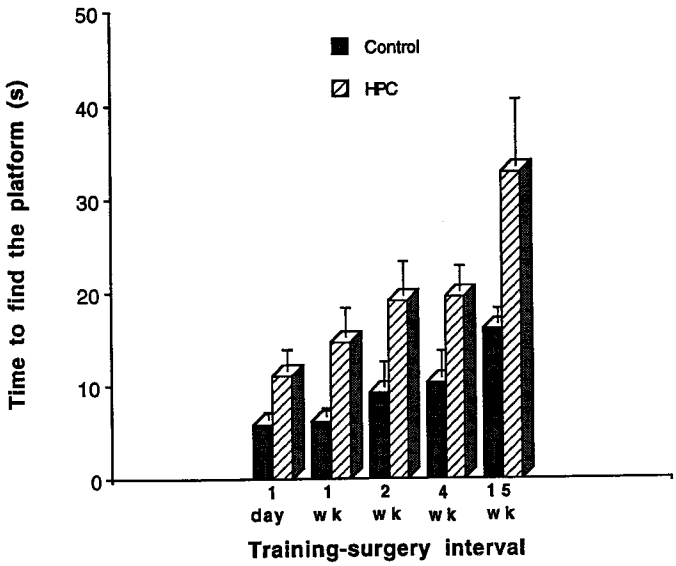

FIGURE 7. Time to find hidden platform on first postsurgical retention block of four trials for both groups at each training-surgery interval.

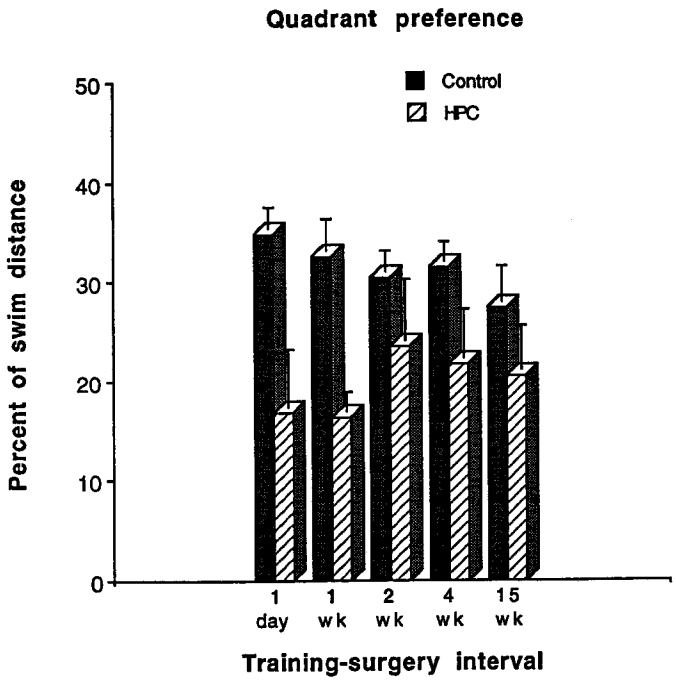

FIGURE 8. Percentage of swimming in correct quadrant during a no-platform probe trial conducted during first postsurgical swim.

pothesis that extrahippocampal damage is important in the disruption of retention of remote information in our tasks was not supported.

DISCUSSION

The studies described here were designed to shed some light on unresolved issues surrounding the retrograde amnesia that follows hippocampal damage and dysfunction. Specifically, the data from these studies addressed two issues: similarity in the specificity in the kinds of memories affected in anterograde and retrograde amnesia resulting from hippocampal damage, and temporal gradient in the severity of retrograde amnesia. First, the results indicate that there can be a dissociation in the content of anterograde and retrograde amnesia. In our earlier experiments with kainate-colchicine lesions (Weisend et al., 1996), hippocampal damage produced retrograde amnesia for both relational/configural and nonrelational/elemental tasks. In contrast, hippocampal damage produced unambiguous anterograde amnesia for only relational/configural information. In the present experiment with NMDA-induced hippocampal damage, we found this same pattern of results. We suggest that the solution to a very wide range of learning tasks, with the possible exception of certain skills, is represented configurally or relationally by rats with an intact hippocampus. Second, there is little support for the idea that increasing the interval between training and hippocampal damage could lessen the severity of retrograde amnesia. The lack of temporally graded retrograde amnesia in our studies calls into question the generality of the hypothesized role of the hippocampus in a long-lasting memory consolidation process involving extrahippocampal storage sites.

Retrograde Amnesia: Specificity

In all of our retrograde amnesia experiments, damage to the hippocampus produced retrograde amnesia for relational/configural information. These results replicate other work showing that hippocampal damage impairs retention of the hidden platform version of the Morris water task, contextual fear, and negative patterning (Sutherland et al., 1987; Kim and Fanselow, 1992; Sutherland and Rudy, 1989).

Our findings that damage to the hippocampus can also produce retrograde amnesia for nonrelational or nonconfigural information (see also Weisend et al., 1996) were surprising, since hippocampal damage does not cause anterograde amnesia in the elemental tasks used in these studies (McDonald and White, 1993; Sutherland et al., 1982; Sutherland and Rudy, 1989). Further, a study using a within-subjects design similar to that used in the experiments reported here showed retrograde amnesia for relational information, but not nonrelational information, in rats with hippocampal damage (Kim and Fanselow, 1992). However, there are other reports of hippocampal damage affecting retention of nonrelational information (Ross et al., 1984; Sara, 1981). The experiments showing retrograde amnesia for nonrelational information have often been viewed as enigmatic. However, our experiments clearly demonstrate that damage to the hippocampus can produce severe retrograde amnesia for nonrelational as well as relational information.

The retrograde amnesia for relational information fits well with most contemporary theories of hippocampal function (Cohen and Eichenbaum, 1993; Hirsh, 1974, 1980; Mishkin, 1978, 1982; O'Keefe and Nadel, 1978; Olton et al., 1979; Rawlins, 1985; Squire, 1986, 1987, 1992; Squire and Zola-Morgan, 1991; Squire and Zola, 1996; Sutherland and Rudy, 1989; Tulving, 1987). However, the retrograde amnesia for the nonrelational information observed in these studies does not. A current prominent view states that nonrelational memories are "supported by memory systems that operate independently of the hippocampal system" (Cohen and Eichenbaum, 1993, p. 74). This view would clearly predict that nonrelational memories would be unaffected by hippocampal damage. The studies reported here, and those of Ross et al. (1984) and Sara (1981), indicate that hippocampal damage may adversely affect nonrelational memories.

It is possible that the hippocampal damage inflicted in these studies caused a functional lesion that went beyond the anatomical damage, or subtle extrahippocampal pathology may have been present. We have no evidence on either of these possibilities. However, it should be noted that the presence of a large functional lesion would predict that anterograde amnesia would not have the specificity that has been shown in our experiments.

There are studies, other than those producing lesions, that suggest the hippocampus is involved in the processing of both relational and nonrelational information. There are well-described responses of hippocampal neurons to environmental stimuli that are

relational in nature, such as places and conjunctions of nonspatial stimuli. However, there are also numerous reports of hippocampal neurons that respond to nonrelational environmental stimuli. For example, hippocampal single units develop firing fields during basic eyelid conditioning in rabbits (Berger et al., 1983) even though basic eyelid conditioning is not affected by hippocampal damage. Hippocampal units also fire during the presentation of auditory, visual, and olfactory discriminative stimuli when the problem does not require a relational solution (Cohen and Eichenbaum, 1993; Eichenbaum et al., 1992). These responses of hippocampal single units to nonrelational stimuli sometimes appear to be as robust as those to places, but are frequently ignored in theorizing about hippocampal function (Cohen and Eichenbaum, 1993; Muller et al., 1987). In a separate study, the strength of the perforant path synapses, the sites of cortical input into the hippocampus, are reported to be modulated by learning in tasks which do not compel a relational/configural solution (Skelton et al., 1987). These electrophysiological data from the intact hippocampus also suggest that the hippocampus plays a role in forming both relational and nonrelational memories.

Having made a case that the hippocampus is involved in relational and nonrelational memory, it is necessary to note that there are examples of retrograde amnesia for only relational information after hippocampal damage or dysfunction. In humans, memories for skills are sometimes reported to be spared after medial temporal lobe damage (Kapur et al., 1992, 1994; Milner, 1959; Penfield and Milner, 1955, 1958; Scoville and Milner, 1957). It is difficult to make specific statements about types of spared and impaired memories in nonhuman primates because there are no published reports of retrograde amnesia after selective hippocampal damage. In rats, fear conditioning to a tone, object recognition, and object discriminations (experiment 1) have been reported to survive hippocampal damage (Kim and Fanselow, 1992; Mumby et al., 1992; Astur et al., 1994). Thus, the question remains: why are nonrelational memories sometimes affected and sometimes not?

There are some clear differences between our studies (see also Weisend et al., 1996) and those in which nonrelational memories are unaffected by hippocampal damage. In the case of Kim and Fanselow (1992), who reported that fear conditioning to a tone is unaffected by hippocampal damage, there are gross differences in lesion size. The lesions in our studies were approximately 80% of the total hippocampal volume. In Kim and Fanselow (1992), the lesions were small, dorsal only, and centered in the dentate gyrus. One possible explanation, which is easily tested, for the differences in the content specificity of retrograde amnesia between Kim and Fanselow (1992) and the experiments reported here, is lesion size.

There are notable differences between the unaffected nonrelational task used in Mumby et al. (1999) compared to our affected nonrelational tasks in other experiments. The object discriminations were trained in an apparatus separate from and in a different room than the Morris water task, whereas the visible platform discriminations were trained in the same pool where the hidden platform training occurred. Furthermore, training on the hidden and visible platform sometimes occurred during a single session of training. Training in the Morris water task and on object discriminations always occurred separately. In addition, the visible platform discrimination was motivated by water escape, similar to the hidden platform version of the Morris water task, while the object discriminations were motivated by food reward. It could be that the similar context, intermixed training, and similar motivational factors between the relational and nonrelational problems in the Morris water tasks in our experiments generated overlapping representations of the relational and nonrelational information. In contrast, the large shift in context, training times, and reward between the Morris water task and the object discriminations generated unique representations of the problems. One possible explanation for the discrepancy in the retrograde amnesia for nonrelational information between the two studies is that the similarity of the problems in the present experiments made the nonrelational information vulnerable to hippocampal damage by creating overlapping representations of the relational and nonrelational information. Training that creates distinct representations may be less likely to produce global retrograde amnesia. In Weisend et al. (1996), all relational and nonrelational versions of the tasks were trained in the same apparatus. If the idea that the training routine in our experiments is important in the observation of similar retrograde amnesia for relational and nonrelational information, then here is another facet of hippocampal function that is open to exploration. We are unaware of any reports that show nonrelational information to be differentially dependent on hippocampal circuitry as a function of these sorts of variations in training routine.

One additional fact to consider is that the animals in the hidden platform version of the Morris water task experiments did not behave as if they were naive when placed into the pool after surgery. Rats are sometimes quicker to escape from the water on the first four trials after surgery than on the first four trials of training prior to surgery (Weisend, et al., 1996; Mumby, et al., 1999). This finding is robust across several other studies (Bolhuis et al., 1994; Sutherland et al., 1987). Thus, there must be some information about the Morris water task that survived the hippocampal damage. This information has been presumed to be nonrelational in nature (although this remains to be demonstrated conclusively and is not important for the current argument). The relational and nonrelational information learned within the hidden platform version of the Morris water task should be more closely related than the relational and nonrelational information learned in the hidden and visible platform discrimination versions of the Morris water task. Yet, the nonrelational information from within the hidden platform version of the task survives and the nonrelational information from the visible platform version of the task does not. This could be viewed as inconsistent with the idea that the similar training contexts produce some kind of overlapping representation between the relational and nonrelational information that is responsible for the retrograde amnesia for nonrelational information that is reported here.

There is another possible explanation for the difference between the retrograde amnesia for nonrelational information in our experiment and that of Mumby et al., 1959. It could be the case that the mnemonic system for objects is truly independent of the hippocampus. Mumby et al. (1992) found that performance on ob-

ject-based, delayed nonmatching-to-sample was unaffected by hippocampal damage. Mumby et al. (1999) found that retention of multiple object discriminations was unaffected by hippocampal damage. A memory system for objects that does not engage the hippocampus could result in spared memory for objects and impaired memory for other nonrelational information.

The retrograde amnesia for nonrelational information in the present experiments might also be explained by deletion of the contextual information in which the task was learned by damage to the hippocampus. The present experiments, and numerous others (Good and Honey, 1991; Kim et al., 1993; Kim and Fanselow, 1992; Nadel and Willner, 1980; Nadel et al., 1985; Phillips and LeDoux, 1992, 1994; Sutherland and McDonald, 1990), demonstrate that hippocampal damage impairs memory for contextual information. Performance based on previously acquired information is also impaired by a change in context (Estes, 1973; Konorski, 1967; Medin, 1975; Nadel and Willner, 1980; Nadel et al., 1985; Spear, 1973). These views suggest that contextual information offers retrieval cues that facilitate performance. Thus, removal of contextual information could affect performance based on nonrelational information. This interpretation of the data would suggest that the hippocampus is involved in only relational memory, as is suggested by current theories, and that removal of the hippocampus in the present experiments has merely interfered with retrieval of nonrelational information.

The finding of retrograde amnesia for both relational and nonrelational information is problematic for current theories of hippocampal function. There is good evidence from lesion studies and electrophysiological investigations that the hippocampus could be more widely involved in memory than current theories suggest. However, there are other plausible ideas that could account for the retrograde amnesia for both relational and nonrelational information observed in the current experiments. For whatever reason, the current studies show that nonrelational tasks are affected by retrograde amnesia after hippocampal damage. This prompts a reexamination of current thinking about the role of the intact hippocampus in memory.

Retrograde Amnesia: Temporal Gradients

In addition to training each animal on multiple tasks, the experiments reported here allowed different periods of time to elapse between training and lesion. Many previous studies have shown that allowing memories to "age" makes them resistant to hippocampal damage (MacKinnon and Squire, 1989; Scoville and Milner, 1957; Squire et al., 1989; Walker, 1957; Penfield and Milner, 1958; Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). The decrease in memory's vulnerability to hippocampal damage as the interval between training and lesion increases produces a temporally graded retrograde amnesia: events in the remote past are recalled better than very recent events. The process by which memories become resistant to retrograde amnesia has been labeled hippocampal-dependent memory consolidation (Squire et al., 1984a; Squire, 1986, 1987, 1992; Squire and Zola-Morgan, 1991; Squire and Zola, 1996; Zola-Morgan and Squire, 1990). There is little evidence for this sort of temporal gradient in the retrograde amnesia in the present experiment or in the work of Weisend et al. (1996) with many more tasks. There was no change in retention of relational or nonrelational information as a function of the interval between training and hippocampal damage.

It has been suggested that memory consolidation interacts with the forgetting process (Squire et al., 1984a; Squire, 1986). We did find some evidence of forgetting in the experiments reported here. Evidence of forgetting was found in most of our tasks. However, it remains possible that our intervals are too short to properly evaluate hippocampal-dependent memory consolidation. Other experiments have shown evidence of memory consolidation over similar (or even shorter) periods in very similar tasks to those we have evaluated (Kim and Fanselow, 1992; Sutherland et al., 1987; Zola-Morgan and Squire, 1990). The experiments presented here are clearly more consistent with others that failed to find temporally graded amnesia resulting from damage to the hippocampus (Astur et al., 1994; Bolhuis et al., 1994; Salmon et al., 1987). Deactivation of the hippocampus with a local anesthetic agent has also been reported to produce retrograde amnesia with a flat gradient for relational information (Bohbot et al., 1996). These experiments call into question the generality of the idea that the hippocampus participates in a long-lasting memory consolidation process.

Another important consideration is whether evidence for extrahippocampal consolidation is sought using initial retention performance, uncontaminated by relearning, or using savings during retraining. Ideally, one would like converging evidence from both types of data. In our experiment with NMDA lesions we come close, showing consistent retrograde amnesia during a no-platform probe trial on the first postsurgical swim, during the first trial of navigation to the hidden goal, and even by the end of retraining. We found a similar pattern without evidence for consolidation in the contextual fear conditioning task in the experiments of Weisend et al. (1996) with kainate-colchicine lesions and the Morris water task in the experiments of Mumby et al. (1999) with ibotenate lesions.

Lesion size and location could account for the differences between our studies and others reporting temporally graded retrograde amnesia after hippocampal damage. Hippocampal lesions similar to those reported in the current study were produced in the studies by Bolhuis et al. (1994). Kim and Fanselow (1992) and Sutherland et al. (1987) reported temporally graded retrograde amnesia. Both studies produced similar lesions. Kim and Fanselow (1992) made electrolytic lesions that were centered in the dentate gyrus. Sutherland et al. (1987) produced damage to the dentate gyrus portion of the hippocampus by injections of colchicine. Temporally graded retrograde amnesia was found in both studies, where damage was directed at the dentate gyrus. An interesting parallel is seen in retrograde amnesia data from nonhuman primates. Salmon et al. (1987) found a flat gradient with concurrent object discriminations, and 3 years later Zola-Morgan and Squire (1990) found temporally graded retrograde amnesia with a similar task. The chief difference between studies was that Salmon et al. (1987) produced larger medial temporal lobe lesions than did Zola-Mor-

gan and Squire (1990). The characterization of lesions in human patients is not sufficient to make similar comparisons. However, data from experiments with nonhumans are consistent with the idea that lesion size and/or location may be critically involved in the pattern of recall in retrograde amnesia.

If there is a tendency for smaller lesions to produce temporally graded retrograde amnesia and larger lesions to produce flat gradients, it would suggest that memory consolidation does not occur outside the hippocampus. Instead, memory consolidation could largely occur within the hippocampus itself. If memory consolidation was a process by which memories initially require hippocampal circuitry but eventually become independent of the hippocampus, recall should be independent of hippocampal lesion size. Regardless of how hippocampal-dependent memory consolidation occurs, there should always be cortical traces that are retrievable in the absence of the hippocampus. Hippocampal-dependent memory consolidation could occur within the hippocampus itself. Intrahippocampal memory consolidation could work in the following manner: memories take some period of time, possibly days to weeks, to be integrated into the network of memories resident in the hippocampus. Once firmly integrated into the network, they are resistant to minor hippocampal damage or dysfunction. However, large or complete lesions would render the memories unrecoverable. This idea is similar to the concept of graceful degradation in artificial neural networks (Arbib, 1987).

Nadel and Moscovitch (1997) provide a similar explanation for memory consolidation within the hippocampus. They suggest that each time a memory is recalled, a new memory trace is formed within the hippocampus. If this view is correct, older memories have greater numbers of traces than newer memories. Thus, damage to the hippocampus has a greater effect on recent memories than on more remote memories because a greater proportion of the traces are damaged or destroyed. This is a possible mechanism of intrahippocampal memory consolidation.

In summary, the data from our experiments replicate other experiments showing retrograde amnesia for relational information. However, there was also severe amnesia for the nonrelational versions of the same tasks. These results are consistent with the idea that all information, with the possible exception of skills, is stored in a relational/configural memory system when the hippocampus is intact. It is only after a lesion of the hippocampus that nonrelational learning can be accomplished by the remaining mnemonic systems. Both relational information and nonrelational information were affected by hippocampal damage across all intervals between training and surgery, at least up to the point where forgetting obscures clear effects of lesions on "pure" measures of retention. The hippocampus appears to be involved in the storage and/or retrieval of relational and nonrelational memories. The current experiments do not support theoretical positions that suggest that the hippocampus participates in a long-term memory consolidation process where information eventually comes to be stored in the neocortex. In contrast, the current data, in combination with other studies, suggest that there may be an intrahippocampal memory consolidation process.

CONCLUSIONS

The present experiments show that damage to the hippocampus can produce retrograde amnesia for relational and nonrelational information. This retrograde amnesia is accompanied by anterograde amnesia for relational but not nonrelational information in the same rats. This dissociation between anterograde and retrograde amnesia in the same rat is consistent with the idea that a great deal of learning in an intact brain engages hippocampal circuitry. It is only in the hippocampus-damaged brain that one sees learning of nonrelational information in the remaining mnemonic systems. In addition, the current experiments failed to reproduce the temporally graded retrograde amnesia that was previously described in similar tasks. The hippocampal lesions in these experiments were much larger than those in most previous studies which showed temporally graded retrograde amnesia. It may be that temporally graded retrograde amnesia is more often associated with partial lesions. Further, we speculate that if there is a long-lasting hippocampal-dependent memory consolidation process, it involves intrahippocampal permanent storage sites.

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