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Impaired Remote Spatial Memory After Hippocampal Lesions Despite Extensive Training Beginning Early in Life

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ABSTRACT: Damage to the hippocampus typically produces temporally graded retrograde amnesia, whereby memories acquired recently are impaired more than memories acquired remotely. This phenomenon has been demonstrated repeatedly in a variety of species and tasks, and it has figured prominently in theoretical treatments of memory and hippocampal function. A striking exception to the finding of temporally graded retrograde amnesia comes from studies with rodents using spatial tasks like the water maze. In these studies, recent and remote memory were similarly impaired following hippocampal lesions. In contrast to work with rodents, studies of patients with medial temporal lobe lesions, including complete hippocampal lesions, indicate that remote spatial memory can be intact. One difference between studies in humans and studies in rodents is that spatial memory in animal studies is acquired during a limited period of time when the animals are adults. In contrast, the spatial memory studied in humans was acquired beginning at an early age and learning continued for a considerable period of time. We initiated training in a standard water maze immediately after rats had been weaned at 21 days of age and continued training until the rats were young adults (90 days old). Large hippocampal lesions were made 100 days after the completion of training. After recovery from surgery, control rats exhibited good retention on the first retention probe trial, but rats with hippocampal lesions performed at chance. Thus, even after extended training beginning early in life, and with a prolonged training–surgery interval, hippocampal lesions impair performance in the water maze task. Possible reasons for these findings are discussed in the context of the specific performance requirements of the water maze task. Published 2005 Wiley-Liss, Inc.†

KEY WORDS: rat; water maze; retrograde amnesia; hippocampus

INTRODUCTION

Studies in humans have documented that damage to the hippocampus produces both anterograde and retrograde amnesia. Typically, the retrograde amnesia is temporally graded, such that information acquired long before hippocampal damage is remembered better than information acquired recently (Manns et al., 2003; Kapur and Brooks, 1999). The phenomenon of temporally graded retrograde amnesia has led to the idea that the hippocampus serves a temporary role in the formation and maintenance of long-term memory (LTM) and that the neocortex is the ultimate repository of memory (Squire and Alvarez, 1995; McClelland et al., 1995; Squire et al., 2001).

During the 1990s, retrograde amnesia began to be studied prospectively in experimental animals, and it is now possible to identify at least 20 studies that have examined both recent and remote memory after damage to the hippocampus (see Squire et al., 2004). Of these, the large majority found that remote memory is spared after hippocampal damage and that more recent memory is impaired. That is, most studies have demonstrated temporally graded retrograde amnesia. A striking exception to this pattern is found in a few studies that employed a widely used test of spatial memory, the Morris water maze (Bolhuis et al., 1994; Mumby et al., 1999; Sutherland et al., 2001). These studies found that recent and remote spatial memory were similarly impaired. We recently completed an extensive study (Clark et al., 2005) of remote spatial memory after hippocampal damage in the rat using three different tests of spatial memory: the standard water maze, the Oasis maze (a dry-land version of the water maze) and the annular water maze (Hollup et al., 2001). In all three tasks, rats with nearly complete hippocampal lesions, as well as rats with dorsal hippocampal lesions, exhibited no evidence of spared spatial memory, even when the training–surgery interval was extended to 98 days.

In contrast to this work with rodents, studies of patients with medial temporal lobe lesions, including complete hippocampal lesions, indicate that remote spatial memory can be intact (Teng and Squire, 1999; Rosenbaum et al., 2000). For example, patient E.P. became severely amnesic in 1992 at the age of 70 and has extensive damage to the medial temporal lobe bilaterally. He has been unable to acquire new spatial memories about the layout of his house or his neighborhood where he moved shortly after he became amnesic (Teng and Squire, 1999; Bayley and Squire, 2005). Yet, E.P. could recall the spatial layout of the neighborhood where he grew up and where he lived until he was 28 years of age. Indeed, E.P. performed as well as age-matched individuals who grew up with

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him in the same town and also moved away (Teng and Squire, 1999). Specifically, E.P. could describe how to travel from his home to other locations in his neighborhood, how to travel from one location to another, and he was able to construct alternative routes for traveling between locations. He was also able to imagine himself in a particular orientation at a designated location and then point to a specific landmark. These findings indicate that in humans remote spatial memory can be spared after damage to the hippocampus and related medial temporal lobe structures and that spatial memory must ultimately be stored outside of the medial temporal lobe.

One difference between studies in humans and studies in experimental animals is that spatial memory in animal studies is acquired during a limited period of time when the animals are adults. In contrast, the spatial memory studied in humans was acquired beginning at an early age and learning continued for a considerable period of time. Perhaps spatial memories must be acquired early in life or be very well learned over a long period of time, or both, if they are to be spared after hippocampal damage.

To examine this possibility, we began training in the standard water maze task immediately after rats had been weaned at 21 days of age. We continued training until the rats were young adults and had reached the age at which we previously trained young adult animals on this task (3 months of age) (Clark et al., 2005). Large hippocampal lesions were then made 100 days after this extensive training, and spatial memory was assessed with retention probe trials.

MATERIALS AND METHODS

Subjects

We tested 16 experimentally naive, male Long-Evans rats. They were 21 days old at the beginning of the experiment and weighed 40–50 g (young adult Long-Evans rats weigh 300–320 g). Animals were housed in pairs and maintained on a 12:12-h light/dark cycle with free access to food and water.

Apparatus

Water maze testing was conducted in a pool of water (1.6-m diameter) that was rendered opaque by the addition of powdered milk. Four 30-W spotlights pointed at a white ceiling illuminated the room. The water was maintained at room temperature. The testing room contained a number of constant, salient visual cues (posters and equipment). A video camera was mounted on the ceiling directly above the pool and was used in conjunction with a video tracking system (San Diego Instruments) to record the swim path of each rat.

We used an Atlantis platform that could be raised or lowered remotely (Spooner et al., 1994). When the platform (12.7-cm diameter) was in the lowered position, the rat could neither detect the platform nor escape from the water. When the platform was in the raised position (1.5 cm below the surface of the water), it remained invisible to the rat but provided a means to escape the water (for details, see Clark et al., 2005).

Behavioral Training

Phase I. Platform training

During 3 days of platform training, curtains surrounded the pool and blocked the distal spatial cues. An object was suspended 20 cm above the hidden platform and served as a beacon for the rats. To begin each trial, the rat was placed in the water, facing the pool wall, at one of 4 start points around the pool (i.e., North, South, East, West). Two trials were given each day from each start point (8 trials/day for 3 days). The hidden platform was raised to within 1.5 cm of the water surface only when the rat was both accurate ($<$20 cm from the platform) and persistent in searching at the correct location (dwell time of 0.5 s on the first day, 1.5 s on the second day, and 2.5 s on the third day). After escaping, the rats remained on the platform for 30 s before being removed. If the rat failed to find the platform within 90 s, it was guided to the platform and then remained there for 30 s. This procedure shaped a focused and sustained search at the platform location.

Phase II. Spatial training

After platform training, the curtains were removed to reveal the distal spatial cues. Rats were given 8 trials each day (intertrial interval approximately 8 min; 2 trials/day from each of the start points and with the sequence of starting points counterbalanced within groups) and were tested for 5 consecutive days each week. When the rat dwelled within 20 cm of the platform for 2.5 s, the platform was raised to permit escape from the water. After escaping, the rat remained on the platform for 30 s. The first and fifth trials of each training day were 30-s reinforced probe trials. During these trials, the platform was initially in the lowered position and was raised after 30 s. This procedure allowed spatial learning to be tracked across training. Training continued until each rat received 49 days of training during the course of 69 days (392 total trials per rat), at which point the rats were 90 days old. After training, animals were divided into two matched groups of eight each (control and lesion), based on performance on the first probe trial during each of the final 5 days of training. Surgery was performed 100 days after the completion of training.

Phase III. Retention probes

To reacclimatize the rats to swimming in water, each rat was allowed to swim for 30 s on each of 4 days in a small tub (H:48 cm W:53 cm L:91 cm) filled with opaque water. These 30-s swims took place 10 days after surgery and were conducted in a different room than the water maze.

Fourteen days after surgery, three 60-s probe trials were administered. The trials began by placing a rat in the water facing the pool wall at one of the 4 start points (counterbalanced within groups). The platform remained lowered for 60 s and

was then raised to provide escape. Each rat remained on the platform for 30 s before being removed. Performance on the probe trials was calculated by measuring the percentage of time that each rat spent in the quadrant of the pool where the platform had been located during training (chance performance = 25%).

At the completion of behavioral testing, rats were administered an overdose of sodium pentobarbital and perfused transcardially with buffered 0.9% NaCl solution, followed by 10% formaldehyde (in 0.1 M phosphate buffer). The brains were then removed and cryoprotected in 20% glycerol/10% formaldehyde. Coronal sections (50 μm) were cut with a freezing microtome. Every fifth section was mounted and stained with thionin to assess the extent of the lesions.

Surgery and Histology

Anesthesia was maintained throughout surgery with isoflurane gas (0.8–2.0% isoflurane delivered in O_2 at 1 L/min). The animal was placed in a Kopf stereotaxic instrument, and the incisor bar was adjusted so that bregma was level with lambda. Thermocoagulation lesions were made with a radiofrequency electrode and generator (Radionics, model RF-4A; for additional details, see Clark et al., 2000). Lesions were intended to damage the dorsal and ventral hippocampus and were made at multiple locations. All coordinates are in millimeters and relative to bregma: anteroposterior (AP) −2.4, mediolateral (ML) ± 1.0, dorsoventral (DV) −3.5; AP −3.2, ML ± 1.4, DV −2.7; AP −3.2, ML ± 3.0, DV −2.7; AP −4.0, ML ± 2.5, DV −2.3; AP −4.0, ML ± 3.7, DV −2.7; AP −4.8, ML ± 4.9, DV −6.8; AP −4.8, ML ± 4.3, DV −7.4, −3.5; AP −5.4, ML ± 4.2, DV −4.2; AP −5.4, ML ±5.0, DV −6.5, −5.5, −4.5. The wounds were then closed, and the rats recovered from anesthesia on a water-circulating heating pad. All animals were allowed to recover for 14 days before behavioral testing. Control animals did not undergo any surgical procedures.

RESULTS

Histological Findings

Figure 1 illustrates the extent of the largest and smallest lesion in each group.

Hippocampal damage

All the animals sustained extensive bilateral damage to all the cell fields of the hippocampus, including the dentate gyrus. The average percent damage to the hippocampus was 82.8% (range 75.2–89.8%). All animals had some damage to the alveus and to the fimbria on the dorsal edge of the dorsal hippocampus. Six animals sustained minor damage to the ventral subiculum. When present, this damage tended to occur in the ventral subiculum just below the ventral hippocampus. One animal had minor unilateral damage to the lateral dorsal nucleus of the thalamus. The primary areas of spared hippocampal tissue were located in the most ventromedial portion of the ventral hippocampus and along the midline of the dorsal hippocampus. This sparing involved primarily the most medial aspects of CA1 and the crest of the dentate gyrus. Occasionally, small islands of spared hippocampal tissue were observed within the damaged areas of the hippocampus. The region of the subiculum posterior to the ventral hippocampus, which accounts for approximately 90% of subicular tissue, was spared in all cases.

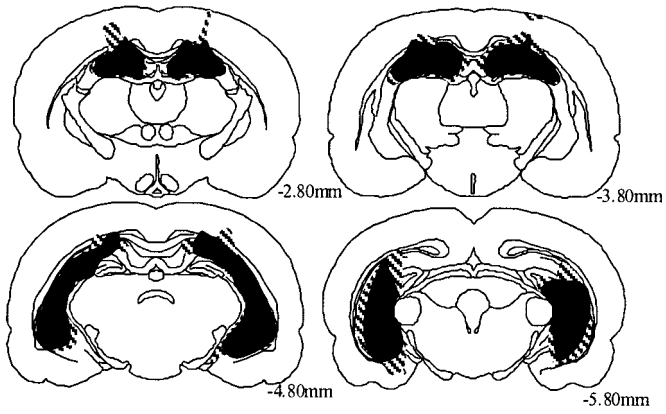

FIGURE 1. Coronal reconstruction showing the largest (striped) and smallest (black) area of damage for rats with hippocampal lesions. The series of sections progress (top to bottom) from anterior to posterior levels. Numbers represent the distance in millimeters posterior to bregma.

Other damage

One animal sustained minor unilateral damage to the entorhinal cortex that amounted to less than 10% of total entorhinal volume. The entorhinal cortex was entirely spared in all other animals. In most cases there was some detectable damage to the cortical regions directly dorsal to the dorsal hippocampus. No animal had damage to the perirhinal cortex or the amygdala.

Behavioral Findings

Acquisition

All rats readily learned the platform location within the first few days of training. Figure 2 shows the mean percentage of time that the rats spent in the training quadrant on the first trial of each day of training (the first and fifth trials of each day were 30-s probe trials). Performance was above chance (chance = 25%) on the first probe trial of the second day of training ($t[15] = 3.37$, $P < 0.01$), and performance continued to improve for about 10 days (repeated-measures ANOVA, $F[9] = 3.29$, $P < 0.01$). A similar analysis for training days 11–49 was not significant ($F[38] = 1.16$, $P > 0.1$), indicating that performance did not improve or decline across 39 additional days of training. Nonetheless, an inspection of Figure 2 suggests that after peak performance on day 14 (54.1% ± 5.2%), average probe trial performance was somewhat lower

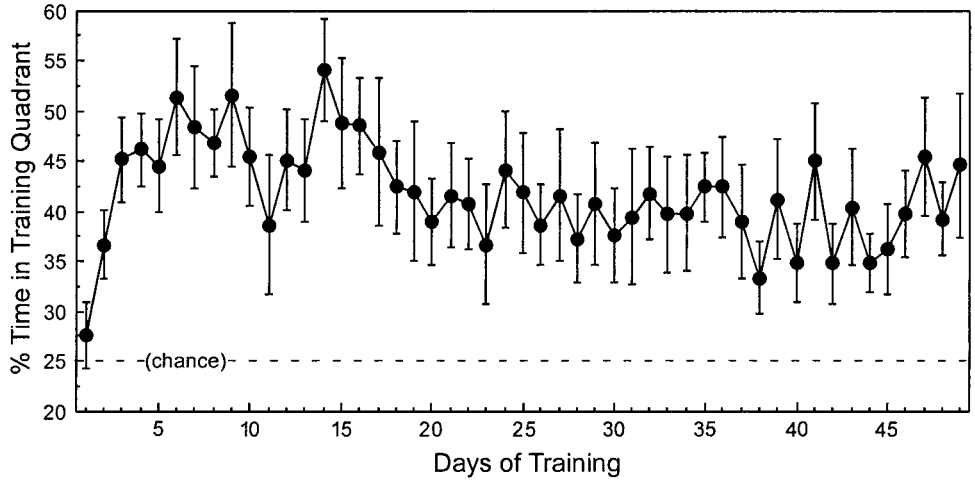

FIGURE 2. Acquisition performance. Percentage of time in the training quadrant during the first 30-s probe trial of each day, across the 49 days of training. Rats (n = 16) were given 8 trials each day for a total of 392 training trials for each rat. Dotted line indicates chance performance (chance = 25%). Error bars show SEM.

for the remainder of training. Indeed, a significant decline in performance did occur across training days 14–23 ($F[9] = 2.23$, $P < 0.05$).

This modest decline in performance appears to have a simple explanation. Presumably because of the extensive training beginning at an early age, rats exhibited less fear of the water than adult rats we have observed who have less water maze experience. Thus, later in training, the young rats in the present study would often leave the area of the hidden platform after it had been reached, and would continue to swim and explore the pool during the remainder of the 30-s probe trial. At the end of the 30-s probe trial, they would promptly return to the correct platform location to escape the water. Figure 3 illustrates this pattern of behavior.

Retention probes: percentage of time in training quadrant

Figure 4 shows the percentage of time that control rats and rats with hippocampal lesions spent in the training quadrant during the first 60-s retention probe trial (chance = 25%) and on the second and third probe trials. For the control group, the scores were 37.7 ± 4.1%, 49.0 ± 2.4%, and 50.2 ± 5.4% for probe trials 1, 2, and 3, respectively. All these scores were greater than chance (all $t > 3.1$, all $P < 0.02$). For the lesion group, the scores were 24.8 ± 0.9%, 29.4 ± 3.0%, and 31.8 ± 2.6% for probe trials 1, 2 and 3, respectively. For the lesion group, only the score on the third probe trial was greater than chance ($t[7] = 2.7$, $P < 0.05$). Finally, the control group performed better than the lesion group on all three probe trials (all $t > 3.1$, all $P < 0.01$).

Retention probes: latency to reach the platform location

On the first retention probe trial we measured the amount of time rats took to swim to a zone (30 cm in diameter) immediately surrounding the platform location. The mean latency for the control group to enter the zone around the platform location was 19.8 ± 6.6 s. The mean latency for the lesion group to enter the zone around the platform location was 47.6 ± 10.5 s (control vs. lesions group; $t[14] = 2.24$, $P < 0.05$).

DISCUSSION

Rats were given extensive spatial training in the water maze, beginning at 21 days of age. Training continued during 49 sessions over the course of 69 days. One hundred days after the completion of training, one-half of the rats received bilateral hippocampal lesions. The rats with lesions performed at chance on the first trial of the retention test. In contrast, control rats performed well above chance. Thus, there was no evidence of spared spatial memory in rats with hippocampal lesions, even when training extended across a good portion of early life and even when the training–surgery interval was more than 3 months. Indeed, if one identifies the time of learning as the time when performance was first above chance (the second training day), then the learning-surgery interval in this study was more than 5 months (67 days from the second training day to the completion of training plus 100 more days until surgery).

During the first retention probe trial, the lesion group spent 24.8% of the time in the training quadrant (chance performance = 25%), and the control group spent 37.7% of the time in the training quadrant. On the second and third probe trials, performance scores improved for both groups such that by the third probe trial the lesion group performed measurably above chance. This above-chance performance in the lesion group could reflect a "reminder" effect from the first two probe trials or it could reflect relearning (the probe trials were reinforced). It is interesting that similar improvement across probe trials has been noted previously in a study in which adult animals were

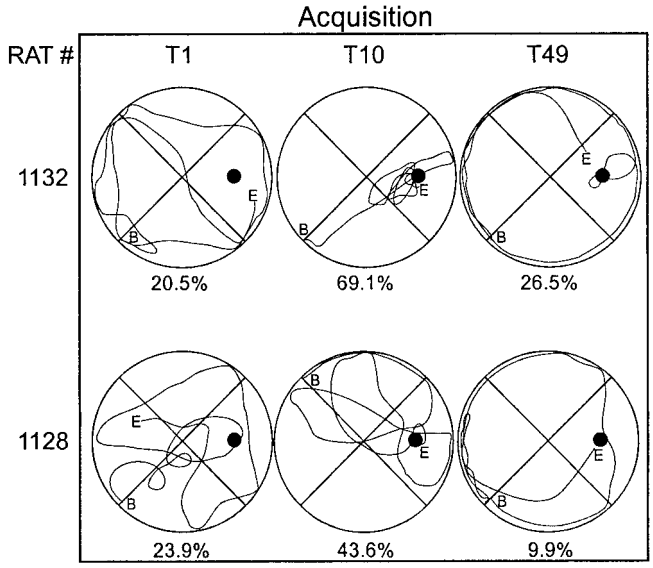

FIGURE 3. Performance of two rats (1132 and 1128) on three different occasions: at the beginning of training day 1 (T1), training day 10 (T10), and training day 49 (T49). Black circle in the center of the east quadrant indicates the platform location. Letters B and E on each path indicate the location of the rat at the beginning and end of the probe trial, respectively. Numbers below each track indicate the percentage of time the rat spent in the training quadrant on each probe trial. On T1, before any spatial training, neither rat exhibited a preference for the quadrant that contained the platform. On T10, both rats showed a strong preference for the trained quadrant. On T49, neither rat spent much time in the training quadrant during the probe trial. Yet, both paths indicate that, early in the probe trial, each rat swam to the platform location but then quickly left the area and explored the perimeter of the pool. Note also that at the end of the 30-s probe trial (denoted by letter E), both rats were returning to the correct platform location. This pattern of performance was exhibited consistently by all rats beginning about 20 days of training.

trained in the water maze (Clark et al., 2005). In that study, performance of rats given large hippocampal lesions 98 days after training improved from 26.1% on the first probe trial (chance = 25%) to above-chance levels on the second probe trial (39.9%). Controls improved from 31.2% to 54.5%. Again, the improvement could reflect a reminder effect produced by the first, reinforced probe trial or it could reflect relearning. It is also worth noting that above-chance performance was not observed on any probe trials in that study for animals given large hippocampal lesions only 1 day or 56 days after training. In any case, in the present study, the above-chance performance on probe trial 3 exhibited by the lesion group indicates that animals with large hippocampal lesions are capable of some spatial learning/memory ability. At the same time, performance on the first retention probe trial provides the most unambiguous measure of retention, and the findings from the first probe trial in the present study provide no evidence for retention of remote spatial memory after hippocampal lesions.

These findings can be contrasted with the results that have typically been observed after hippocampal damage in tasks of nonspatial memory such as trace eyeblink conditioning (Kim et al., 1995; Takehara et al., 2002, 2003), social transmission of food preference (Winocur, 1990; Winocur et al., 2001; Clark et al., 2002), and in tasks other than the water maze that appear to have a spatial component, such as contextual fear conditioning (Kim and Fanselow, 1992; Anagnostaras et al., 1999), but that do not require the animal to navigate to a specific point in space (for a discussion of this issue, see Clark et al., 2005). In all the studies just cited, as well as in others (for review, see Squire et al., 2004), hippocampal lesions made soon after training impaired performance, and lesions made at a later time had no effect.

The present findings can also be contrasted with reports from memory-impaired patients that remote spatial memory is spared after lesions that include the hippocampus (Teng and Squire, 1999; Rosenbaum et al., 2000). Thus, patient E.P., who has large bilateral lesions of the medial temporal lobe, was able to recall the spatial layout of the neighborhood in which he grew up more than 50 years earlier. He could mentally navigate, construct novel routes, and point correctly to landmarks while imagining himself at various locations. Yet E.P. has no knowledge of the neighborhood where he has lived since 1993, the year after he became amnesic (Teng and Squire, 1999).

Similarly, patient K.C., who has bilateral hippocampal damage in addition to other significant cortical damage, was also able to demonstrate considerable remote spatial memory (Rosenbaum et al., 2000). For example, K.C. performed as well as controls when he was asked to draw a detailed sketch map of his neighborhood, provide a detailed description of the most efficient route from one landmark to another (given that the most direct route was blocked), use heading vectors to navigate between two locations, judge distances between pairs of landmarks, and judge which of two landmarks was closest to a third landmark

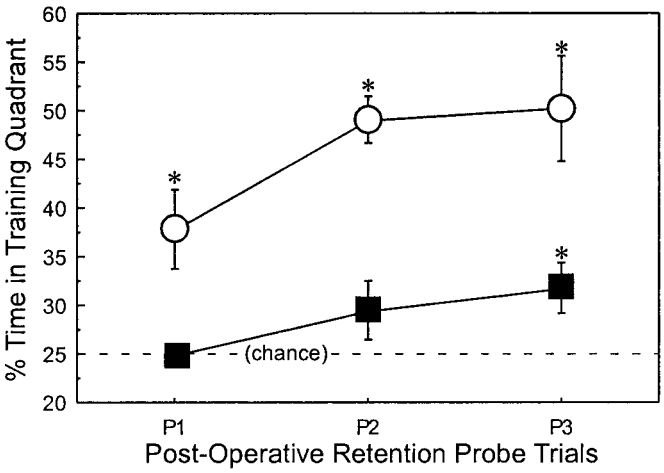

FIGURE 4. Retention test. Percentage of time in the training quadrant during three retention probe trials given 14 days after surgery and 114 days after training for control rats (white circles; $n = 8$) and rats with hippocampal lesions (black squares; $n = 8$). The control group performed better than the lesion group on all three probe trials. Asterisks indicate above chance performance (chance = 25%, $P < 0.05$). Error bars show SEM.

(Rosenbaum et al., 2000). Notably, he did have difficulty recognizing photographs of neighborhood landmarks, and had difficulty identifying the location of cities on a map. The authors suggested that this impairment reflected a lack of the incidental details and environmental features that provide for a rich spatial representation of a neighborhood. It is not obvious that recognizing landmarks or locating cities on a map requires more detailed spatial knowledge than the feats of route finding that K.C. performed successfully. Nonetheless, K.C.'s remote memory may not be entirely normal. However, it is important to note that K.C. has damage to the left frontal, left parietal, left retrosplenial, and left occipital cortex (Tulving et al., 1991; Rosenbaum et al., 2004), and it is therefore difficult to attribute whatever remote memory impairment he has to his hippocampal damage.

As discussed previously (for discussion, see Clark et al., 2005), one difference between these studies in humans and earlier studies in rats is that spatial learning in rats occurred during a limited period of time when the animals were adults, whereas the spatial learning studied in the patients occurred beginning at an early age and continued for many years. The present results appear to rule out the importance of this factor in understanding why the findings differ for rodents and humans. We established spatial memory in rats soon after they were weaned, and the memory was repeatedly rehearsed until the rats were young adults. Yet, these manipulations did not result in the sparing of remote spatial memory after hippocampal damage. Accordingly, these findings make the point that protocols involving the water maze are unlikely to reveal spared remote spatial memory after permanent hippocampal lesions.

The findings from the present study notwithstanding, other examples from work with rodents suggest that spatial memory can become independent of the hippocampus with the passage of time. For example, in a 5-arm radial maze expression of Zif268 was high in the hippocampus when testing occurred 1 day after training but substantially lower when testing occurred 30 days after training (Maviel et al., 2004). The opposite pattern (greatest Zif268 expression when testing occurred 30 days after training than when testing occurred 1 day after training) was found in widespread cortical regions including prefrontal, anterior cingulate, and retrosplenial cortices. These findings suggest that the hippocampus becomes less involved in the storage and retrieval of spatial memory during the 30 days after training and that cortical structures take on an increasingly important role. The effects of reversible lesions are consistent with this idea. Inactivation of the dorsal hippocampus by lidocaine 1 day after training impaired performance, whereas inactivation 30 days after training had no effect (Maviel et al., 2004). Spared remote memory after hippocampal (or fornix) lesions has also been reported in other tasks in which animals must use spatial information to discriminate between multiple arms of a maze (Cho et al., 1993; Ramos, 1998).

Winocur and colleagues have developed another paradigm where spatial memory appears to survive hippocampal lesions (G. Winocur, personal communication). In this case, rats became very familiar with a complex maze as a result of spending 8 h/day in the maze for 3 months. After this experience, the rats learned to find food (or water) at specific locations within the maze. Rats that were then given hippocampal lesions performed as well as control rats and better than other rats with lesions that had also been trained but that did not have the experience of living in the maze. The finding that knowledge of a highly familiar spatial environment can survive hippocampal lesions is consistent with the findings from memory-impaired patients (Teng and Squire, 1999; Rosenbaum et al., 2000).

It is interesting to consider that the rats in the just-described study would have become familiar with multiple routes to different goal locations (similar to the way in which humans become familiar with neighborhoods). It is possible that this variety of accumulated experiences with the maze (and with neighborhoods in humans) is an important feature that makes remote spatial memories resistant to hippocampal damage.

It is also interesting to note that in the water maze task, where expression of memory requires an animal to move to a specific location in space within a featureless open area, remote spatial memory has consistently been impaired after hippocampal lesions (Bolhuis et al., 1994; Mumby et al., 1999; Sutherland et al., 2001; Clark et al., 2005; present study). In contrast, in tasks where animals must use spatial information only to discriminate between arms of a maze (Cho et al., 1993; Ramos, 1998), remote spatial memory has been spared after hippocampal lesions.

One possibility is that hippocampal lesions deprive the animals of the rich spatial details that might be required to perform the water maze task, while leaving enough spatial "gist-memory" to discriminate arms of a maze. However, it is also possible that, in the water maze, hippocampal lesions might impair the ability to perform the task rather than impair memory of remotely acquired spatial information. That is, the navigational demands of expressing spatial memory in the water maze may require an intact hippocampus because navigation to a specific point in space requires new learning. Specifically, the animal may have to continually update (encode) its position in space in order to express any specific spatial memory (Knowlton and Fanselow, 1998). The idea is that such a requirement would impair the ability to express remote spatial knowledge. For example, an amnesic patient would not be expected to be able to express an otherwise intact spatial memory, if the performance test required moving along several routes and executing a number of turns. In this case, the memory demands of the performance test would exceed what can be maintained in immediate memory.

Interesting findings with the water maze task have recently been reported in rats with selective lesions of the direct entorhinal layer III projection (temporoammonic [TA]) to hippocampal area CA1 (Remondes and Schuman, 2004). The TA lesion spared the projection from entorhinal layer II (the perforant path) and the connection from CA1 neurons to the subiculum. Rats with this lesion acquired spatial memory in the water maze as well as control rats, although retention was impaired 28 days later. When rats were trained just before receiving the TA lesion, and then tested 28 days later, they performed at

chance. In contrast, if the TA lesion was delayed until 21 days after training, no impairment was observed. Remote spatial memory may be spared in this case because the lesion leaves intact intrinsic hippocampal circuitry with the result that new spatial learning can still occur, the task can be performed, and remote spatial memory can be expressed.

With permanent hippocampal lesions, it will be difficult to test the idea that hippocampal lesions impair performance, i.e., the expression of memory, rather than impair the storage and retrieval of a remote memory. Reversible lesion methods afford the important advantage that retention can be tested after the lesion has been reversed and during a time when the hippocampus is functional. Some progress has been made using reversible lesions in studies of spatial memory (e.g., Riedel et al., 1999; Maviel et al., 2004), and more work using this method will be useful.

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