HIPPOCAMPUS 18:996–1007 (2008)

The Extended Hippocampal-Diencephalic Memory System: Enriched Housing Promotes Recovery of the Flexible Use of Spatial Representations After Anterior Thalamic Lesions

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ABSTRACT: The anterior thalamic (AT) nuclei constitute an important component of an extended hippocampal-diencephalic system, and severe persisting memory deficits are normally found after AT damage. This study examined whether postoperative enrichment promotes the recovery of the flexible use of spatial representations in rats with AT lesions. After training to swim from a single constant start position to a submerged platform in a Morris water maze, rats with AT lesions that were housed in standard cages (AT-Std) performed poorly when required to swim to the platform from novel start positions during probe trials. By contrast, rats with AT lesions but housed in enriched environments (AT-Enr), like sham-lesion rats, showed relatively little disruption when tested with novel start positions. AT-Std rats also initially showed impaired acquisition of the task, whereas AT-Enr rats learned at a similar rate to that of the Sham-Std group. Beneficial effects of enrichment were replicated in the subsequent standard water maze procedure that used varying start positions throughout training to acquire a new platform location. Although it is clear that AT damage can severely disrupt episodic-like memory processes, and appear to be a core part of the interlinked neural systems subserving episodic memory, the current findings strongly encourage study on the adaptive response of the brain to thalamic lesions and prospects for the development of rehabilitation programs in cases of anterograde amnesia associated with diencephalic injury. © **2008 Wiley-Liss, Inc.**

KEY WORDS: anterior thalamus; diencephalic amnesia; hippocampal-diencephalic system; enriched environment; allocentric spatial memory

INTRODUCTION

There has been increasing recognition that hippocampal-diencephalic interactions provide an important substrate for declarative memory processes (Aggleton and Brown, 1999; Moscovitch et al., 2005; Piekema et al., 2007). Even though several thalamic regions may contribute to learning and memory, damage to the anterior thalamic nuclei (AT), in particular, is associated with severe anterograde amnesia in humans and a disconnection syndrome that often resembles with that produced by medial temporal lobe pathology (Warrington and Weiskrantz, 1982; Parkin et al., 1994; Kopelman et al., 1999; Harding et al., 2000; Van der Werf et al., 2000; Sullivan and Marsh, 2003; Van der Werf et al., 2003a,b; Gold and Squire, 2006). The impact of specific AT injury has been confirmed by experimental evidence of substantial impairments in spatial memory, memory for the temporal order of nonspatial items, and the acquisition of object-place associations, which are similar to deficits found after hippocampal lesions (Aggleton et al., 1996; Byatt and Dalrymple-Alford, 1996; Sziklas and Petrides, 1999; Warburton and Aggleton, 1999; van Groen et al., 2002; Mair et al., 2003; Moran and Dalrymple-Alford, 2003; Mitchell and Dalrymple-Alford, 2005, 2006; Gibb et al., 2006; Wolff et al., 2006). These similarities are presumed to reflect the many direct and indirect anatomical connections between the hippocampal formation and the AT (Aggleton et al., 1986; Shibata, 1993; van Groen et al., 1999). The importance of an extended hippocampal memory system may also explain why early cases of semantic dementia have less severe episodic memory deficits than those with early Alzheimer's disease, because both dementias have comparable medial temporal lobe atrophy, but only the latter dementia is associated with dysfunctional limbic-diencephalic networks (Nestor et al., 2006).

The long-lasting memory deficits that follow bilateral AT lesions, together with evidence of similar deficits after disconnection lesions of the AT and the hippocampal system, add considerable weight to the potential importance of this thalamic region as a core part of a distributed system supporting episodic memory (Warburton et al., 2000, 2001; Henry et al., 2004; Aggleton and Brown, 2006). Given this perspective, and the severity of the amnesic syndrome that often results from diencephalic injury, there is considerable merit in determining whether memory deficits produced by AT lesions are amenable to experimental therapeutic intervention. We have recently shown that postoperative-enriched housing conditions, even when introduced 40 days after AT lesion surgery, markedly improved the otherwise permanent and severe spatial working memory deficits revealed using a forced-choice alternation procedure in a cross-maze (Loukavenko et al., 2007). There was, however, no

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Accepted for publication 26 April 2008
DOI 10.1002/hipo.20457
Published online 11 June 2008 in Wiley InterScience (www.interscience.wiley.com).

beneficial effect of enrichment on the lesion-induced deficits in acquiring fixed spatial discriminations in a radial-arm maze, irrespective of the difficulty of the pattern separation between the arms used. This pattern of findings raises the question of whether reference memory in general is resistant to the effects of an enriched environment in rats with AT lesions. More importantly, the cross-maze procedure provided unambiguous evidence of improved working memory, but it was not clear that the overall improvement reflected allocentric spatial memory specifically. Thus more explicit behavioral evidence is required before we can address the issue of how critical the interdependency of the hippocampus and the AT is for episodic-like memory processes. If enriched environments facilitate the expression of allocentric spatial memory in rats with AT lesions, then this would provide strong support for potential opportunities for therapeutic intervention in the human domain.

One of the most important features of allocentric spatial memory, in the context of its association with declarative memory, is that it reflects the use of relational spatial representations such that overlapping representations can be synthesized to generate new behavior based on their flexible use in novel test conditions (Eichenbaum, 2000). A convincing example of this kind of spatial learning was provided by a procedure introduced by Eichenbaum et al. (1990). When trained from a constant start position in a Morris water maze, rats with fornix lesions were able to learn the location of a fixed platform, but they performed extremely poorly during subsequent probe trials that examined their ability to swim to the same platform location from previously unused start points, whereas intact rats readily located the platform when challenged with these novel positions. Electrolytic dorsal hippocampal lesions in rats also elicit similar effects with initial training from a single start position (Compton et al., 1997). Thus training to locate a submerged platform from a single start position, when followed by probe trials that question performance by using new start positions, provides a particularly clear test for the flexible use of relational spatial representations and recovery of a critical facet of declarative memory. Although the potential of enriched environments to improve spatial memory after brain injury has been examined previously (Will et al., 2004; Nithianantharajah and Hannan, 2006), it is not yet known whether this aspect of allocentric spatial memory and the associated deficits after hippocampal-diencephalic injury are amenable to therapeutic intervention.

After examining the influence of AT lesions and enrichment on Eichenbaum's task, we examined whether enrichment also influences performance in the standard procedure with four different start points that vary across trials, using acquisition to a new platform location. It was expected that rats with AT damage would have moderate to severe acquisition deficits when tested with this conventional procedure, coupled with evidence of a preference for the target quadrant during a probe trial (Warburton et al., 1997; Wolff et al., in press), as is often the case after hippocampal system damage (Bannerman et al., 1999; Zhang et al., 2004). Any beneficial effect of enrichment in this second task would reinforce the value of this intervention in terms of allocentric spatial reference memory.

MATERIALS AND METHODS

Subjects and Housing Conditions

Female PVGc hooded rats, bred in-house and weighing 180–220 g (10 months old) at surgery, were housed in standard (Std) groups of three or four in opaque plastic cages (27 cm × 45 cm wide × 22 cm high), except for those rats that were housed for 40 consecutive days in an enriched environment (Enr) 2 weeks after lesion surgery. For enriched housing, groups of 12 rats were maintained in a large wire mesh cage (85 cm × 60 cm wide × 30 cm high) in which numerous objects were renewed on a daily basis as was the position of food and water as well as the position of the cage in the colony room. After 40 days of continuous enrichment, the Enr rats were housed in standard plastic cages during the day (reversed light schedule, off 8 am to 8 pm), but returned to the enriched environment overnight (lights on). Testing occurred during the dark portion of the cycle. Food and water was available ad libitum. All protocols conformed to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of the University of Canterbury.

Surgery

Anesthetized rats (75 mg/kg pentobarbitone, 20 min after atropine at 0.12 mg/kg, ip) were placed in a stereotaxic apparatus with the incisor bar set 7.5-mm below the interaural line to minimize or avoid fornix injury. After craniotomy, neurotoxic AT lesions were made using microinfusions of 0.12 M NMDA (Sigma Chemicals, Australia) dissolved in phosphate buffer pH 7.20 via a 1-μl Hamilton 7001 syringe connected to a motorized infusion pump. The Hamilton needle (25S, outer diameter: 0.51 mm; inner diameter: 0.13 mm) remained in situ for 3 min after each infusion to allow for diffusion prior to its slow retraction (see Table 1 for details and coordinates). Sham surgery followed identical procedures except that the Hamilton needle was lowered into the cortex without any infusion. After a 2-week recovery period, AT and sham rats were randomly allocated to enriched housing or standard housing, resulting in four groups: AT-Enr (n = 12, prior to lesion analysis), AT-Std (n = 13, prior to lesion analysis), Sham-Enr (n = 12), and Sham-Std (n = 12). New cage-mates, including both AT and Sham rats, were present in each cage for both standard and enriched housing conditions.

Water Maze

The circular pool, 180 cm in diameter and 40 cm high, was located to one side of a 5.4 m × 4.0 m windowless room, which provided numerous distal cues (sink, tables, posters, door, curtain fittings) and was illuminated by table lights, over-

TABLE 1.

Coordinates and Infusion Rates for the NMDA Lesions of the Anterior Thalamus (AT)

	AT	
	Anterior	Posterior
AP coordinates for B-L distance (cm)		
0.60–0.61	−0.24	−0.25
0.62–0.63	−0.25	−0.26
0.64–0.66	−0.26	−0.27
0.67–0.72	−0.27	−0.28
ML (cm)	±0.120	±0.150
DV (cm)	−0.580	−0.555
Volume (μ1, 0.12 M)	0.09	0.11
Infusion rate (μl/min)	0.03	0.03

The anterior-posterior (AP) coordinates relative to Bregma varied with the Bregma-Lamda (B–L) distance obtained for any given rat when in the stereotaxic apparatus. ML = lateral to the midline; DV = dorsoventral from dura.

head fluorescent lights, and a double halogen lamp that faced one corner of the room (Fig. 2E). The pool was filled with water (30-cm depth) maintained at 22°C and rendered opaque by the addition of nontoxic acrylic white paint (Educational Colors P/L, Australia). A movable circular (10 cm in diameter) Perspex platform was located inside the pool, the top of which rested 1-cm below the surface of the water at the center of the target quadrant. Data were collected using a video-camera fixed to the ceiling and subsequently analyzed using a video-tracking system (Ethovision 3.1, Noldus), which provided measures of escape latency, path length, and swim speed.

Behavioral Procedures

All training and testing was conducted after the continuous 40-day period of postoperative differential housing. On two successive days, the rats were given a familiarization trial in the pool by being placed near to and encouraged to climb onto the hidden platform located at the center of the pool. During these trials, a beige curtain surrounded the pool to minimize the acquisition of spatial information and the rats were guided to the platform by the experimenter's hand if they had not escaped onto the platform after 60 s. All rats were then trained on the two successive spatial memory tasks in the water maze. The rat was allowed to remain on the platform for 15 s after the completion of any given acquisition trial and gently guided to the hidden platform if it failed to locate the platform after 60 s. The intertrial interval (ITI) was about 6 min in both tasks and the water was stirred between trials.

Task 1—Constant Start Position: Locating a Fixed Hidden Platform

The first task was adapted from the procedure described by Eichenbaum et al. (1990), which used only a single constant start point for all acquisition trials (here, "S," see Fig. 2E). Unlike Eichenbaum's procedure, we used a hidden platform from the start of training and its position was located further from the start point (E quadrant). By subsequently challenging the rat to locate the same platform location by using probe trials with uniquely novel start locations, this procedure examined spatial learning when the usual requirement for the acquisition of flexible spatial representations was minimized and tested whether the spatial representations created using this procedure could be used in a flexible manner when subsequently required in novel situations. After 10 days of testing using the constant start position for each of the four daily trials, probe trials with new start positions were introduced on Days 11, 12, and 13. During probe-trial testing, the number of daily trials was increased to six. The additional trials enabled the third and sixth trials on each of these days to be probe trials with one of six novel start positions (SE, SW, W, NW, N, NE; Fig. 2E), used only once, whereas the remaining trials continued with the previous constant start position (i.e., Trials 1, 2, 4, and 5). Performance on these six novel-start position trials was then compared with that from the six immediately preceding trials (2nd and 5th), per Eichenbaum et al. (1990). Two weeks after completion of this first task, a conventional probe trial (60 s) was given for which the platform was removed and the rat released from the constant start point used during acquisition of the task. This test assessed long-term recall of the platform location based on swims from the initial constant start position.

Task 2—Standard Task: Acquisition of a New Platform Location Using Variable Start Positions

To examine the acquisition of spatial memory with variable start points, the hidden platform was switched to a new location in the opposite quadrant (W; see Fig. 3C). Testing in the standard procedure, for 8 days, began the day after the conventional probe test for Task 1 (15 days), using four daily trials. Each trial used one of the four counterbalanced start positions (NW, NE, SW, and SE) that were different to the constant start position used for Task 1. On the ninth day a conventional probe trial was introduced, with the platform removed, and preference for the four quadrants was assessed for a 60-s duration.

Histology

At the completion of the experiment, all rats were transcardially perfused with cold saline followed by 4% formalin. The brains were removed and postfixed for 2 days in 4% formalin and cryoprotected in 30% sucrose. Frozen coronal 50-μm sections were obtained with a cryostat and all sections throughout the thalamic region were stained with cresyl violet. MW and JDA agreed the lesion extent in each rat using the relevant plates of a rat brain atlas (Paxinos and Watson, 1998) while blind to any individual behavioral data. These lesions were replicated on electronic copies of the atlas so that automated

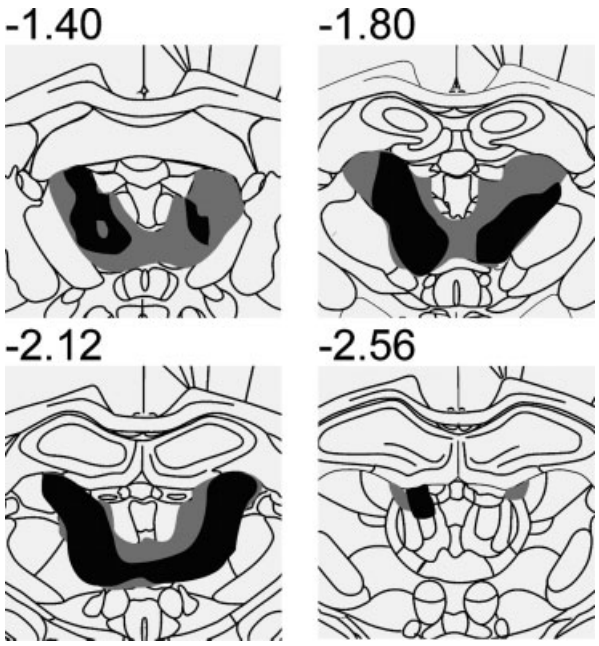

FIGURE 1. Schematic representation of the smallest (black) and largest (gray) anterior thalamic lesions (schematic modified from Paxinos and Watson, 1998). Distances in the figure are relative to the atlas Bregma, but note that a different stereotaxic head orientation was used for the lesion surgery (incisor bar −7.5 mm below the interaural line). The lesions were comparable across the group housed in enriched environments and that housed in standard (grouped) cages (see Results section).

pixel counts of the damaged regions could be used to estimate lesion volumes by factoring in the distances provided by the atlas. Collapse of areas surrounding the AT lesion and variation in angle of sections required a conventional visual, rather than direct image, analysis.

RESULTS

Histology

Figure 1 depicts the largest and smallest AT lesions that met an a priori criterion of at least 50% injury to the AT region together with minimal damage to adjacent thalamic regions. These adjacent regions may also contribute to some learning deficits, whereas excitotoxic AT lesions that are smaller than 50% damage generally produce only minor or less severe deficits (Hunt and Aggleton, 1998; Mair et al., 2003; Mitchell and Dalrymple-Alford, 2005). Among rats with acceptable AT lesions, the 10 rats housed in standard group conditions (AT-Std rats) and the nine rats housed in enriched conditions (AT-Enr rats) sustained equivalent AT injury, with a median of 69.0% (range: 50.7–99.3%) and 70.7% (range: 51.2–92.0%) damage, respectively. In these AT rats, there was only minimal damage to the adjacent lateral thalamic nuclei (comprising the rostral intralaminar nuclei and lateral mediodorsal thalamic nuclei), with a median of 15.6% (range: 3.3–38.0%) and 12.9% (range: 4.1–39.5%) damage in the AT-Std and AT-Enr groups, respectively. There was also only minor damage to the more medial thalamic nuclei (comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus), with a median of 2.4% (range: 1.0–18.1%) and 3.3% (range: 0.9–20.4%) damage in the AT-Std and AT-Enr groups, respectively. Median damage to other thalamic structures was minimal with the exception of the interanteromedial nucleus, which received substantial injury in most but not all AT rats (Std: 74.8%, range: 3.2–90.5%; Enr: 70.1%, range: 2.4–88.3%); laterodorsal nucleus, Std: 8.4% (range: 4.2–10.7%), Enr: 8.8% (range: 4.1–30.3%); paratenial nucleus, Std: 15.0% (range: 4.2–42.2%), Enr: 8.6% (range: 1.0–17.0%); rhomboid nuclei, Std: 3.6% (range: 0.0–10.4%), Enr: 4.8% (range: 0.0–13.2%); paraventricular plus posterior paraventricular nuclei, anterior paraventricular nucleus, and reuniens nucleus, all intact in both Std and Enr rats. Six rats were excluded from analysis, four because of the insufficient damage to the AT (two Std: 26.1 and 41.8%; and two Enr: 34.2 and 39.3%) and two because the damage to the adjacent thalamus was excessive (one Std: 50.0% AT damage, but 55.6% damage to the adjacent lateral region; and one Enr: 98.7% AT damage, but 64.5% damage to the adjacent lateral region). The four rats excluded due to insufficient damage to the AT performed better than the included AT rats and virtually no impairment was evident in the enriched cases. The two rats excluded for additional damage to the adjacent thalamus exhibited impairments that were comparable to the rest of their respective group, but were not included because of the a priori lesion criteria.

Behavior

The path length taken to locate the hidden platform provided the primary performance measure for the two tasks, as this measure is independent of swim speed (Contet et al., 2001; Wolff et al., 2002). Performance was also examined in terms of standard escape latency.

Task 1—Constant Start Position: Locating a Fixed Hidden Platform

Acquisition

The first task was adapted from the procedures described by Eichenbaum et al. (1990). Rats were required to find a platform in a fixed location (center of the E quadrant) from only one start position (S; white arrow) that remained constant for all four trials per day during the acquisition phase, but in our case the platform was hidden throughout the training and was more distant from the start position (see Fig. 2E). As shown in Figure 2A, all groups produced similar path lengths on the first day, which reduced across the 10 days of acquisition [$F(9,351) = 65.91$, $P < 0.0001$]. The most important finding during this phase was that postoperative enrichment led to substantially improved acquisition, especially in the AT-Enr group. Although the AT-Std group demonstrated a clear deficit in

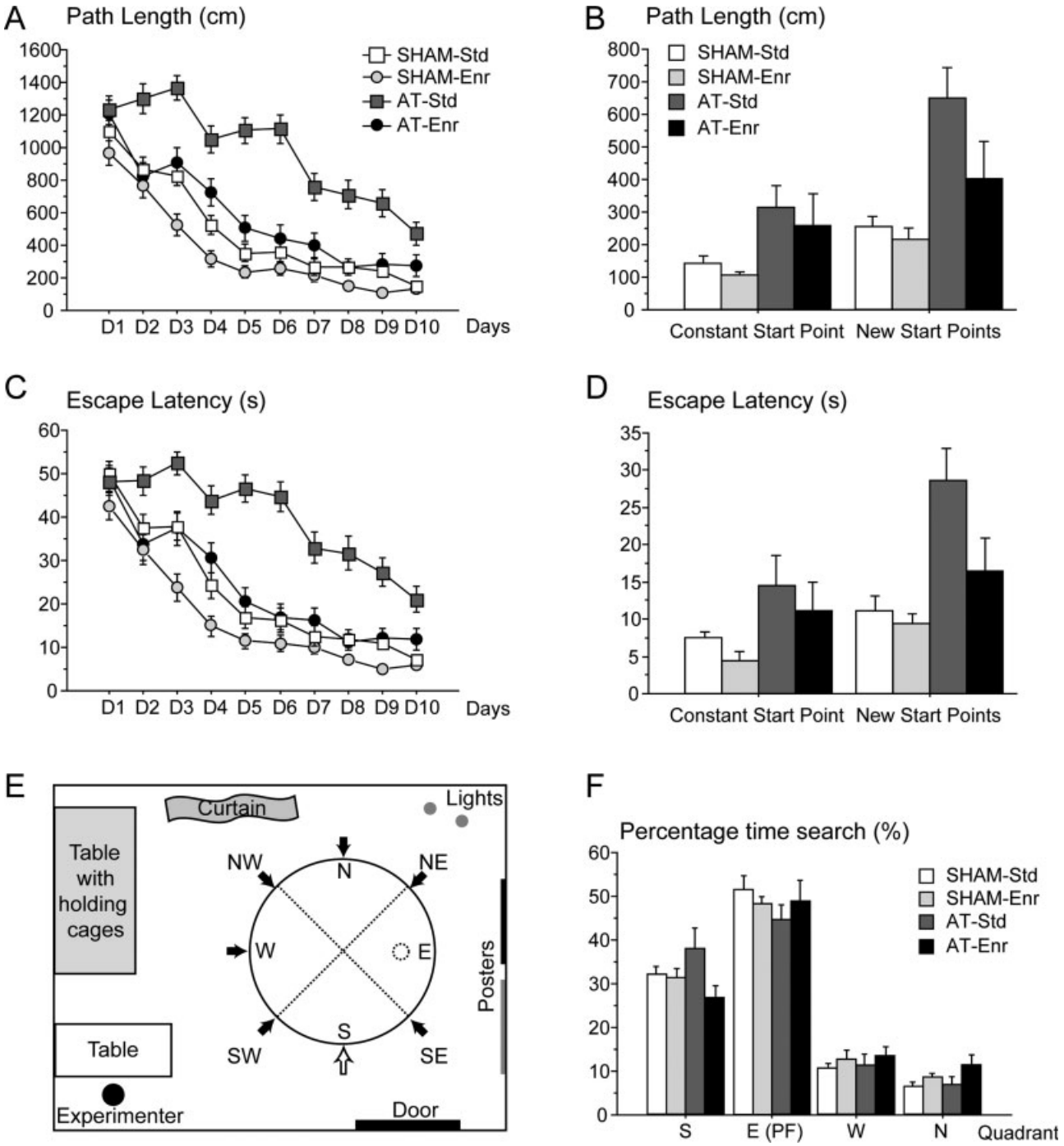

FIGURE 2. Task 1: Spatial reference memory during initial acquisition to locate a submerged platform in the East quadrant from a constant start position (blocks 1–10; mean of four daily trials per block, ± SEM) and subsequent probe tests (platform remained in place) comparing performance using novel start points as opposed to the previous constant start point. A schematic representation of the room is provided in (E) showing the constant start position (white arrow; throughout acquisition and for the 1st, 2nd, 4th, and 5th trials of 3 days of probe testing) and the novel start positions (black arrows; 3rd and 6th trial per day of probe testing). Performance is expressed as mean path length (cm, A and B, initial acquisition and probe testing, respectively) and escape latency (s, C and D, initial acquisition and probe testing, respectively); the six new start positions were contrasted with the immediately preceding trials that used the constant start position (2nd and 5th trials on each day of probe testing). (F) The percent time search in each quadrant during the conventional probe trial (removal of the platform, PF) when started from the constant start point, 14 days after novel start probe tests is shown.

acquiring the location of the hidden platform, the AT-Enr and Sham-Std groups exhibited similar mean path lengths across acquisition testing and the Sham-Enr group showed an even faster rate of acquisition. Nonetheless, the AT-Std group attained good performance by the end of acquisition. These observations were supported by highly significant Lesion [$F(1,39) = 55.14$, $P < 0.0001$] and Housing [$F(1,39) = 30.78$, $P < 0.0001$] effects, as well as significant Lesion × Housing [$F(1,39) = 7.91$, $P < 0.01$] and Lesion × Day [$F(9,351) = 2.65$, $P < 0.01$] interactions, whereas the Lesion × Housing × Day interaction approached significance [$F(9,351) = 1.78$, $P = 0.07$]. Over the 10 days of testing, the Housing effect was significant in both Sham rats [$F(1,22) = 12.15$, $P < 0.01$] and AT rats [$F(1,17) = 16.97$, $P < 0.001$]. The same statistical conclusions were evident for escape latency (Fig. 2C) with significant main effects of Day [$F(9,351) = 61.79$, $P < 0.0001$], Lesion [$F(1,39) = 36.29$, $P < 0.0001$] and Housing [$F(1,39) = 28.57$, $P < 0.0001$], as well as significant Lesion × Housing [$F(1,39) = 5.51$, $P < 0.05$] and Lesion × Day interactions [$F(9,351) = 3.08$, $P < 0.01$]. For this measure, the Lesion × Housing × Day interaction was also significant [$F(9,351) = 2.26$, $P < 0.05$]. In terms of swim speed, rats with AT lesions swam slightly more quickly than those with sham lesions [Lesion effect, $F(1,39) = 6.06$, $P < 0.02$], irrespective of housing [Housing effect and Housing × Lesion, $Fs < 1$] but swim speeds were similar at the end of the acquisition. The means (±standard deviation (SD)) in cm/s for the averaged swim speeds across the 10 days were as follows: Sham-Std: 23.2 (±4.0); Sham-Enr: 23.6 (±4.3), AT-Std: 25.4 (±4.31); AT-Enr: 24.6 (±3.8).

Probe trials using new start positions

On Days 11, 12, and 13, two novel start positions were used each day, on the third and last of six daily trials, so that six new start positions in total were employed (see Fig. 2E). Figure 2B shows the mean path length taken by the four groups for the probe trials that used the six new start points when compared with the six immediately preceding trials (second and fifth trials per day) that used the constant start position (S) that had been used previously during the 10 days of acquisition training. The two sham groups displayed shorter (i.e., more precise) path lengths than the two lesion groups when tested from the constant start point, but all four groups performed accurately during these "regular" trials. There was, however, no longer any difference between the AT-Enr group and the AT-Std group when seeking the platform from the constant (regular) start point, as the latter group continued to improve relative to their performance during the previous acquisition trials. The introduction of the new start points produced an increase in the path lengths taken by all groups [Start Position: novel vs. constant, $F(1,39) = 44.12$, $P < 0.0001$]. Although one novel finding was that rats with AT lesions required much longer path lengths to find the platform from the novel start positions [Start Position × Lesion, $F(1,39 = 6.18$, $P < 0.05$], the most important finding was that this relative increase was substantial in the AT-Std group, whereas the relative increase in the AT-Enr group on these probe trials was similar to that shown by the two sham groups [Start Position × Lesion × Housing interaction, $F(1,39) = 4.20$, $P < 0.05$]. The same conclusions in terms of the effects of enrichment in AT rats were evident from the analysis of escape latencies (Fig. 2D), which were longer for the new start points [novel start positions vs. constant start position, $F(1,39) = 41.54$ $P < 0.0001$]. Although rats with AT lesions showed increased escape latencies when tested on the new start positions [Start Position × Lesion [$F(1,39 = 5.99$, $P < 0.05$], this measure again showed that AT-Enr rats performed far better than the AT-Std rats on these trials [Start Position × Lesion × Housing interaction [$F(1,39) = 4.38$, $P < 0.05$]. Difference scores across new start point trials versus constant start trials revealed significant Lesion × Housing interactions for both path length and escape latency [$F(1,39) = 4.20$, $P < 0.05$, and $F(1,39) = 4.38$, $P < 0.05$, respectively]. For both difference measures, the Lesion simple main effect was significant for the two standard groups [$F(1,20) = 7.57$, $P < 0.02$ and $F(1,20) = 7.36$, $P < 0.02$, respectively], but there were no differences between the Sham-Enr and AT-Enr groups [$F(1,19) < 1.0$ for both measures]. Thus, the beneficial effect of postoperative enrichment extended to the ability to find the hidden platform from novel start positions, after training to locate the platform from only one fixed start point, showing that the flexible use of allocentric spatial memory representations was restored in the AT-Enr rats. There were no significant effects in terms of swim speed during probe testing.

Probe trial—Long-term retention with platform removed

Retention of the position of the platform was assessed 2 weeks after completion of acquisition training, using a classic probe trial for which the platform was removed. All rats were placed in the pool at the constant ("regular") start point used during initial acquisition. In terms of percentage time spent in each quadrant (Fig. 2F), all groups exhibited strong preference for the previously correct quadrant [$F(3,117) = 174.28$, $P < 0.0001$], regardless of Lesion [$F < 1$] or Housing condition [$F(1,39) = 2.26$, $P > 0.1$; Lesion × Housing, $F < 1$]. Similarly, there were no between-group differences when the analysis was restricted to the time spent in the correct quadrant only [Lesion, $F(1,39) = 1.16$, $P > 0.2$; Housing, $F < 1$; Lesion × Housing, $F(1,39) = 1.78$, $P > 0.1$)] or the number of platform crossings [Lesion, $F < 1$; Housing, $F(1,39) = 1.39$, $P > 0.2$; Lesion × Housing, $F(1,39) = 2.84$, $P > 0.1$)]. The mean number of platform crossings (±SD) were as follows: Sham-Std: 2.2 (±0.5); Sham-Enr: 1.9 (±0.4), AT-Std: 1.8 (±0.4); AT-Enr: 3.2 (±0.6). Thus, 2 weeks after the end of acquisition and testing with probes requiring swims from new positions to the hidden platform, retesting the rats from the initial start position with a conventional probe trial revealed that all groups focused their search on the previously correct quadrant (E) and the previous location of the platform.

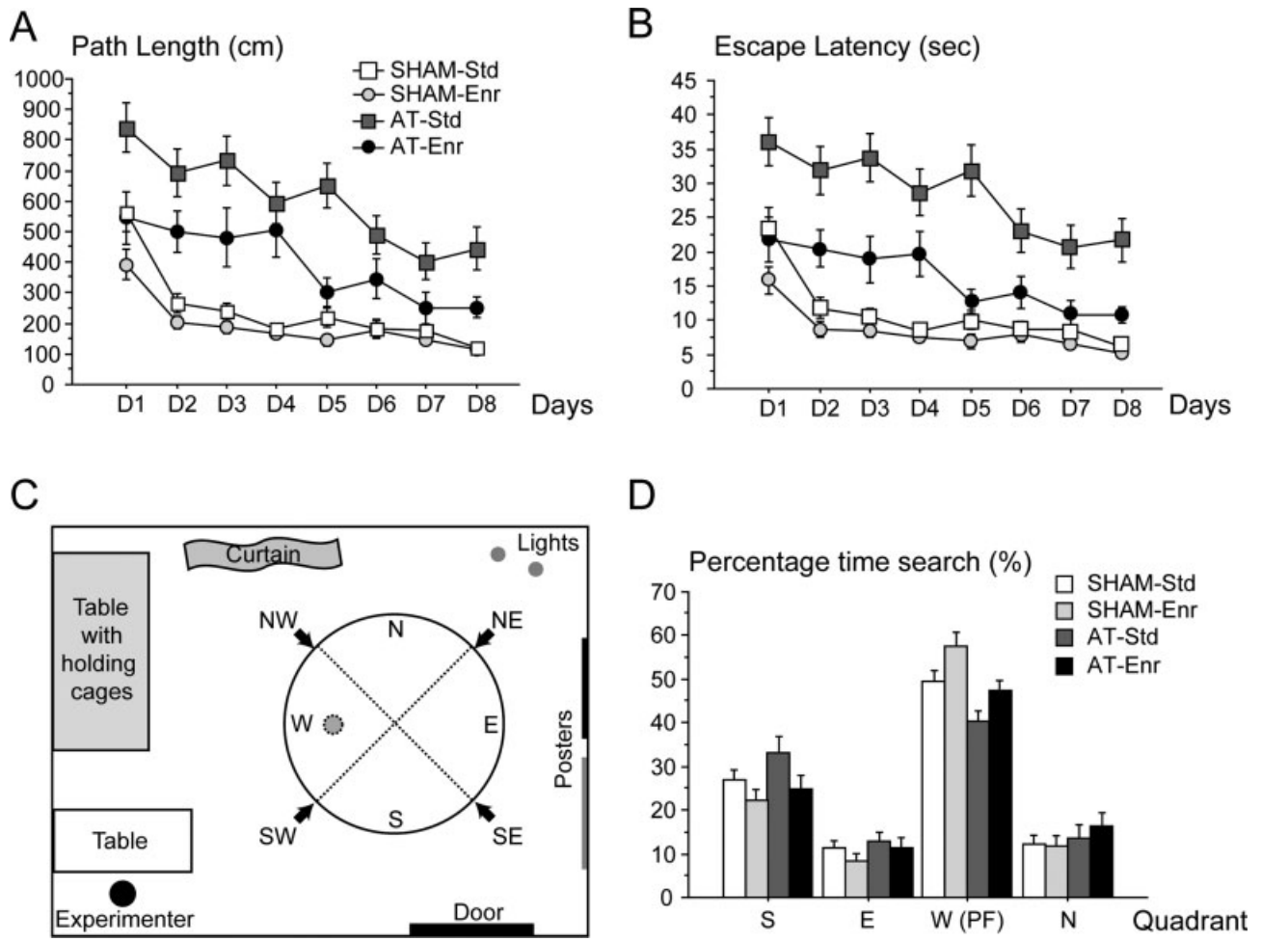

FIGURE 3. Task 2: Spatial reference memory performance (mean ± SEM) using the standard procedure of four different start points per day for the acquisition of the location of the submerged platform (PF) that was switched to the West quadrant (A: path length, cm; B: escape latency) and the subsequent conventional probe trial (D: percentage time search in each quadrant with platform removed). A schematic representation of the room is provided on (C), with black arrows corresponding to the four counterbalanced start points used for the second task, which began the day following the conventional probe test for the first task.

Task 2—Standard Task: Four Start Positions, New Hidden Platform Location

Acquisition

The day after the conventional probe was used for Task 1, the platform was switched to a new location (W quadrant) and rats were trained for 8 days using the conventional procedure (i.e., four trials a day using four different start positions in a pseudorandom order that varied each day; see Fig. 3C). On the first day of testing in the second task, all groups showed relatively poor performance, but the AT-Std group, in particular, performed more inadequately than the other three groups, with equal mean performance shown by the AT-Enr and Sham-Std groups and slightly better performance shown by the Sham-Enr group (Figs. 3A,B). All groups subsequently improved their performance [$F(7,273) = 19.38$, $P < 0.0001$ and $F(7,273) = 17.18$, $P < 0.0001$, for path length and latency, respectively], but clear differences between groups were evident across the 8 days of testing. The sham groups learned the new position of the platform by the second day of testing and improved thereafter, whereas AT rats failed to reach a similar level of performance, which produced highly significant effects of Lesion [$F(1,39) = 52.31$, $P < 0.0001$ and $F(1,39) = 38.43$, $P < 0.0001$, for path length and latency, respectively] and significant Day × Lesion interactions [$F(7,273) = 2.78$, $P < 0.01$ and $F(7,273) = 2.82$, $P < 0.01$, for path length and latency, respectively]. Although the AT-Enr group performed worse than the two sham groups, postoperative enrichment still substantially reduced the lesion-induced impairment relative to that shown by the AT-Std group, which was confirmed by significant Housing effects [$F(1,39) = 11.02$, $P < 0.01$ and $F(1,39) = 13.42$, $P < 0.001$, for path length and latency, respectively] and a significant Lesion × Housing interaction [$F(1,39) = 5.68$, $P < 0.05$] for latency, whereas the Lesion × Housing interaction for path length just failed to reach significance [$F(1,39) = 4.01$, $P = 0.052$]. Consistent with the probe trials of the first task, mean swim speeds no longer differed between groups.

Conventional probe trial

After completion of acquisition for Task 2, the rats received a probe trial the following day in which the platform was removed (Fig. 3D). Based on the percentage of time spent in each quadrant, all groups exhibited a strong preference for the new correct quadrant (W) that had contained the platform [$F(3,117) = 130.56$, $P < 0.0001$]. Although there were no main effects for Lesion ($F < 1$) or Housing [$F(1,39) = 2.25$, $P > 0.1$], there were significant Quadrant × Lesion [$F(3,117) = 4.66$, $P < 0.01$] and Quadrant × Housing [$F(3,117) = 4.04$, $P < 0.01$] interactions. Restricting the analysis to the correct quadrant for the new position of the platform revealed a beneficial effect of enrichment [$F(1,39) = 6.52$, $P < 0.05$] and a detrimental effect of the lesion [($F(1,39) = 9.90$, $P < 0.01$), but no Housing × Lesion interaction ($F < 1$)], with the AT-Enr group showing similar preference to that of the Sham-Std group for the previously correct quadrant. A beneficial effect of enrichment was also supported by the analysis of the number of platform crossings [Housing, $F(1,39) = 7.93$, $P < 0.01$]. The mean number of crossings (±SD) was as follows: Sham-Std: 2.2 (±0.5); Sham-Enr: 3.5 (±0.4); AT-Std: 1.5 (±0.5); AT-Enr: 2.8 (±0.4). This measure was not significantly affected by lesion status ([$F(1,39) = 2.25$, $P > 0.1$]; Lesion × Housing interaction [$F < 1$]). Thus, at the end of Task 2, all groups were clearly able to identify the new correct quadrant, but there was some evidence of a beneficial effect of enrichment in both sham rats and rats with AT lesions. There were no differences in terms of time spent in the quadrant in which the platform had been located during the first task.

DISCUSSION

This study showed that postoperative enrichment can promote the flexible use of allocentric spatial representations in rats with AT lesions and, to our knowledge, provides the first report of a beneficial effect of enriched environments on an explicit assessment of the flexible use of spatial memory representations. Training rats to swim from a constant single start point to a submerged platform held in a fixed position in a water maze encourages the establishment of spatial representations that emphasize escape-specific associations, either with simple direction or a relatively fixed set of extra-maze cues and a relatively fixed swim trajectory (Eichenbaum et al., 1990). As multiple visual cues were available during training, a strong test of whether these representations can be used in a flexible manner was provided by the comparison of performance on probe trials that used novel start positions and those trials that used the previous constant (regular) start position. As expected, rats with AT lesions that were housed in standard conditions showed a substantial deficit when probe trials with new starts were used that explicitly challenged the flexibility of the spatial representations that they had acquired. It is therefore particularly impressive that AT rats housed in enriched environments, like sham rats, showed accurate and only mildly decreased performance for these probe trials. As the performance of the AT-Enr group and that of the AT-Std group was comparable on the "regular" trials during probe testing, and as the size and extent of the AT lesions was comparable in the two groups, the dramatically superior performance shown by the AT-Enr group on the novel-start probe trials provides convincing evidence for recovery of both allocentric spatial reference memory in general and its flexible use in novel task demands. Although a diversity of strategies may help a rat to learn the location of a platform (e.g., Oswald and Good, 2000; Zheng et al., 2003), the use of probe testing after training from a constant start point makes it unlikely that the improvement in enriched AT rats reflected the engagement of multiple strategies to solve the probe task.

The failure of AT-Std rats to use the representations gained during initial training in the constant start procedure to locate the platform rapidly when challenged with new views of the environment provides a new similarity between the effects of AT lesions and those of hippocampal system damage. This finding reinforces the view that both the AT and the hippocampus are normally critical components of an integrated hippocampal-diencephalic system. The poor performance by the AT-Std group during initial acquisition with the constant start procedure is a modest difference to the more mildly impaired acquisition shown by rats with fornix or hippocampal lesions (Eichenbaum et al., 1990; Compton et al., 1997). There have been some reports that AT, fornix, and hippocampal lesions may not always produce equivalent deficits, with mixed differences found in terms of conditional memory tasks that test the acquisition of various contextual or visually guided arbitrary associations (Sziklas and Petrides, 2002, 2004, 2007). Sometimes, rats with AT lesions show more severe spatial memory and conditional learning deficits than that shown by rats with fornix injury (Sziklas et al., 1998; Sziklas and Petrides, 1999; Warburton and Aggleton, 1999). However, we believe that procedural differences probably account for the discrepancy between this study with AT rats and those with hippocampal system lesions when trained in the water maze with a constant start procedure. In the study by Eichenbaum et al. (1990), rats were first purposefully trained with a visible platform and a fading procedure (about 8–9 sessions), to increase the chance that they would use a direct escape trajectory, and only then trained to acquire the same location of a submerged platform (another 9–10 sessions). As in this study, Compton et al. (1997) also omitted the use of a visible platform during acquisition training, but it seems likely that the explanation for the poorer acquisition shown by AT rats housed in standard conditions, when compared with that shown by rats with hippocampal lesions, was the position of the escape platform. The platform was placed in a quadrant immediately adjacent to their constant start point in the studies by Eichenbaum et al. (1990) and Compton et al. (1997), but further away in a nonadjacent quadrant in this study. Nonetheless, the main new effect of AT lesions in this study, namely poor performance when probe trials were introduced that used new start positions, closely replicated the findings with hippocampal system lesions (Eichenbaum et al., 1990; Compton et al., 1997).

Although the AT rats did not reach as precise performance as that shown by the sham rats on the current constant-start task, this does not negate the ameliorative impact of enrichment on the subsequent probes that used novel start positions, because the two AT groups were equivalent when tested from the constant start point during probe testing. Moreover, performance during the initial acquisition phase of the constant start procedure provided another striking example of the benefits of enrichment in the case of AT lesions in rats. Indeed, the rate of acquisition shown by the AT-Enr group paralleled with that of the Sham-Std group until the very end of testing. Enrichment also conferred an improved rate of acquisition in sham rats in the constant start procedure. These findings are generally consistent with evidence that enrichment tends to improve the rate of learning in the Morris maze, both in intact rats and in rats with brain injury, although previous work has only employed conventional testing procedures that do not directly challenge the flexibility of allocentric spatial representations and may depend on many other strategies or factors (Galani et al., 1997; Frick and Fernandez, 2003; Jankowsky et al., 2005; Pereira et al., 2007).

Our second task employed the conventional procedure of training the rats to locate a submerged platform from four start positions that varied across trials within each daily session, which again reflects the use of relational properties of ambient cues to find an escape location as well as elements of behavioral flexibility because the platform was moved to the quadrant opposite to that used during the initial constant start procedure. The magnitude of the amelioration in the enriched AT rats as compared with those housing in standard conditions was consistent with the clear improvements observed for the first (constant start procedure) task. During the conventional probe test for the first task, on the day prior to training on the second task, all groups demonstrated strong recall of the previously correct training quadrant (E), which confirmed that the second task demanded an element of reversal learning in its early stages. The profound deficit by AT-Std rats to learn a new location in this reversal learning procedure again provides similarity to the deficits in rats with hippocampal system lesions evident when standard, cued, or fixed start-position training protocols are used (Eichenbaum et al., 1990; Whishaw and Tomie, 1997). Although the AT-Enr group once again showed clear evidence of superior acquisition for this second task when compared with the AT-Std group, the performance of the AT-Enr group was also clearly inferior to that of both sham groups. Significantly, the rapid acquisition of the reversal response by the sham groups contrasted with the far slower acquisition shown by the AT-Std group and to a lesser extent than that shown by the AT-Enr group. This difference implies that although the acquisition of allocentric spatial memory was markedly enhanced by enrichment in AT rats, some aspects of behavioral flexibility may have been impaired despite the use of enriched housing. Conversely, it is possible that the improvements seen in the second, standard task actually benefited from the prior exposure to training from a constant start location. That is, we cannot be sure that the benefits of enrichment on the flexible use of spatial representations would be greater or less if training commenced with varying start positions.

This study provides a significant extension to prior work from our laboratory that housing in an enriched environment can promote recovery of memory function after thalamic injury (Loukavenko et al., 2007). This previous work provided robust evidence that enrichment reduced the severe and long-lasting deficits in a spatial working memory task in AT rats housed in standard conditions. There was clear evidence for some improvement in the use of either allocentric and/or directional cues to solve working memory problems in the alternation task, because AT-Enr rats performed above chance when the test run used the opposite start direction to that used for the sample run, but T-mazes and plus-mazes are particularly likely to encourage the use of multiple strategies and cues even in sham rats (Futter and Aggleton, 2006). This limitation, plus the lack of enrichment effects when AT rats showed deficits in acquiring discriminations between one of the three arms in a radial maze, restricted the generality of the conclusions from the previous study in terms of spatial memory. This study showed that AT-Enr rats are able to make use of overlapping spatial representations to guide novel allocentric responses in a Morris water maze when probe tests imposed previously unexperienced demands only once the standard behavioral task had been acquired. It is therefore uncertain why the AT-Enr rats in the previous study did not show improvements in the acquisition of simultaneous spatial discriminations, particularly in the instance when the radial-maze arms were adjacent and the spatial cues to guide performance would engage spatial pattern separation processes that were presumably utilized by the enriched AT rats in the tasks used in the present study. It is likely that subtle procedural differences in the cognitive demands of various tasks may have contributed to these differences. The radial-arm maze used previously enclosed the rat inside the central hub from which the rat was required to make a choice, whereas both the use of more distant start positions and more open environments afforded by the elevated plus-maze used for the alternation task and the Morris maze used here would more readily encourage the use of distal environmental cues and path integration strategies. In addition, vestibular stimulation by passive rotation of the rats during the previous radial-arm maze testing, which is known to impair the use of spatial information (Zheng et al., 2003; Kirwan et al., 2005), may have adversely disrupted the AT-Enr rats in the previous study.

Enriched environments are known to influence a diverse array of morphological and biochemical changes in the rat brain (Will et al., 2004). AT damage is known, however, to be associated with widespread limbic system dysfunction (Jenkins et al., 2002) and the specific recovery of allocentric spatial memory in the two tasks used here encourages speculation that enrichment may influence one or more of the various interconnected neural systems that subserve spatial memory (Aggleton et al., 2000). For instance, AT lesion-induced reductions in c-Fos activity are most dramatic in the retrosplenial cortex (Jenkins et al., 2004) and the same pattern can be seen after

hippocampal lesions (Albasser et al., 2007). Similarly, it has been suggested that the stimulation of acetylcholine (ACh) release in the hippocampus is decreased following thalamic injury (Savage et al., 2003, 2007) and even that the volume of the hippocampus itself may be subtly diminished following diencephalic damage (Kopelman et al., 2003). Evidence that enrichment induces changes in the hippocampal formation (most notably in the recent literature, neurogenesis; Olson et al., 2006) and the prefrontal cortex (Del Arco et al., 2007a,b) is consistent with an hypothesis that the enrichment effects in this study may be related to changes in multiple relevant brain regions. The possibility that enrichment encourages recovery, rather than sparing of loss of function in the immediate consequences of injury to the AT, is supported by evidence that an enriched environment produced substantial long-term improvements in spatial working memory even if its introduction was delayed until 40 days postsurgery and after spatial working memory deficits had been elicited (Loukavenko et al., 2007).

A global approach such as the use of enriched environments is attractive because it is generally recognized that the distinction between pathologies from damage to the temporal lobe and the diencephalon may have only limited value (Parkin et al., 1994; Sullivan and Marsh, 2003; Caulo et al., 2005; Gold and Squire, 2006). Despite success in revealing substantial improvements by using enrichment in rats with AT lesions, their behavior remained less efficient than that of intact rats, and additional tests of episodic-like memory are warranted that include questions concerning when or what events occur at given locations (Eacott et al., 2005; Kart-Teke et al., 2006). Secondary treatments, including a pharmacological approach, may also be necessary before a convincing case is made for translation of the current line of research to the human domain of diencephalic amnesia. But these findings pose an intriguing prospect and may add to knowledge concerning the adaptive response of hippocampal-dependent processes to thalamic injury.

Acknowledgments

The authors gratefully acknowledge the support of the Neurological Foundation of New Zealand and the Department of Psychology of the University of Canterbury. MW was supported by a Lavoisier postdoctoral fellowship from the French Government; EAL was supported by a NZ Tertiary Education Commission Top Achiever Doctoral Scholarship; and BEW was supported by a Canterbury Erskine Fellowship.

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