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Anterior but not intralaminar thalamic nuclei support allocentric spatial memory

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Abstract

Medial thalamic damage is a common cause of severe memory disruption in humans. Both the anterior thalamic nuclei (ATN) and the intralaminar thalamic nuclei (ILN) have been suggested as primary sites of diencephalic injury underlying learning and memory deficits, but their respective roles have yet to be resolved. The present study explicitly compared two spatial memory tasks in male PVGc hooded rats with selective neurotoxic lesions to either (1) the ATN or (2) the rostral ILN (and adjacent lateral mediodorsal thalamic nuclei; ILN/LT lesions). As predicted, the ATN group, but not the ILN/LT group, exhibited clear deficits in the Morris water maze task for the initial acquisition of a fixed hidden platform and its reversal to a new position. The second task examined acquisition of egocentric spatial reference memory for a left or right body turn, using any three arms in an 8-arm water maze on any given trial; contrary to predictions, both lesion groups performed as well as the Sham group. The lack of deficits in ILN/LT rats on this second task contrasted with previous findings reporting a detrimental effect of ILN/LT lesions on egocentric working memory. The clear dissociation between the influence of ATN and ILN/LT lesions with respect to allocentric spatial reference memory in the Morris maze emphasizes that caution is required when interpreting the effects of non-ATN thalamic lesions on spatial memory when the lesions encroach substantial areas of the adjacent ATN region.

Keywords: Anterior thalamic nuclei; Intralaminar thalamic nuclei; Allocentric spatial memory; Egocentric spatial memory; Water maze; Rat

1. Introduction

Medial thalamic injury is a common cause of severe memory disruption in humans (Kopelman, 2002; Van der Werf, Witter, Uylings, & Jolles, 2000; Van der Werf et al., 2003). The critical thalamic regions that contribute to diencephalic amnesia are, however, unclear as non-specific brain damage often occurs in clinical cases. Separate lines of evidence in rat lesion models have focussed on the anterior thalamic nuclei (ATN) or the adjacent intralaminar thalamic nuclei (ILN) as two key regions that are likely to cause memory impairment after injury (Aggleton & Brown, 1999, 2006; Aggleton & Pearce, 2001; Mair, 1994; Mair, Burk, & Porter, 2003). Unfortunately, the interpretation of many of these experimental studies is confounded by the potential influence of overlap in lesion extent or the use of conventional lesions that disrupt the complex fiber pathways that traverse this region. The present study explicitly addressed this problem by providing a direct comparison between the effects of highly selective neurotoxic lesions to the ATN and the ILN in rats using behavioral tasks that compared different spatial abilities.

Previous studies that examined lesions targeted at either the ATN or ILN provide some indications as to the comparative learning and memory processes that are

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disrupted by injury to these regions. The view that the ILN play a significant role in learning and memory is supported by delay-independent memory deficits in rats with ILN lesions when tested in a variety of matching and non-matching to sample tasks, including object, auditory, olfactory, retractable-lever and maze-arm stimuli (Bailey & Mair, 2005; Burk & Mair, 1998; Harrison & Mair, 1996; Young, Stevens, Converse, & Mair, 1996; Zhang, Burk, Glode, & Mair, 1998). Damage to the ATN is most commonly associated with allocentric spatial memory impairment (Byatt & Dalrymple-Alford, 1996; Celerier, Ognard, Decorte, & Beracochea, 2000; Mitchell & Dalrymple-Alford, 2005; Moran & Dalrymple-Alford, 2003; van Groen, Kadish, & Wyss, 2002; Warburton & Aggleton, 1999; Warburton, Baird, & Aggleton, 1997), which may reflect an interdependency between the ATN and the hippocampal system (Warburton, Baird, Morgan, Muir, & Aggleton, 2000, 2001). Such findings support the hypothesis that the ATN and the hippocampus constitute essential components of an extended system underlying episodic memory (Aggleton & Brown, 1999; Aggleton & Pearce, 2001), which is consistent with recent studies on clinical cases that emphasize the deleterious effect of ATN damage in diencephalic amnesia (Caulo et al., 2005; Gold & Squire, 2006; Harding, Halliday, Caine, & Kril, 2000). A severe impairment in allocentric spatial memory in the Morris water maze has also been reported in rats with ILN lesions (Mair, Burk, & Porter, 1998; Savage, Castillo, & Langlais, 1998), but it is unclear whether encroachment of these ILN lesions to the adjacent ATN can account for these results (Mair et al., 2003). In a similar vein, there is mixed evidence whether the extension to adjacent thalamic structures also contributes to spatial memory impairments found after large ATN lesions (Warburton & Aggleton, 1999; Warburton, Morgan, Baird, Muir, & Aggleton, 1999; Warburton et al., 1997).

Recent studies have begun to focus on more selective, subtotal lesions to the ATN and the ILN. For example, Mair and his colleagues have shown that ATN lesions induce a delay-dependent impairment when varying arms in a radial maze are used for a non-matching to sample task (Mair et al., 2003), whereas restricted ILN lesions have no effect (Bailey & Mair, 2005). Our laboratory has explicitly contrasted rats with selective ATN and ILN lesions that have as minimal overlap as possible from one region to the next. As these ILN lesions included the adjacent lateral region of the mediodorsal (MD) thalamic nucleus, we have previously labeled these "lateral thalamic" (LT) lesions. This lateral MD region is impossible to avoid when making neurotoxic ILN lesions, but all the nuclei in this ILN/LT region have overlapping prefrontal and striatal connections (Berendse & Groenewegen, 1991; Mitchell & Dalrymple-Alford, 2005; Van der Werf, Witter, & Groenewegen, 2002). We found that ATN lesions severely impaired preoperatively-trained working and reference memory in a radial-arm maze, whereas rats with ILN rats exhibited only a very mild and transient working memory deficit (Mitchell & Dalrymple-Alford, 2005). A second study revealed a double dissociation in which only ATN lesions impaired the post-operative acquisition of spatial working memory in a radial-arm maze, whereas only ILN lesions produced a deficit on a preoperatively acquired response-related (egocentric) working memory task in a cross maze (Mitchell & Dalrymple-Alford, 2006). However, both ATN and ILN lesions produced severe impairments when the rats were required to learn arbitrary associations between an odor and a place (Gibb, Wolff, & Dalrymple-Alford, 2006), an ability that also requires the functional integrity of the hippocampus (Gilbert & Kesner, 2002). Together with uncertainty in terms of their effects on acquisition of spatial memory in the water maze, the latter finding suggests that the ATN and the ILN may sometimes produce similar impairments on learning and memory tasks and that both perhaps mediate some aspects of hippocampal-dependent learning.

A direct examination of the involvement of these two thalamic regions on spatial memory that does or does not require the hippocampus is therefore warranted. Hippocampal system functions are believed to support allocentric spatial memory but not egocentric spatial processing, whereas the reverse is generally true of the dorsal striatum (Cook & Kesner, 1988; DeCoteau & Kesner, 2000; Kesner, Bolland, & Dakis, 1993; McDonald & White, 1993, 1994; Morris, Schenk, Tweedie, & Jarrard, 1990; Packard & Teather, 1998). It is particularly interesting that one perspective that has emerged from the recent thalamic lesion literature is that ILN lesions, but not ATN lesions, impair egocentric spatial working memory tasks (Bailey & Mair, 2005; Mair et al., 1998, 2003; Mitchell & Dalrymple-Alford, 2006), which is consistent with the above-mentioned fact that some of the prominent connections of the ILN/LT region are with the dorsal striatum and dorsal prefrontal cortex (Van der Werf et al., 2002). If ILN/LT lesions impair functions associated with the dorsal striatum, then these thalamic lesions should also disrupt other egocentric spatial memory and response-related learning tasks that have been shown to be sensitive to caudate lesions. A severe impairment with dorsal caudate lesions has been reported when rats were trained on a left/right discrimination task in a Y-maze, especially when distal spatial cues are minimized (Mitchell & Hall, 1987, 1988). As ATN damage appears to influence hippocampal-dependent, allocentric spatial memory, but does not appear to disrupt egocentric (response-related) spatial reference memory (Aggleton, Hunt, Nagle, & Neave, 1996; Warburton et al., 1997), we tested the prediction that selective ATN and ILN lesions would produce a double dissociation across spatial memory in the Morris water maze and a water adaptation of left/right discrimination in a Y-maze. The use of two swimming tasks ensured that the basic motivational and motor requirements remained the same while the spatial memory demands differed across the two tasks.

2. Methods

2.1. Subjects and housing conditions

Male PVGc hooded rats, bred in-house, were maintained in groups of three or four in standard opaque plastic cages (27 cm × 45 cm wide × 22 cm high). All rats were housed under a reversed light schedule (off 8am to 8pm) and testing occurred during the dark phase of the cycle. Food and water was available ad libitum. They were 7–8 months old with a mean body weight of 355 g at surgery and were 8–9 months old at the start of testing. 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.

2.2. Surgery

Anesthetized rats (100 mg/kg pentobarbitone, 20 min after atropine at 0.12 mg/kg, ip) were placed in a stereotaxic apparatus with atraumatic ear bars (Kopf, Tujunga, CA) and the incisor bar set 7.5 mm below the interaural line to minimize or avoid fornix injury. After craniotomy, neurotoxic AT ($n = 12$) and ILN/LT lesions ($n = 12$) 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 (needle: 25S, outer diameter 0.51 mm; inner diameter 0.13 mm) connected to a motorized Stoelting microinfusion pump (Reno, NV). Two bilateral lesion sites were used to maximize ATN damage, directed at the anteroventral nucleus (AV) and the anteromedial nucleus (AM). To improve target accuracy, one of four anterior–posterior coordinates was used based on an individual rat's bregma to lambda (B–L) distance (in millimetres). For the AV lesion, the AP coordinates from bregma were: −2.2 for B–L = 6.0 and 6.1; −2.3 for B–L = 6.2 and 6.3; −2.4 for B–L = 6.4–6.6 and −2.5 for B–L larger than 6.6. The AV lesion was ±1.50 mm lateral from the midline and −5.70 mm ventral from dura. The AM lesions followed an identical scheme except that lesions were placed ±1.10 mm lateral from the midline, −5.90 mm ventral from dura and 0.1 mm more anterior than the AV site. The volumes of NMDA injected were 0.11 μl for the AV and 0.09 μl for the AM site. For the ILN/LT lesions, three bilateral sites were used at two different AP coordinates (same AP coordinates for the most anterior site where two injections were made). As for the ATN lesions one of four anterior–posterior coordinates was used based on an individual rat's B–L distance. For the anterior site, the AP coordinate from B to L were: −3.3 for B–L = 6.0–6.1; −3.4 for B–L = 6.2–6.3; −3.5 for B–L = 6.4–6.6 and −3.6 for B–L larger than 6.6. At the anterior sites, the infusions were made at −5.50 DV and then at −5.90 from dura. For the posterior sites an identical scheme was followed except that the lesions were −0.4 mm more posterior and only one ventrality site (DV −5.50) was used. All sites were ±1.50 mm lateral from the midline and all NMDA volumes were 0.05 μl. The needle remained in situ for three min after each injection to allow for diffusion. After verification of the lesions the final group number was $n = 8$ for ATN and $n = 9$ for ILN/LT rats (see Section 3.1. Histology). Sham surgery ($n = 10$) followed identical procedures except that the Hamilton needle was lowered into the cortex without any infusion. Behavioral training commenced two weeks after surgery.

2.3. Apparatus

The first task used a circular pool, 180 cm in diameter and 40 cm high, located in a large windowless room providing numerous distal cues (sink; tables; posters; door; drawn curtain fittings) and illuminated by table lights and overhead fluorescent lights. The pool was filled with water (30 cm) maintained at 22 °C and rendered opaque by the addition nontoxic acrylic white paint (Educational Colours P/L, Australia). The surface of the circular (10 cm diameter) Perspex platform was 1 cm below water level. Data were analyzed using a video-tracking system (Ethovision 3.1, Noldus) to provide measures of escape latency, swim speed, path length and mean distance to the platform. The mean distance to the platform measure, which is based on the average distance between the subject and the center of the platform, is useful because it is totally independent of latency and thus of swim speed. A low value generally reflects spatial strategies characterized by correct initial orientations toward the platform, which minimize the distance between the subject and the goal (Buhot et al., 2003).

The second task used a clear Perspex radial-arm water maze that comprised eight arms (16 cm wide × 45 cm long) radiating from a central area (40 cm diameter), placed in a different room. The 10 cm long platform used for that task occupied the entire width of the end of an arm, resting 1 cm below the water surface. Removable clear Perspex doors block access to arms that were not used on any given trial. Throughout testing for this second task, the entire apparatus was surrounded by a beige curtain to minimize distal visual cues.

2.4. Behavioral procedures

2.4.1. Pretraining

After the post-surgery recovery, rats were familiarized to swim in the pool, during which time the pool was surrounded by a beige curtain to minimize spatial information. Two familiarization trials were used to encourage the rats to climb onto the hidden platform located at the center of the pool, being guided there by the experimenter's hand if 30 s had elapsed. Four additional pretraining trials (each 30 s maximum) occurred on the subsequent day in which a cued platform (mounted by a 5 cm high black tube) was placed in a different quadrant for each trial, again with additional shaping by the experimenter's hand if 30 s had elapsed. These trials were used to ensure that all rats had demonstrated some escape behavior and experienced swimming throughout the entire pool. All rats were then trained on the two successive spatial memory tasks, using first standard water maze procedures, followed by radial-arm water maze testing.

2.4.2. Task 1—allocentric spatial memory in a water maze

For the allocentric spatial reference memory task, the hidden platform was located in a fixed position throughout 6 days of testing, using four daily trials with different cardinal start points presented in a pseudorandom order and counterbalanced across rats and across days. Rats were trained in squads of 11–12, with an intertrial interval (ITI) of about 10 min. At the beginning of a trial, the rat was placed gently in the water facing the pool wall and allowed a maximum of 60 s to find the platform (and guided towards the platform otherwise). The day after initial acquisition (Day 7) a 60 s probe trial was given for which the platform was removed. The start point for the probe trial was the farthest from the vicinity of the platform and was the same for all rats. At the end of the 60 s probe trial, the rat was reminded of the previous location of the platform by being guided there before removal from the pool. Two days after the probe trial, acquisition of a new platform location was examined using 4 days of testing. The procedure was exactly the same as for the initial acquisition, except that the hidden platform was now located at the center of the quadrant opposite to where it had been located previously.

2.4.3. Task 2—egocentric spatial memory in a radial-arm water maze

This task began four weeks after completion of Task One. A 2-day pretraining period was used to acclimate the rats to the new apparatus and conditions. For pretraining, the rat was placed on the platform for 10 s at the end of a randomly chosen arm and then placed in the central area with only that arm accessible. Formal testing started on the following day. Rats were placed at the end of a start arm, pseudorandomly-chosen from any of the eight available arms, facing towards the central arena. Three arms were open, the start arm and two evenly spaced goal arms that were 90° apart to create a "Y-shaped" maze. Variation of the start-arm and related goal arms for the Y-maze configuration on each trial ensured that allocentric place learning could not lead to successful performance and that rats had to rely on (egocentric) body-turn cues. One goal-arm of the Y contained the submerged platform at the distal end, while the incorrect arm had no platform. Rats were required to swim out of the start arm and choose between the two goal arms. A choice was defined by the rat's hind feet being inside an arm. Re-entries into the start arm were not

counted as a choice. If the rat made an incorrect choice it was allowed to self-correct but guided to the correct arm after two incorrect goal-arm entries. For half of the rats the correct response was to select the goal arm to the left of the start arm whereas the arm to the right of the start arm was correct for the other rats, using a counterbalanced procedure. Rats were given four daily trials (ITI of about 6–8 min) for 4 days and then eight daily trials for the remaining 8 days of testing when the two daily sessions conducted 3 h apart (one in the morning and one in the afternoon).

2.5. Histology

At the completion of testing all rats were transcardially perfused with cold saline followed by 10% formalin. The brains were removed and post-fixed overnight and coronal 50 μm sections were obtained with a vibratome throughout the thalamic region. One-in-five sections were immunostained for NeuN (Jongen-Relo & Feldon, 2002) while the remaining sections were processed using Cresyl Violet. For NeuN, free-floating sections were washed several times in 0.1 M PBS containing 0.3% of Triton X-100 (PBST) and treated with 0.5% H_2O_2 in PBST to quench endogenous peroxidase. The sections were incubated overnight at room temperature with the mouse monoclonal anti-NeuN antibody (Chemicon, MAB377) diluted at 1:5000 in PBST. The next day, the sections were rinsed several times and then incubated for 2 h with biotinylated horse anti-mouse serum (Vector Laboratories, BA-2001) diluted at 1:1000 in PBST containing 1% of Horse Serum (Vector Laboratories, S-2000). After further rinses, the sections were incubated for 2 h in 1:200 avidin–biotin–horseradish peroxidase complex (ABC elite, Vector Laboratories) and visualized using a 0.001% diaminobenzidine in 0.0004% H_2O_2 solution. The reaction was stopped by cold PB rinses and sections were mounted and dried on gelatine-coated slides. MW and JDA agreed the lesion extent in each rat using the relevant plates of a rat brain atlas (Paxinos & Watson, 1998) while blind to any individual behavioral data. These lesions were replicated on electronic copies of the atlas so that automated 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 ATN and ILN/LT lesions and variation in the angle of sections required a conventional visual, rather than direct image, analysis.

3. Results

3.1. Histology

As in previous work (e.g., Gibb et al., 2006), acceptable lesions were defined as having significant (50%) bilateral damage to the intended target as long as there was little damage to the comparison region (i.e. ATN or ILN/LT). Fig. 1 shows the largest and smallest acceptable ATN (Fig. 1A) and ILN/LT (Fig. 1B) lesions as well as typical ATN (Fig. 1C) and ILN/LT (Fig. 1D) lesion visualized with NeuN staining. Four ATN rats and three ILN/LT rats experienced either a failed or small lesion and were discarded from behavioral analysis. Three of the excluded ATN rats had minimal visible damage and were not examined further, while the fourth had 32.6% ATN damage and 0.4% ILN/LT damage and showed intermediate performance during initial acquisition of the allocentric spatial memory task compared to the Sham controls and the group with at least 50% ATN damage. One excluded ILN/LT rat had minimal visible damage; one had 41.7% ILN damage and 19.5% ATN damage; and the third had 41.1% ILN damage and 7.3% ATN damage. Apart from the above-mentioned ATN rat, none of these discarded rats

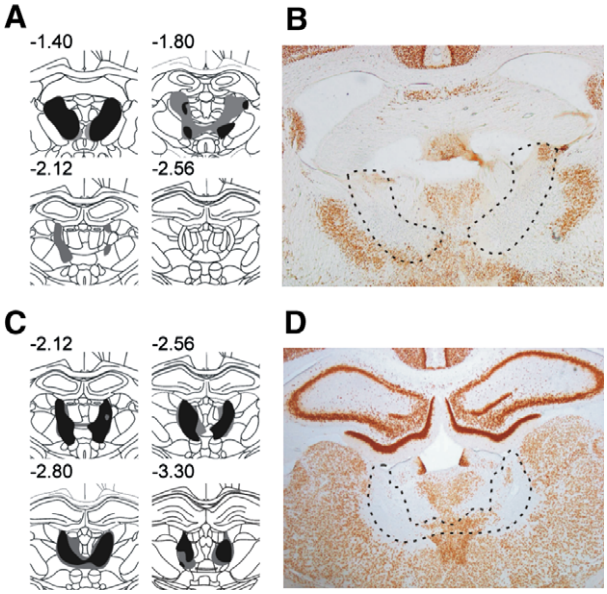

Fig. 1. Schematic representation of the smallest (gray) and largest lesions for the anterior thalamic lesion group (ATN; A) and the intralaminar/lateral thalamic lesion group (ILN/LT; B). (C) Representative ATN lesion, NeuN protein stain; (D) same for ILN/LT lesion. The ATN and ILN/LT regions are depicted by the area within the dashed line in (C) and (D), respectively.

were impaired in either task. In the acceptable 8 ATN rats there was a median of 71.8% damage (range: 53.0–89.5%) to the ATN, but only 3.7% damage (range: 1.8–8.2%) to the ILN/LT region, with 1.4% damage (range: 0.5–2.8%) to the remaining mediodorsal (MD) region. This MD region is of interest because it may give rise to some memory impairments, although allocentric deficits appear to require additional ATN damage (Hunt & Aggleton, 1998; Mitchell & Dalrymple-Alford, 2005). In the acceptable 9 ILN/LT rats there was a median of 64.2% damage (range: 59.5–74.1%) to the ILN/LT, but only 1.3% damage (range: 0.1–11.5%) to the ATN region and 22.3% damage (range: 10.9–54.6%) to the remaining MD region. Two ILN/LT rats had significant damage to the MD region (52.1% and 54.6%, respectively), but performed equally to other rats from that group on both tasks and were thus retained for all behavioral analyses. Median damage to other thalamic structures including midline nuclei was generally minimal to modest with the exception of the interanteromedial nucleus (ATN rats: median, 35.7%, range: 14.4–48.5%; LT rats: median, 0.0%, range: 0.0–32.0%) and the parataenial nucleus (ATN rats: median, 21.0%, range: 2.1–47.3%; LT rats: median, 0.0%, range: 0.0–5.3%). Little or no damage occurred to other thalamic nuclei adjacent to the ATN and ILN/LT: laterodorsal nucleus: ATN rats, 0.5% (range: 0.0–1.9%) and ILN/LT rats, 2.6% (range: 0.8–4.0%); paraventricular and posterior paraventricular nuclei: ATN rats, 0.0% and ILN/LT rats, 0.0% (range: 0.0–1.6%); anterior paraventricular nucleus: ATN rats, 0.0% (range: 0.0–21.7%) and ILN/LT rats, 0.0%; reuniens nucleus: ATN rats, 0.4% (range: 0.0–4.8%) and ILN/LT rats, 0.0%; and rhomboid nuclei: ATN rats, 0.3% (range: 0.0–3.0%) and

ILN/LT rats, 0.2% (range: 0.0–1.7%). Although the rats retained for behavioral analyses received subtotal damage, this was specific to the ATN or ILN/LT and comparable to previous work (Gibb et al., 2006; Mitchell & Dalrymple-Alford, 2006), and there was minimal damage to the alternate target or other thalamic nuclei.

3.2. Task 1—allocentric spatial reference memory in a Morris water maze

As predicted, ATN lesions, but not ILN/LT lesions, impaired acquisition of the Morris task. Fig. 2 shows the performance (escape latency, path length, mean distance to the platform) and swim speed during acquisition of the first and second platform locations. Marked improvement of performance was evident in all three groups throughout the 6 days of acquisition of the first platform location (Days 1–6), which resulted in a highly significant effect of Day for escape latency ($F(5,120) = 27.90$, $p < 0.0001$), path length ($F(5,120) = 39.43$, $p < 0.0001$) and mean distance to the platform ($F(5,120) = 62.72$, $p < 0.0001$). The Lesion by Day interaction was significant for mean distance to the platform ($F(10,120) = 2.22$, $p < 0.05$) but not for path length and escape latency (both $ps > 0.1$). Overall, the improvement across trials per daily session was also highly significant (escape latency, ($F(3,72) = 4.10$, $p < 0.01$); path length, ($F(3,72) = 6.81$, $p < 0.001$); mean distance to platform, ($F(3,72) = 5.53$, $p < 0.01$), irrespective of lesion group (Lesion by Trial and Lesion by Day by Trial, all $ps > 0.07$). The main finding was that the ILN/LT group exhibited similar performance to the Sham group, but the ATN rats showed a clear impairment on all performance measures (Lesion main effects: escape latency, $F(2,24) = 12.04$, $p < 0.001$; path length ($F(2,24) = 15.71$, $p < 0.0001$; and mean distance to the platform, $F(2,24) = 17.73$, $p < 0.0001$). Fisher post hoc analyses confirmed that the ATN group was markedly impaired relative to both the Sham group and the ILN/LT group and for all performance parameters (all $ps < 0.001$).

All groups engaged in thigmotaxic behavior during acquisition, evidenced by the percent time spent within a 15 cm wide annulus from the edge of the pool. This measure reduced across Days ($F(5,120) = 28.21$, $p < 0.0001$) and across Trials ($F(3,72) = 7.31$, $p < 0.001$). Although the ATN group exhibited far higher levels of thigmotaxis ($F(2,24) = 12.44$, $p < 0.001$) compared to both Sham and ILN/LT rats ($p < 0.0001$), this difference was substantially reduced to a level comparable to that of the Sham and ILN/LT groups (less than 10% of time for all rats, i.e. 3 s or less) by the last 3 days of testing in the first acquisition task (Day × Lesion, $F(10,120) = 2.46$, $p < 0.05$). There were no group differences for this thigmotaxis measure for the remainder of any allocentric spatial memory testing.

Another difference was found in terms of swim speed. All groups decreased their swim speed across successive Days ($F(5,120) = 34.81$, $p < 0.0001$), but there was also a

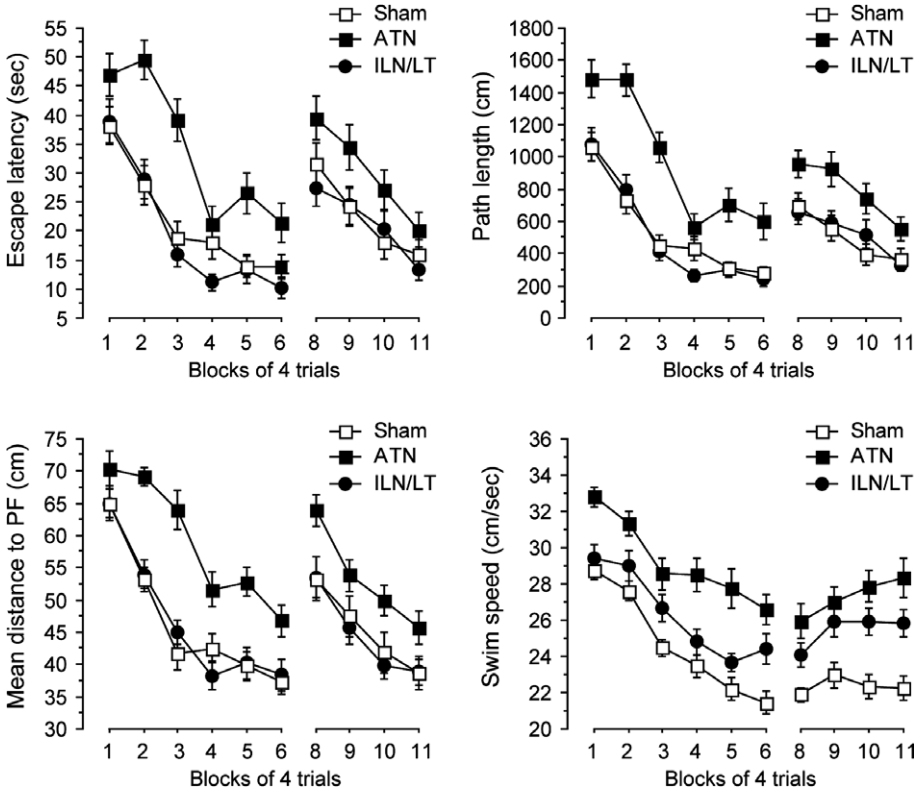

Fig. 2. Allocentric spatial memory: Initial acquisition (blocks 1–6; mean of four daily trials per block, ±sem) and reversal learning (blocks 8–11). Escape latency (left upper panel), path length (right upper panel), mean distance to the platform (left lower panel) and swim speed (right lower panel).

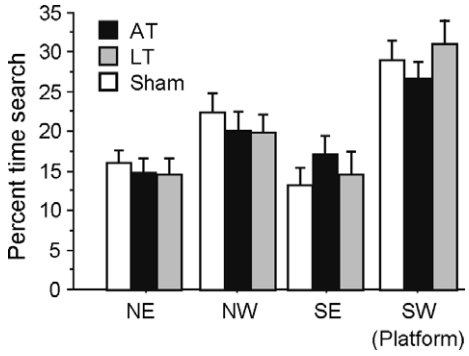

Fig. 3. Allocentric spatial memory: Percent time spent in each quadrant during the probe trial following initial acquisition in the Morris maze (Day 7). The 15 cm wide thigmotaxis annulus, adjacent to the wall of the 180 cm diameter pool, was excluded from this analysis.

Lesion effect ($F(2,24) = 7.20$, $p < 0.01$), with the ATN group swimming more quickly than both Sham ($p < 0.001$) and ILN/LT ($p < 0.05$) groups, which did not differ.

During the probe trial (Day 7; Fig. 3) all groups, including the ATN group, exhibited a strong preference in terms of time spent in the quadrant that previously contained the platform (Quadrant, ($F(3,72) = 17.493$, $p < 0.0001$), but there was no effect of Lesion on this measure ($F < 1$; Lesion × Quadrant, $F < 1$). All groups spent a also limited time (less than 8%) in the thigmotaxis annulus region during this probe trial (Lesion main effect, $F(2,24) = 1.65$, $p > 0.2$). There was, however, a significant effect of the lesion ($F(2,24) = 4.14$, $p < 0.05$) in terms of the number of crossings into the vicinity of the platform, due to the fact that ATN group crossed the previous platform location less frequently than the ILN/LT rats ($p < 0.01$), while the Sham groups showed an intermediate number of platform crossings that did not differ significantly from either of the other two groups (mean number of crossings ± sem: Sham, 1.20 ± 0.39; LT 2.20 ± 0.49; AT, 0.50 ± 0.33). The main conclusion of this probe trial was that despite the delayed acquisition of the location of the platform by the ATN group, these rats were able to acquire and use spatial information.

The performance of all groups was disrupted by the relocation of the platform to the opposite quadrant but all groups quickly adapted to the new platform location during this reversal learning (Days 8–11; Fig. 2, right panels; and Fig. 4). These observations were confirmed by highly significant effects of Day for escape latency ($F(3,72) = 15.15$, $p < 0.0001$), path length ($F(3,72) = 11.50$, $p < 0.0001$) and mean distance to the platform ($F(3,72) = 28.23$, $p < 0.0001$). The main effect of Trial was again significant for all measures with all groups improving their performance across successive daily trials (escape latency, $F(3,72) = 6.25$, $p < 0.001$; path length, $F(3,72) = 5.76$, $p < 0.01$; mean distance to platform, $F(3,72) = 9.46$, $p < 0.0001$). However, the main finding was that the ATN group again exhibited an impairment relative to the other two groups, which produced a significant effect of Lesion for path length, ($F(2,24) = 5.22$, $p < 0.05$) and mean distance to the platform ($F(2,24) = 4.32$, $p < 0.05$). The escape latency measure was not significant across groups ($F(2,24) = 2.47$, $p > 0.1$) on this occasion. There was no significant Lesion × Day interaction (Fs < 1). These findings thus confirmed that despite prior spatial learning experience the ATN group still showed impaired spatial learning and highlighted again the fact that ILN/LT rats exhibited unimpaired robust allocentric spatial learning.

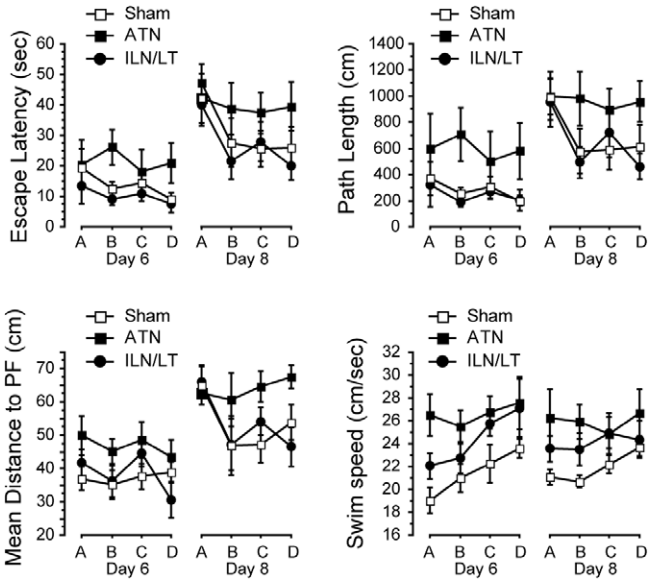

Fig. 4. Allocentric spatial memory: Means (±sem) for the four successive trials for the last day of initial acquisition (Day 6) and first day of reversal learning (Day 8). Escape latency (left upper panel), path length (right upper panel), mean distance to the platform (left lower panel) and swim speed (right lower panel).

Combined across groups, swim speeds increased during reversal learning (Days, $F(3,72) = 4.31$, $p < 0.01$) relative to that at the end of training to the initial platform location. There was also a significant effect of Lesion ($F(2,24) = 3.98$, $p < 0.05$; Lesion × Day interaction, $F < 1$). The ATN group again swam more quickly than the Sham group ($p < 0.05$), but on this occasion the ILN/LT group also tended to swim more quickly than the Sham group, although the latter difference did not reach significance ($p < 0.09$).

An additional examination of reversal learning was conducted by comparing the first day of reversal learning (Day 8) with the last day of acquisition on the initial task (Day 6). Differences are illustrated by performance across the four trials for these 2 days (Fig. 4). All groups showed a marked increase in escape latency, path length and mean distance to platform on the first trial of the first reversal day. Across the four trials, there was a significant Lesion effect for mean distance to the platform ($F(2,24) = 3.50$, $p < 0.05$), with ATN rats being impaired relative to both Sham and ILN/LT rats ($p < 0.05$) and this effect was close to significance for path length ($F(2,24 = 2.84)$, $p = 0.08$)

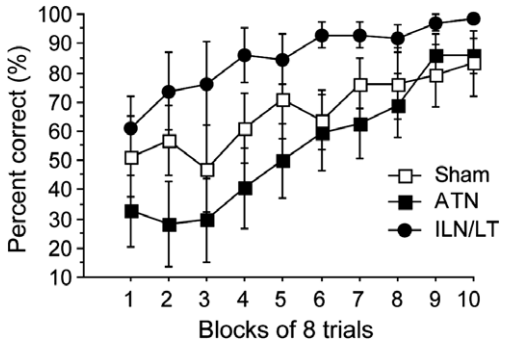

Fig. 5. Egocentric spatial memory. Mean percent correct (±sem) for the three groups across 10 blocks of eight trials.

with the ATN group different to ILN/LT group ($p < 0.05$) and close to significantly different to the Sham group ($p = 0.06$); there were no significant differences in terms of escape latency ($F(2,24) = 2.09$, $p > 0.1$). Although the ATN group displayed little or no learning after the first reversal trial (trial A), whereas the Sham and ILN/LT groups displayed improved but even performance on trials B–D, the Lesion by Trial interactions were nonsignificant ($F < 1$).

3.3. Task 2—egocentric spatial reference memory in a radial-arm water maze

The prediction that the ILN/LT group would exhibit poorer acquisition of the egocentric spatial task, while the ATN group would behave similarly to controls, was clearly not supported. If anything, the ILN/LT group displayed a faster rate of acquisition on the egocentric spatial reference memory task than did the ATN group. All three groups acquired the egocentric spatial memory task relatively quickly (Block main effect, $F(9,207) = 13.55$, $p < 0.0001$; Fig. 5). The Lesion main effect just failed to reach significance ($F(2,23) = 3.18$, $p = 0.06$), but this was due to the ILN/LT group unexpectedly showing superior overall performance relative to the ATN group ($p < 0.05$), while the Sham group revealed an intermediate overall level of performance. Although these group differences seemed more evident at the start of training, the Lesion by Day interaction was not significant ($F(18,207) = 1.13$, $p > 0.3$). The apparent difference in the initial three blocks of trials did not produce any significant effects (Lesion main effect, ($F(2,23) = 2.40$, $p > 0.1$); Lesion by Trial Block, ($F(4,46) = 1.48$, $p > 0.2$).

4. Discussion

The current study contrasted the effects of neurotoxic thalamic lesions to the ATN and the ILN/LT region in rats on two different spatial memory tasks taxing either allocentric or egocentric spatial reference memory that required the same general motivational and sensori-motor demands. The prediction that selective ATN lesions, but not ILN/LT lesions, would impair allocentric spatial memory in the Morris maze was confirmed and this direct comparison helps clarify some conflicting previous evidence of the effects of these lesions on this task. By contrast, there was no evidence to support the prediction that ILN/LT lesions would impair egocentric spatial reference memory in a Y-maze. As expected from previous work that used a fixed T-maze (Aggleton et al., 1996; Warburton et al., 1997), ATN lesions did not markedly disrupt the acquisition of an egocentric spatial memory response.

The lack of effect of ILN/LT lesions in the current study contrasts with previous experimental evidence suggesting an involvement of the ILN in spatial navigation in a water maze (Mair et al., 1998; Savage et al., 1998) and is consistent with the view that these previous reports may reflect unintended damage to the adjacent ATN region. It is also possible that damage to the laterodorsal nucleus in previous ILN lesions also contributed to the previously reported spatial memory deficits with large ILN lesions (van Groen et al., 2002). It is extremely difficult to make consistently large ILN lesions without affecting significant portions of the surrounding thalamus, which is why we elected to make subtotal lesions that would minimize damage to the alternate thalamic region. It may be the case that our subtotal ILN/LT lesions were insufficiently large to produce behavioral deficits, but this interpretation seems unlikely because we have shown that similar ILN/LT lesions can produce marked behavioral impairments, at least in terms of poor egocentric working spatial memory and disrupted acquisition of an arbitrary odor-place association (Gibb et al., 2006; Mitchell & Dalrymple-Alford, 2006). The median size of the ILN/LT lesion in the present study was 64.2%, which is intermediate to the 60.7% median in the Gibb et al. (2006) study and the 68.8% median in the Mitchell and Dalrymple-Alford (2005) study, and the overall placements were similar, so ILN/LT lesion differences are unlikely to account for any lack of effect in the present study. Whether other subtle lesion variations account for the current findings is difficult to state with certainty. Damage to the MT region was slightly larger in these previous studies (25.2% and 30.4%, respectively, versus 23.2% here), which suggests that the current lesions did not extend as far medially to this adjacent region, plus there was less damage to the ventrolateral nucleus (14.4% here; 30.1% in Mitchell & Dalrymple-Alford, 2005; not recorded in Gibb et al., 2006). The suggestion that previous ILN lesion effects on water maze performance were due to adjacent ATN damage is supported by the effects of subtotal ATN lesions similar to those in the current study as well as those found when subcomponents of the ATN are explicitly targeted (e.g., Aggleton et al., 1996; Bailey & Mair, 2005; Byatt & Dalrymple-Alford, 1996; Mitchell & Dalrymple-Alford, 2005, 2006; Moran & Dalrymple-Alford, 2003), although small neurotoxic ATN lesions seem unlikely to cause major deficits. Future work is required to test the possibility that a combination of large ATN lesions with large adjacent ILN/LT lesions may create yet greater spatial memory

deficits than lesions restricted to the ATN and to answer the question of what extent or subregional characteristics of ATN injury will produce deficits when rats receive ILN damage.

The prediction that lesions of the ILN/LT region would impair egocentric spatial reference memory was based on evidence that some of the prominent neural connections of this region are with the dorsal striatum and dorsal prefrontal cortex (Berendse & Groenewegen, 1991; van der Werf et al., 2002). Consistent with this perspective, ILN lesions impair egocentric working memory tasks (Bailey & Mair, 2005; Mair et al., 1998; Mitchell & Dalrymple-Alford, 2006), so it is possible that these lesions fail instead to disrupt the consolidation of consistently rewarded egocentric responses, which may be supported by alternate brain pathways. Our Y-maze task was adapted from an earlier work by Mitchell and Hall (1987, 1988) that showed that caudate lesions severely impaired the ability to locate a food reward based on body response in a static Y-maze in which the start-arm changed from trial to trial and distinctive cues were minimized. In our case, we further minimized the utility of local or distal cues, and intramaze (e.g., olfactory) cues, by using the eight Y-maze configurations embedded in an 8-arm water maze, rather than only the three start points in a single Y-maze, and by surrounding the maze with a uniform curtain. These procedural additions were expected to increase the emphasis on egocentric responding and the likelihood of deficits after the ILN/LT lesions. Given the negative findings reported here, it would be informative to determine the effects of similar selective ILN lesions on other non-matching working memory tasks including olfactory tasks that are reported to be impaired by extensive ILN lesions (Burk & Mair, 1998; Harrison & Mair, 1996; Kesner & Rogers, 2004; Young et al., 1996; Zhang et al., 1998). If deficits were found on those tasks, it would suggest that ILN lesions influence non-spatial working memory in general, rather than egocentric responding per se. One complication for such a view is, however, that subtotal ILN/LT lesions do not impair working memory for reward magnitude (Mitchell & Dalrymple-Alford, 2005), but there are precedents from the examination of selective prefrontal cortex lesions for various combinations of impaired and unimpaired working memory that do not readily coincide with traditional dichotomies among various attributes (Kesner, 2000; Kesner & Rogers, 2004). It has been suggested that the ILN contribute to "complex attention", "cognitive awareness" and the "flexibility of executive processes", but these concepts do not readily explain the existing pattern of spared and impaired performance associated with ILN lesions (Van der Werf et al., 2002, 2003). For example, the prospect of decreased flexibility after ILN lesions was not supported here because there was no evidence that these lesions disrupted reversal learning in the Morris pool task, but the effects of ILN lesions on extramodal shifts require examination to test this possibility more fully. Although the inter-task duration (4 weeks) makes it unlikely that transfer from the Morris task to the radial-arm egocentric task might reflect the requirement of an extramodal shift in strategy, it was the ATN group rather than the ILN group that appeared to show a mild initial deficit in the egocentric task.

The dissociation between impaired allocentric spatial memory after ATN lesions and the lack of effect after ILN/LT lesions adds support for the view that ATN damage is one of the key sources of episodic memory deficits in human cases of diencephalic amnesia (Aggleton & Brown, 1999; Harding et al., 2000; Van der Werf et al., 2003). The general consistency across the three performance measures (latency, path length and distance to platform), together with marked impairment on the reversal task when non-specific factors such as increased thigmotaxic behavior had diminished, suggests that the ATN rats have a spatial memory acquisition deficit in the Morris maze. While it is possible that there were motivational or other effects of ATN lesions, their increased swim speeds in the Morris maze suggests that poor motivation was unlikely to be responsible for this acquisition deficit. The probe trial data revealed adequate retention for the ATN group after initial learning, with no deficit in terms of time spent in the training quadrant but slightly poorer locale search of the platform, a pattern that is similar to previous work on ATN lesions (Warburton et al., 1999). The general assumption is that the effects of ATN lesions in the Morris task reflect a disruption to an extended diencephalic–hippocampal memory system, which is supported by evidence from the effects of contralateral ATN-hippocampal lesions (Warburton et al., 2001). Similarly, hippocampal lesions can also impair performance during acquisition but without preventing the formation of a preference for the target quadrant during a probe trial (Bannerman et al., 1999; Morris et al., 1990; Zhang, Pothuizen, Feldon, & Rawlins, 2004). Residual spatial abilities in hippocampal rats have been suggested to be based on non-spatial strategies (Pouzet, Zhang, Feldon, & Rawlins, 2002). It is therefore also interesting that the similarities between the effects of hippocampal and ATN lesions in rats extend beyond spatial memory performance to other general aspects of behavior. Rats with complete excitotoxic hippocampal lesions exhibit increases in locomotor activity (Cassel et al., 1998; Good & Honey, 1997; Whishaw & Jarrard, 1995) a feature likely to be linked with increased swim speed in the water maze (Bannerman et al., 1999; Zhang et al., 2004). We also observed consistently increased swim speed in ATN rats throughout all phases of allocentric spatial memory testing, which emphasizes the importance of performance measures based on path length and mean distance to platform. In addition, increased thigmotaxis was evident in ATN rats at the beginning of testing, a feature that has long be known to be associated with hippocampal lesions (Hostetter & Thomas, 1967). These similarities strongly reinforce the view that the hippocampus and the ATN constitute an interdependent system that is essential for

spatial navigation that may also support episodic memory more generally (Aggleton & Brown, 1999, 2006).

In conclusion, the present study provides an important clarification concerning the respective involvement of the ILN and the ATN in spatial memory. Using rat models with highly specific neurotoxic lesions, it is clear that the ILN by themselves clearly do not have a critical influence on allocentric spatial memory whereas the ATN constitute a more crucial thalamic region that contributes to these spatial abilities. These abilities are generally regarded as among the closest analogs to the declarative memory system in humans (Aggleton & Pearce, 2001). Understanding the respective involvement of the different thalamic nuclei has long proven to be virtually impossible in diencephalic amnesia cases because of the non-specificity of the brain damage in the thalamic region. This clarification has important consequences with respect to the amnesia literature and may help interpret the consequences of thalamic damage in humans. However, the involvement of the ILN in cognitive learning should not be minimized and further work is required to better understand the function of this region and its influence on related brain pathways.

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