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Behavioural Brain Research 172 (2006) 155–168
BEHAVIOURAL BRAIN RESEARCH
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Research report

# Odour–place paired-associate learning and limbic thalamus: Comparison of anterior, lateral and medial thalamic lesions

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Received 29 January 2006; received in revised form 8 May 2006; accepted 12 May 2006
Available online 12 June 2006

**Abstract**

Several subregions in the limbic thalamus have been suggested as the key locus for diencephalic amnesia, including the anterior thalamic nuclei, intralaminar nuclei and mediodorsal nuclei. There is, however, no consensus as to a single critical site and recent research has suggested instead that different thalamic areas may contribute to diencephalic amnesia in subtly different ways. This study compared the effects of lesions to anterior (AT), lateral (LT) and posteromedial (MT) aggregates of thalamic nuclei on Gilbert and Kesner's [Gilbert, PE, Kesner, RP. Role of the rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. Behav Neurosci 2002;116(1):63–71; Gilbert, PE, Kesner, RP. Localization of function within the dorsal hippocampus: the role of the CA3 subregion in paired-associate learning. Behav Neurosci 2003;117(6):1385–94] paired-associate task, in which rats were postoperatively trained to form an arbitrary association between odours and spatial locations in a circular open field. Both AT and LT lesions, but not MT lesions, severely impaired odour–place paired-associate learning. Probe trials revealed that the rats were not using specific location information after acquisition training. All groups were able to learn non-associative odour and place discrimination tasks quickly, with only the AT group showing delayed acquisition. This study provides the first direct comparison of different thalamic lesions on paired-associate learning and new evidence on the importance of the LT region in learning and memory. The results support the notion that injury to both the AT and LT subregions of the thalamus may each be major contributors to diencephalic amnesia. There is need for traditional models of memory function to take greater account of the contributions of thalamic nuclei.


*Keywords:* Thalamus; Paired-associate learning; Anterior thalamus; Intralaminar nuclei; Mediodorsal nuclei; Rat; Amnesia

## 1. Introduction

The role of the diencephalon, especially the limbic thalamus and its related neural pathways, has become increasingly influential in elucidating the brain systems responsible for episodic memory and amnesia [1,4,44,68,70,72,77]. There is, however, considerable ambiguity over which structures within the thalamus are responsible for the range of deficits associated with diencephalic amnesia. Strong support for the idea that the essential features of episodic memory rely on a neural circuit that includes the anterior thalamic nuclei (AT) as part of an extended hippocampal system [1] has come from several animal studies showing substantial deficits in spatial learning and memory after AT lesions [3,15,45,47,49,68,73,78,79,81]. Despite this recent emphasis on the AT, other experimental evidence suggests that damage to the intralaminar thalamic nuclei (ILn) or mediodorsal thalamic nuclei (MDn) may instead or at least in addition cause many of the features of diencephalic amnesia. Mair and others have amassed an impressive list of studies that implicate the ILn [6,43,44,59,87]. For example, ILn lesions in rats impair retention and relearning of a delayed match-to-sample task using retractable levers, an effect that is extremely severe when the ILn lesions extend to the adjacent MDn and other midline structures whereas restricted MDn lesions have relatively little effect [6,12]. Conversely, recognition memory, runway alternation, scene learning and object-reward associative memory have been reported to be markedly impaired by MDn lesions [8,16,27,53].

The small size and close proximity of thalamic nuclei mean that lesions to one area often cause unintentional damage to an adjacent region and this uncertainty has probably contributed to many of the inconsistent or conflicting results in previous

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doi:10.1016/j.bbr.2006.05.017

studies [6,37,44,45,50,59,82]. To unravel the influence of the limbic thalamus on learning and memory, it is clear that studies are needed that explicitly compare the effects of selective lesions to different thalamic subregions. It is likely that highly specific, but subtotal, lesions that minimise the problem of the close proximity of these neural structures may help answer both the general question of whether several thalamic regions may be responsible for diencephalic amnesia and the specific issue of whether different regions make varying contributions to memory processing.

Our laboratory recently reported the first direct comparative evidence that lesions of three key aggregates of thalamic nuclei may influence independent memory systems [47]. The focus on these aggregates was based on anatomical evidence that while they each have a degree of overlapping neural connections at the level of the prefrontal cortex there are several important similarities and differences in terms of their principal afferent and efferent connections. The rostral ILn (centrolateral, paracentral and rostral central medial nuclei) have connections that strongly overlap with those of the lateral MDn, which lies medial and adjacent to the ILn, so these thalamic nuclei comprised one key aggregate. Of particular relevance, both the rostral ILn and the lateral MDn have strong connections with the dorsal prefrontal cortex and the dorsal striatum [9,71]. Another factor that separates the lateral MDn from the remainder of the MDn, is that the former also has a prominent afferent connection with lower brain–stem structures including the substantia nigra [56]. The aggregate that provided the basis for the second lesion, a posteromedial region (MT), included the medial and central MDn and the intermediodorsal nucleus, which have prominent connections with the medial and lateral prefrontal cortex as well as the ventral striatum and the amygdala [32,33,71]. The conventional AT comprised the third aggregate and included the anterodorsal, anteroventral and anteromedial thalamic nuclei, but not the laterodorsal thalamic nucleus. Although the laterodorsal nucleus warrants closer attention, as it has many similar connections to those of the AT, lesions of the AT are sufficient to cause severe spatial memory deficits [15,73,75]. The prominent signature of the connections of the AT is with the supracallosal limbic cortex and the retrohippocampal region [60,61,74,76]. In our comparative lesion study, selective AT damage severely impaired a preoperatively trained spatial working memory task in the radial-arm maze but not postoperative acquisition of working memory for reward value, whereas MT lesions produced the opposite pattern of impairments and LT lesions produced only minor transient deficits in spatial memory [47]. A subsequent study revealed that LT lesions impaired a preoperatively trained response-based working memory task (for a left or right body turn) but had no effect on postoperative acquisition of spatial working memory in the radial maze, whereas AT lesions produced the converse pattern of effects [48]. This initial work suggested that AT, LT and MT thalamic regions may make distinct contributions and can independently influence working memory for spatial, response and reward-related cues, respectively.

Tasks that assess the binding of individual elements of an event or the acquisition of arbitrary associations are believed to provide a close analogy to declarative memory, including 'episodic-like' memory [4,21,22,34]. Such tasks include tests of scene learning, object-in-place memory, and memory for arbitrary paired-associates, particularly tasks that require the integration of specific items or events with a place or context. Whereas several studies have evaluated the effects of hippocampal system lesions on these memory tasks [5,11,28,30,31,67,80], surprisingly little research has addressed association memory processes after thalamic lesions. Connections between the prefrontal cortex and the MT region, LT region and, to a lesser extent, the AT region [9,32,33,56,62,71], provide an additional reason to question the effects of thalamic injury, because the prefrontal cortex has also recently been implicated in associative memory tasks [10,39].

The aim of the present study was to extend our earlier work on the comparative influence of selective AT, LT and MT lesions by examining their effects on Gilbert and Kesner's [30,31] odour–place paired-associate task. This task assesses the ability to learn an arbitrary association between a spatial location and the presence of one of two types of odourised sand in which the rat digs for a food reward. It is highly sensitive to hippocampal lesions [30,31], so an involvement of the AT was expected given the existing behavioural and anatomical evidence that this region is a key part of an "extended hippocampal system" [1,84]. Indeed, there are already data that conventional (non-neurotoxic) AT lesions produce impaired performance in two related tasks, when monkeys must choose the place of a visual object embedded in a background scene [54] and when rats must choose the correct of two objects depending on their general spatial context [36,68]. Yet hippocampal lesions, but not AT lesions, also impair learning to make a left or right response (body turn) based on a visual cue, whether or not spatial cues are present [68,69]. The ability to obtain a reward that is conditional on the spatial layout of objects was reported in another study to be unimpaired after either AT or MDn lesions in monkeys, unless the lesion included both structures [58]. In terms of the LT region, and specifically the ILn, no previous study to our knowledge has explicitly examined memory for arbitrary associations after these lesions, although evidence that ILn lesions may have widespread effects on learning and memory in rats suggested that this region may also influence associative memory tasks [12,44,47]. The importance of associative memory tasks, the uncertainty with respect to the influence of AT lesions and their comparability with hippocampal lesions on these tasks and the scarcity of related evidence after lesions that include the ILn and MDn prompted the current study of the comparative effects of selective neurotoxic AT, LT and MT lesions on spatial conditional associative learning.

## 2. Methods and materials

### 2.1. Subjects

The 35 naïve female PVGc Hooded rats used were bred in-house. They were approximately 10 months old and weighed 150–200 g at surgery. Groups of three or four rats were housed in standard plastic cages (27 cm × 45 cm wide × 22 cm high) on a 12 h reversed light–dark cycle (off 8 a.m. to 8 p.m.). Testing was conducted during the dark portion of the cycle. Apart from free access to food during

Table 1
Methodology for 0.12 M *N*-methyl-D-aspartate lesions of the three medial thalamic aggregates: coordinates (cm) for various Bregma–Lambda (B–L) measurements, infusion volumes and rates

| B–L distance for co-ordinates (cm) | AT | | MT | | LT | | |
|---|---|---|---|---|---|---|---|
| | Anterior (AM) | Posterior (AV) | Anterior | Posterior | Anterior (two sites) | | Posterior |
| 0.60–0.61 | −0.24 | −0.25 | −0.35 | −0.39 | −0.345 | | −0.385 |
| 0.62–0.63 | −0.25 | −0.26 | −0.36 | −0.40 | −0.355 | | −0.395 |
| 0.64–0.66 | −0.26 | −0.27 | −0.37 | −0.41 | −0.365 | | −0.405 |
| 0.67–0.68 | −0.27 | −0.28 | −0.38 | −0.42 | −0.375 | | −0.415 |
| 0.69–0.70 | −0.27 | −0.28 | −0.38 | −0.42 | −0.375 | | −0.415 |
| 0.71–0.72 | −0.27 | −0.28 | −0.38 | −0.42 | −0.375 | | −0.415 |
| ML | ±0.123 | ±0.148 | 0.0 | 0.0 | ±0.130 | | ±0.130 |
| DV | −0.58 | −0.555 | −0.56 | −0.57 | −0.56 | −0.60 | −0.560 |
| Volume (μl) | 0.09 | 0.10 | 0.16 | 0.18 | 0.06 | 0.05 | 0.05 |
| Rate (μl/min) | 0.03 | 0.03 | 0.04 | 0.04 | 0.03 | 0.03 | 0.03 |

AM: anteromedial site; AT: anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; AV: anteroventral site; B–L: Bregma–Lambda; DV: dorsal–ventral distance from dura; LT: lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei); ML: medial-lateral distance from midline; MT: posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus.

the post-surgery recovery period and prior to an open field activity test, rats' body weights were maintained at 80–85% of free-feeding weight throughout preoperative and postoperative training. Water was available ad libitum throughout. All procedures conformed to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of Canterbury Animal Ethics Committee.

### 2.2. Surgery

Rats were anaesthetized with sodium pentobarbitone (50 mg/ml, at a dose of 1.40 ml/kg IP), 20 min after atropine (0.13 mg/ml at a dose of 1.5 ml/kg IP), supplemented by mepivicaine (2.0 mg/ml/kg) and ketofen (1.0 mg/ml at a dose of 0.50 mg/kg), and were placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga) with the incisor bar set 7.5 mm below the interaural line to minimise damage to the fornix. Microinfusions of 0.12 M NMDA (Sigma Chemicals, Australia) dissolved in phosphate buffer pH 7.20 were made via a 1-μl Hamilton syringe connected to a motorized infusion pump (Stoelting, Wood Dale, IL) using the coordinates and infusion parameters described in Table 1. To improve lesion accuracy, anterior–posterior (AP from Bregma) co-ordinates in the horizontal plane were varied according to the Bregma to Lambda distance in each rat. The infusion needle was lowered slowly to a given site, allowed to rest at the site for 30 s prior to infusion, left in situ for 3 min post-infusion and then slowly retracted. Sham lesion controls received the same surgery but no infusion; some controls ($N = 6$) received a clean infusion needle lowered to 0.30 cm above a lesion site to avoid any damage in the thalamus (3 AT, 1 MT, 2 LT), while the remaining controls ($N = 3$) received no needle in the brain (these groups showed equivalent performance and were treated as a single control group).

### 2.3. Apparatus

The circular wood board used for the odour–place paired-associate task and the related simple discrimination tasks measured 119 cm diameter × 3.5 cm thick and stood 65 cm above the floor. It was painted white, had no perimeter wall and, other than being a flat surface rather than one with numerous holes, was identical to that described by Gilbert and Kesner [30,31]. A start box (24 cm long × 15 cm wide × 17 cm high, painted black), with a manually operated door, was placed on the maze at position A for the main part of the experiment with its rear wall adjacent to the perimeter of the board or, after initial acquisition training, at position B on half the trials where it was supported at the level of the maze but rested with its front wall adjacent to the perimeter of the board (Fig. 1). The board was located in the same position throughout all testing, slightly to one side of a well-lit windowless room (3.2 m × 3.3 m, with a short corridor to the single door). A chair and low white table, a beige curtain covering half of one wall and pictures on the walls provided additional spatial cues to those provided by the room itself. Small black-painted terracotta pots (6 cm wide at the top × 6 cm high) were filled with sand to 1 cm below the rim (only one pot was present on any trial). The pots were attached to small wooden black-painted platforms (15 cm × 15 cm) to prevent movement of the pots and minimise spillage onto the board. At the bottom of each pot was an inaccessible layer of Froot Loops pieces (Kellogg's) covered with wire mesh to minimise the use of any food odour cues. General activity was later measured on a second board in the same location and room as previously. The only difference for this second board was that it was marked into 18 equal-sized areas and the outside edge was surrounded by four equal-sized sections of clear plastic, 30 cm high and 2 mm thick, joined by 4 cm wide pieces of wood. A camera mounted to the ceiling was used to record all behavioural data.

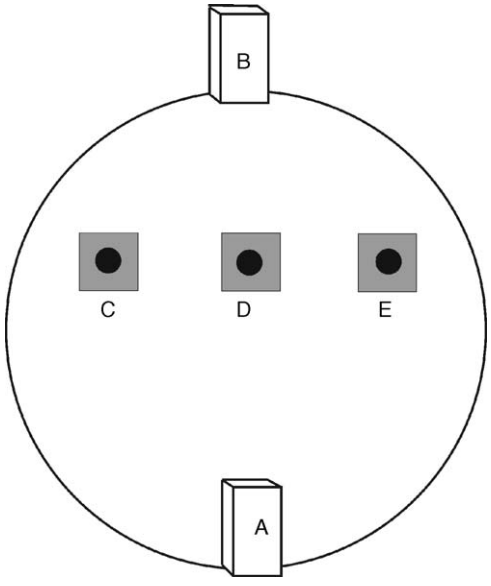


Fig. 1. Schematic of the board used for discrimination tasks. The start box is shown in the position used during acquisition training (A) and the position used in the spatial probe trials during half of the remainder of testing (B). Locations of the digging pots on the odour–place paired-associate task and spatial discrimination task (C and E) and pretraining and odour discrimination task (D) are indicated by the filled squares. Only one start box and one digging pot were used on any given trial.

### 2.4. Preoperative familiarisation

Home-cage groups of three or four rats were given access to pieces of Kellog's Froot Loops scattered across the empty board (10 min per day, 2 weeks) and then individual rats were shaped in a cage in the experimental room to retrieve a 1/2 piece of Froot Loop buried 2 cm below the surface of some non-odourised sand in a terracotta pot, before being shaped to run from the start box at position A to a pot placed at position D on the board (Fig. 1). Rats were run 12 times per day, 5 days per week for 2 weeks, then every 2–3 days for a week preceding surgery.

### 2.5. Odour–place paired-associate task

Three weeks post-surgery rats were re-familiarised with the board and then the odour–place task was introduced in which the rat retrieved a hidden food reward (1/2 piece of Kellogg's Froot Loop) by digging in a pot of odourised sand (either cinnamon 1% or cumin 0.4%, w/w with the sand, using odour-specific pots). Only one pot was present on the board on any trial and it could appear at one of two locations (C and E), 67 cm apart and equidistant from the centre of the board, 43.5 cm from the door of the start box which was placed at position A (Fig. 1). When the rat approached the pot, it received a food reward if one odour–place pairing was present (go trial) but received no reward if the alternate odour was present at that place (no-go trial), with the reward contingency for the odour–place pairing reversed for the second location for that rat (counterbalanced across rats per group and home-cage mates). Hence there were two correct and two incorrect pairings per rat and it received a 1/2 piece of Froot Loop cereal, by digging down 2 cm in the sand when a correct odour–place pairing occurred, but was allowed to withhold digging for up to 10 s if a mispaired odour–place occurred. Six correct and six incorrect trials were used per day, 5 days per week over 14 weeks of testing, using Fellows' [24] pseudorandom sequences to counterbalance correct and incorrect pairings across trials. The time from when the rat's back feet exited the start box to when it began digging in the sand was recorded. Digging was defined as 2 or more consecutive strokes in the sand with one or both front paws; resting the front paws on the sand or making swiping motions that did not touch the sand were not counted. If a rat did not begin digging within 10 s of exiting the start box, this latency was recorded and the rat was returned to the start box for the next trial. Following Gilbert and Kesner [30,31], the dependent measure for the odour–place paired-associate task was the daily average of the difference in latency for rewarded trials subtracted from the latency for non-rewarded trials. Optimal performance on the odour–place paired-associate task required that rats withheld responses (maximum of 10 s) on non-rewarded trials, but responded quickly on rewarded trials.

### 2.6. Spatial probe trials

For the rat to solve the odour–place association, it was presumed that spatial cues processed either on the outward trajectory to the pot of odourised sand or specific spatial cues relevant to this location were associated with an odour cue. To examine these assumptions, spatial probe testing was introduced immediately after the 14 weeks of training on the initial odour–place task. Performance on probe and non-probe trials was examined for a 3-week period. As before, rats were run for 12 trials per day, 5 days per week, but with half the daily trials used as probe trials. For probe trials, the start box was transferred to the opposite side of the board (B, Fig. 1), where it was placed on a white platform (68.5 cm high × 29 cm long × 20 cm wide) adjacent to and level with the edge of the board, such that the distance from the start box to the pot remained the same when the rat exited from either start location. On the remaining trials, the start box was in location A, as before. For each rat, the location of the start box was randomly assigned and balanced so that there was approximately the same number of start location A and B trials for each odour–place pairing and mispairing each day, using pseudorandomly varied sequences over the week. The procedure was otherwise identical to that described for the initial odour–place paired-associate learning. The dependent variable was the same as the odour–place paired-associate task (average latency difference).

### 2.7. Simple odour and spatial discrimination tasks

The start-box was placed at location A for all trials for both simple discrimination tasks. In the simple spatial discrimination task, a pot with non-odourised sand appeared at either location C or E. In the simple odour discrimination task, a pot appeared at location D directly in front of and 28 cm from the start box (Fig. 1). Thus, as with all previous testing, only one of the pots was present on the board on any trial. Latency and digging were defined as previously. One subset of rats per group completed a simple odour discrimination task and the other subset completed a simple spatial discrimination task. The simple odour discrimination task used the same two odours as in the odour–place paired-associate task, to ensure that rats were able to make the specific odour discrimination used in the association memory task. Rats were now trained to dig when a 'correct' odour was presented and to withhold digging if an 'incorrect' (non-rewarded) odour was presented, with the designation of odours balanced across rats and pseudorandom sequences for the order of presentation of odours [24]. Similarly, the simple spatial discrimination task examined the ability of rats to discriminate the two spatial locations that had been used in the paired-associate task and rats were rewarded for digging when the pot was in their designated 'correct' location (correct location counterbalanced across rats). The same locations as had been used in the initial task were used to avoid changing the relative difficulty of the spatial component of the original task. For both simple discrimination tasks, rats received 12 trials per day, 5 days per week and a correct trial was defined as less than 2 s latency on a reward trial and 10 s latency on a non-reward trial. The dependent measure on each task was the same as used previously, but once a rat reached a criterion of at least 10 correct trials on each of two consecutive days testing ceased for that rat.

### 2.8. Activity level

At the end of discrimination training, locomotor behaviour on a new board was measured to determine general activity levels in the four groups. Single rats were placed on the empty board for 6 min following a 2-min holding period alone in a cage in the experimental room. The number of equal-sized areas entered per minute provided the dependent measure.

### 2.9. Histology

On completion of the experiment all rats were transcardially perfused with cold saline followed by 4% formalin. The brains were post-fixed for two days in 4% formalin, cryoprotected in 30% sucrose, and a cryostat used to collect all the coronal 50 μm sections throughout the thalamic region for cresyl violet staining of cell bodies. SG and JDA, who were both blind to individual behavioural data, agreed upon the lesion extent in each rat using the relevant plates of a rat brain atlas [55]. We chose to make a consensus of the lesions as inter-rater reliability across lesion cases does not ensure greater accuracy. The lesions were then replicated on electronic copies of the atlas and automated pixel counts of the relevant brain regions in this electronic version were used to generate estimated lesion volumes by factoring in the distances provided by the atlas. This procedure is an elaboration of the conventional 'by eye' estimation used in the literature, as collapse of areas surrounding a lesion and variation in angle of sections precluded a direct image analysis. Acceptable lesions were defined as having more than 50% bilateral damage to the intended target (i.e., AT, LT or MT), but not more than 40% damage to the corresponding adjacent thalamic regions (adjacent LT and MT for the AT group; AT and MT for the LT group; and AT and LT for the MT group).

## 3. Results

### 3.1. Histological analysis

The largest and smallest lesions that met our criteria for acceptable lesions for each group are shown in Fig. 2 and photomicrographs of the largest lesions are shown in Fig. 3. Only two rats (both MT) failed to meet our lesion criteria, both due

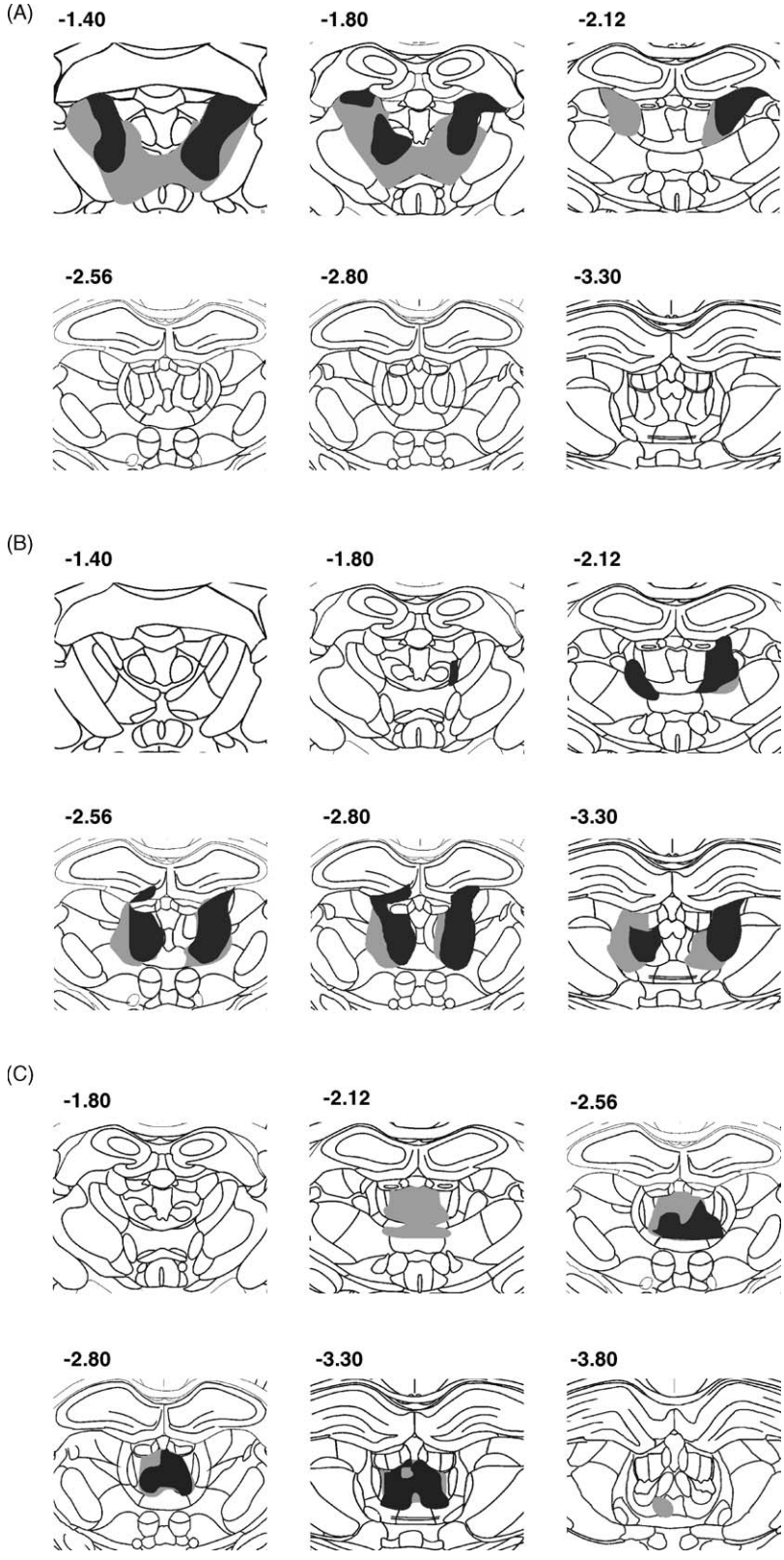


Fig. 2. A series of coronal schematics throughout the medial thalamus showing the area of cell loss in the smallest (black) and largest (gray) thalamic lesions in each lesion group. (A) Group with lesions to the anterior thalamic aggregate (AT) comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei. (B) Group with lesions to the lateral thalamic aggregate (LT), comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei). (C) Group with lesions to the posteromedial thalamic aggregate (MT) comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus. Numbers refer to the distance from bregma (adapted from Paxinos and Watson [55]).

to insufficient damage to the intended aggregate, so these rats were excluded from the main behavioural analyses. The final group sizes were: AT = 9; MT = 7; LT = 8; and control = 9. As shown in Table 2, selective lesions were achieved for the three intended targets. In keeping with this aim, the median damage for the three groups was subtotal (medians: AT, 69.7%; LT, 60.7%; MT 56.6%) with less than 75% damage in all cases bar two AT rats. One of the larger AT lesions included modest damage to the LT (36%) and mild damage to the MT (15%), but the remaining AT rats had relatively little damage to these regions (LT: range 4–12%; MT: range, 1–9%). The LT lesions tended to include modest damage to the adjacent MT region (range, 16–38%), but there was little or no damage to the AT region in these cases (range, 0–13%); there was occasional minor damage to the overlying ventral blade of the dentate gyrus, but this was unrelated to behavioural performance. The MT rats had about 10% or less damage to the LT region and only one had any damage (<1.0%) to the AT region. As intended, the lateral MDn damage was far higher in the LT than the MT group, whereas the MT rats had more severe medial MDn and intermediodorsal nucleus damage; central MDn damage was, however, higher on average in the LT group than the MT group (see Table 2). It is important to note, however, that the MT and LT groups received equivalent mean damage when calculated in terms of a more traditional grouping of the MDn (for the MDn alone, MT = 44.8% [range, 40.5–56.0%], and LT = 43.8% [range, 28.8–51.1%]), but differed markedly in terms of a traditional grouping of the rostral ILn (for ILn alone, MT = 4.3% [range, 0.4–9.4%], and LT = 55.8% [range, 40.9–64.2%]). Hence any differences between the LT and the MT groups can be assumed to be primarily due to either differences in ILn damage, lateral MDn damage, or both. The effects of AT lesions are unlikely to be due to additional damage to the LT or MT and the effects of MT lesions are unlikely to be due to the effects of lateral MDn, ILn or AT damage. As expected from their close proximity to the AT nuclei, the interanteromedial nucleus and the paratenial nucleus showed minor to moderate damage in AT rats, while MT rats tended to have moderate damage to the adjacent paraventricular region. Otherwise, all lesion groups had minimal damage to other non-target thalamic structures.

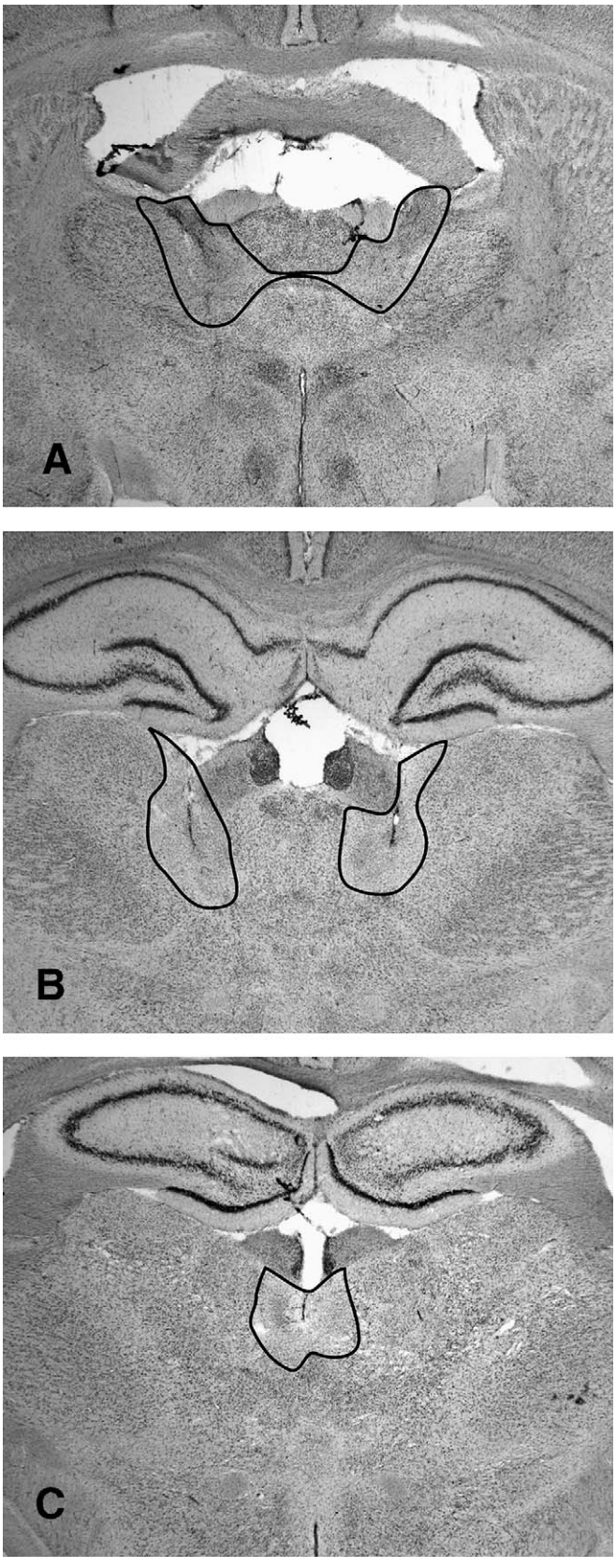


Fig. 3. Photomicrographs of the largest lesion in the three groups. (A) The largest lesion to the anterior thalamic aggregate (AT), comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; the photomicrograph is approximately between −1.40 and −1.80 relative to Bregma. (B) The largest lesion to the lateral thalamic aggregate (LT), comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei); this section is between −2.80 and −3.30. (C) The largest lesion to the posteromedial thalamic aggregate (MT), comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus; this section is between −2.12 and −2.56. Note that differences in the angle of section and partial collapse of the thalamus result in differences relative to the standard atlas plates.

### 3.2. Odour–place paired-associate task

The main findings in this study are shown in Fig. 4, which provides acquisition data for the odour–place association task in terms of mean latency difference scores, expressed as the weekly mean latency for paired (rewarded) trials subtracted from the latency for mispaired (non-rewarded) trials. Each week represents 30 paired and 30 mispaired trials. For the paired trials,

Table 2
Percent bilateral damage (volume) to selected areas for each of the rats in the study, and performance on week 14 of the odour–place paired-associate task

| Lesion group | AT and components | | | | LT and components | | | | | MT and components | | | | Other nuclei | | | | | | | Week 14 score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AD | AM | AV | AT | CL | MDI/MDpl | PC | CMr | LT | IMD | MDc | MD/MDm | MT | IAM | LD | PT | PVA | PV/PVP | Re | Rh | |
| AT—included rats | | | | | | | | | | | | | | | | | | | | | |
| # 6R | 76.1 | 38.0 | 71.7 | 54.2 | 4.4 | 0.0 | 13.2 | 6.9 | 6.1 | 0.0 | 1.4 | 0.0 | 2.1 | 7.2 | 6.1 | 17.7 | 0.1 | 0.0 | 0.0 | 0.0 | 0.930 |
| # 3G | 86.7 | 29.9 | 70.8 | 56.0 | 3.2 | 0.0 | 9.6 | 1.1 | 3.6 | 0.0 | 0.0 | 1.7 | 1.1 | 11.6 | 4.5 | 7.8 | 0.0 | 0.0 | 0.0 | 0.0 | 1.587 |
| # 9G | 60.5 | 65.3 | 69.8 | 64.6 | 4.7 | 0.0 | 18.3 | 16.2 | 9.5 | 0.0 | 0.1 | 0.1 | 4.1 | 34.7 | 8.9 | 19.4 | 0.0 | 0.0 | 0.0 | 0.0 | 4.394 |
| # 5R | 66.0 | 72.8 | 61.5 | 66.1 | 6.3 | 0.0 | 22.4 | 21.2 | 10.9 | 0.0 | 0.0 | 0.1 | 8.8 | 57.6 | 13.7 | 63.6 | 46.5 | 0.0 | 0.8 | 8.8 | 3.794 |
| # 3P | 98.9 | 44.6 | 81.2 | 69.7 | 9.3 | 0.0 | 12.4 | 1.3 | 6.7 | 0.0 | 0.0 | 0.0 | 2.0 | 15.0 | 6.0 | 6.3 | 0.0 | 0.0 | 2.6 | 7.1 | 0.049 |
| # 1R | 89.9 | 43.9 | 78.0 | 74.0 | 6.9 | 0.0 | 18.1 | 5.2 | 8.0 | 0.0 | 0.0 | 0.0 | 1.7 | 7.1 | 5.0 | 10.6 | 0.0 | 0.0 | 0.4 | 0.0 | −0.029 |
| # 4B | 99.8 | 63.4 | 64.6 | 74.9 | 5.0 | 0.0 | 13.7 | 1.7 | 5.9 | 0.0 | 0.0 | 0.0 | 1.7 | 18.2 | 2.9 | 8.2 | 0.0 | 0.0 | 0.0 | 0.1 | 0.018 |
| # 4G | 97.1 | 80.5 | 100.0 | 84.5 | 38.4 | 0.3 | 33.3 | 36.2 | 35.7 | 0.0 | 18.6 | 0.1 | 14.7 | 66.7 | 18.3 | 39.0 | 0.9 | 0.0 | 0.0 | 4.8 | 0.015 |
| # 1B | 99.2 | 90.1 | 71.0 | 91.0 | 9.2 | 0.1 | 20.5 | 15.1 | 12.2 | 0.0 | 0.1 | 0.1 | 3.3 | 56.9 | 7.3 | 21.6 | 0.1 | 0.0 | 3.5 | 3.6 | −0.050 |
| AT median, $N=9$ | 89.9 | 63.4 | 71.0 | 69.7 | 6.3 | 0.0 | 18.1 | 6.9 | 8.0 | 0.0 | 0.0 | 0.1 | 2.1 | 18.2 | 6.1 | 17.7 | 0.0 | 0.0 | 0.0 | 0.1 | 0.049 |
| LT—included rats | | | | | | | | | | | | | | | | | | | | | |
| # 10R | 3.6 | 6.2 | 17.6 | 4.3 | 56.0 | 74.7 | 32.2 | 17.6 | 50.1 | 0.7 | 61.9 | 23.5 | 32.7 | 3.4 | 8.4 | 0.0 | 0.0 | 0.6 | 0.0 | 0.0 | 0.915 |
| # 6B | 15.1 | 12.7 | 25.9 | 13.3 | 58.0 | 72.1 | 41.1 | 25.1 | 53.3 | 0.0 | 69.0 | 16.9 | 30.4 | 4.2 | 3.3 | 1.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.649 |
| # 9P | 0.3 | 2.9 | 10.7 | 2.8 | 78.0 | 63.1 | 39.1 | 16.4 | 56.1 | 0.0 | 37.4 | 9.1 | 16.4 | 0.0 | 1.8 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 4.665 |
| # 8R | 0.0 | 0.0 | 0.0 | 0.0 | 70.8 | 78.2 | 42.9 | 3.3 | 56.9 | 0.0 | 63.8 | 19.0 | 30.3 | 0.0 | 1.4 | 0.0 | 0.0 | 1.2 | 0.0 | 0.0 | 0.873 |
| # 7G | 3.0 | 10.1 | 11.9 | 5.7 | 72.3 | 81.3 | 52.4 | 32.0 | 64.5 | 0.0 | 74.2 | 23.7 | 36.2 | 2.6 | 2.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.5 | 6.285 |
| # 7B | 3.6 | 10.2 | 39.4 | 9.0 | 81.9 | 87.5 | 43.6 | 22.8 | 66.1 | 0.2 | 72.6 | 27.0 | 37.9 | 0.9 | 3.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.426 |
| # 9B | 7.1 | 0.2 | 37.2 | 2.9 | 90.3 | 88.4 | 41.4 | 6.9 | 66.6 | 0.0 | 73.0 | 10.8 | 27.7 | 0.0 | 6.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4.296 |
| # 7R | 0.0 | 0.8 | 13.5 | 0.9 | 89.0 | 87.6 | 55.4 | 16.3 | 70.6 | 0.0 | 67.8 | 19.9 | 32.0 | 0.7 | 2.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 1.572 |
| LT median, $N=8$ | 3.3 | 4.6 | 15.6 | 3.6 | 75.2 | 79.8 | 42.2 | 17.0 | 60.7 | 0.0 | 68.4 | 19.5 | 30.4 | 0.8 | 2.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 2.934 |
| MT—included rats | | | | | | | | | | | | | | | | | | | | | |
| # 5B | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.5 | 6.6 | 11.3 | 4.7 | 70.1 | 54.7 | 50.5 | 53.1 | 0.0 | 0.0 | 0.0 | 0.0 | 30.6 | 0.0 | 0.0 | 7.991 |
| # 6G | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 0.1 | 2.1 | 0.7 | 87.1 | 45.8 | 58.5 | 57.0 | 0.0 | 0.0 | 0.0 | 0.0 | 62.0 | 0.0 | 0.0 | 9.211 |
| # 3B | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.2 | 0.9 | 10.1 | 3.0 | 88.7 | 48.4 | 58.4 | 57.8 | 0.0 | 0.0 | 0.0 | 0.1 | 52.0 | 0.0 | 0.0 | 5.585 |
| # 2P | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 12.2 | 16.2 | 20.3 | 10.2 | 64.4 | 47.0 | 59.9 | 56.6 | 7.5 | 0.0 | 0.0 | 0.0 | 53.7 | 0.0 | 3.9 | 8.017 |
| # 4P | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 2.3 | 23.0 | 4.0 | 81.5 | 72.1 | 66.4 | 69.1 | 0.0 | 0.0 | 9.7 | 18.7 | 51.8 | 0.0 | 0.0 | 3.348 |
| # 9R | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 7.7 | 3.2 | 17.5 | 5.2 | 100.0 | 74.9 | 66.9 | 71.6 | 0.0 | 0.0 | 0.0 | 1.4 | 72.0 | 0.0 | 0.0 | 2.500 |
| # 3R | 0.0 | 1.7 | 0.0 | 0.5 | 0.0 | 10.0 | 2.2 | 42.0 | 8.9 | 95.9 | 70.4 | 70.8 | 72.6 | 4.0 | 0.0 | 2.7 | 10.9 | 67.6 | 0.0 | 0.0 | 7.581 |
| MT median, $N=7$ | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.5 | 2.3 | 17.5 | 4.7 | 87.1 | 54.7 | 59.9 | 56.6 | 0.0 | 0.0 | 0.0 | 0.1 | 53.7 | 0.0 | 0.0 | 7.581 |
| MT—excluded rats | | | | | | | | | | | | | | | | | | | | | |
| # 2R | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 7.7 | 1.0 | 32.8 | 0.0 | 2.9 | 4.3 | 0.0 | 0.0 | 0.0 | 10.7 | 33.5 | 0.0 | 0.0 | 6.669 |
| # 5G | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 39.6 | 0.0 | 2.9 | 4.8 | 0.0 | 0.0 | 0.0 | 0.0 | 46.8 | 0.0 | 0.0 | 6.401 |

See text for inclusion/exclusion criteria. AD: anterodorsal nucleus; AM: anteromedial nucleus; AT: anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; AT median: median percent damage for all included AT rats; AV: anteroventral nucleus; CL: centrolateral nuclei; CMr: rostral central medial nuclei; IAM: interanteromedial nucleus; IMD: intermediodorsal nucleus; LD: laterodorsal nucleus; LT: lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei); LT median: median percent damage for all included LT rats; MDn: mediodorsal nucleus; MDc: central segment of the mediodorsal nucleus; MDl: lateral segment of the mediodorsal nucleus; MDm: medial segment of the mediodorsal nucleus; MDpl: paralamellar segment of the mediodorsal nucleus; MT: posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus; MT median: median percent damage for all included MT rats; PC: paracentral nucleus; PT: paratenial nucleus; PVA: anterior paraventricular nucleus; PV/PVP: paraventricular nucleus/posterior paraventricular nucleus; Re: reunions nucleus; Rh: rhomboid nucleus; week 14 score: average latency difference score for week 14 of the odour–place paired-associate task.

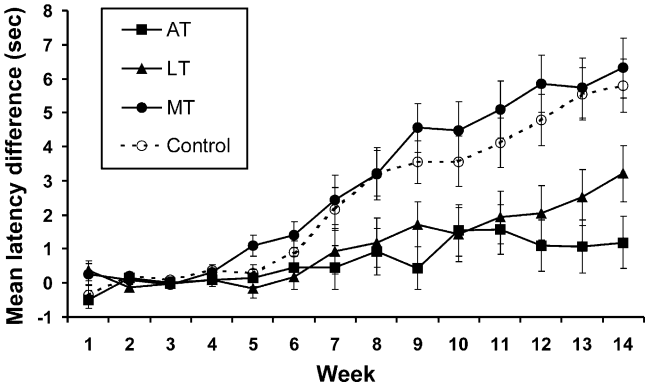


Fig. 4. Mean latency differences (s) on the odour–place paired-associate task for the AT (anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei), LT (lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei)), MT (posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus) and control groups over the 14-week testing period. Vertical bars are ±standard error of the mean (S.E.M.).

latency was about 3.5 s in the first week and reduced to about 1 s thereafter and did not differ as a function of group ($F(3, 29) = 1.06$, $p > 0.38$; data not shown). High mean latency differences therefore indicated high latencies on mispaired trials where a 10 s maximum was allowed. This measure showed that the control and MT groups acquired the odour–place association at a similar rate, starting after the 5th or 6th week of training. By contrast, both the AT and LT groups were markedly impaired at learning the odour–place association and many of these rats failed to show any acquisition at all despite the extensive period of testing. A 4 (group) × 14 (week) repeated measures ANOVA confirmed these observations, with highly significant effects for group ($F(3, 29) = 6.49$, $p < 0.002$), week ($F(13, 377) = 52.06$, $p < 0.0001$) and group × week interaction ($F(39, 377) = 4.83$, $p < 0.0001$). Post hoc comparisons (Newman Keuls) confirmed that, over all weeks, both the AT group and the LT group were significantly impaired relative to both the control group ($p < 0.02$ and 0.04, respectively) and the MT group ($p < 0.004$ and 0.02, respectively), but the MT and control groups showed no difference ($p > 0.40$). During the final weeks of training the mean performance of the LT group appears to diverge from that of the AT group, which remained poor. Post hoc comparisons (Newman Keuls) even on week 14 did not, however, reveal a significant mean difference between AT and LT groups ($p > 0.50$).

Fig. 5 provides the latency difference scores on week 14 for individual rats expressed in terms of the percent bilateral damage to the AT, MT and LT aggregates (note that some symbols may overlap and therefore represent more than one rat). The controls and the two excluded MT rats have been included for comparison. Most of the AT rats (7/9) and half of the LT rats (4/8) completely failed on the task, with only two of these rats, both LT, showing performance comparable to the majority of controls and MT rats at week 14. One control rat also failed on the task and one control and two MT rats performed relatively poorly (using 5 s as an arbitrary criterion). These data showed that AT and LT

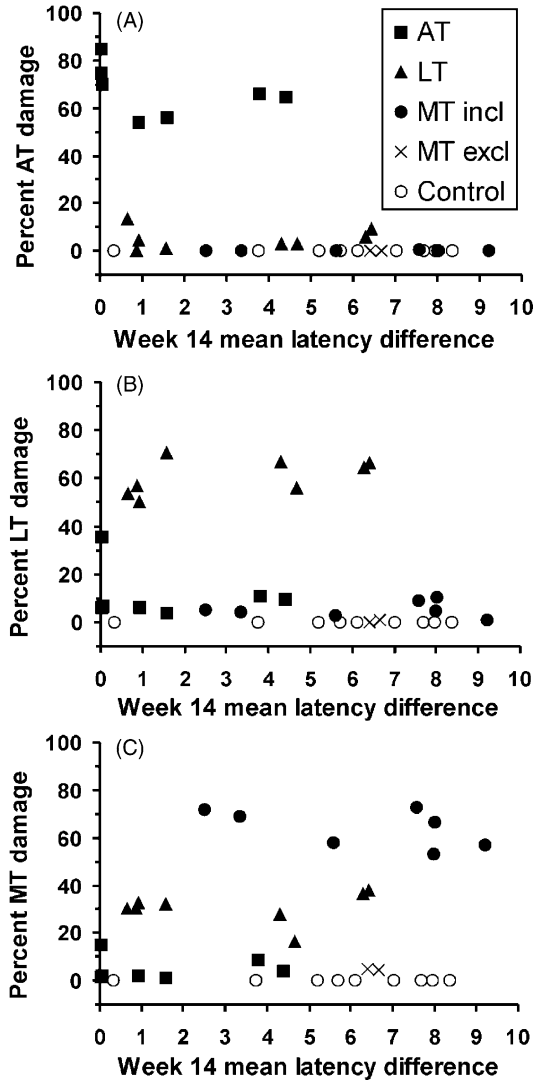


Fig. 5. Scatterplots of performance on the final week of the odour–place paired-associate task and percent damage to: (A) AT (anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei); (B) LT (lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei)); (C) MT (posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus).

lesion volumes above 50% were sufficient to impair performance and that larger AT or LT lesion sizes did not determine the final level of performance. It was also clear that the AT and LT lesion effects were completely independent (e.g., poor performance in AT rats was not associated with LT damage or vice versa).

### 3.3. Spatial probe task

Fig. 6 shows the mean latency difference scores for the 3 weeks that included spatial probe trials, when two opposite start positions were used (A and B; Fig. 1), relative to performance in weeks 13 and 14 at the end of acquisition training when only start position A was used. Performance dropped significantly in week 1 of the probe task when week 14 was compared to

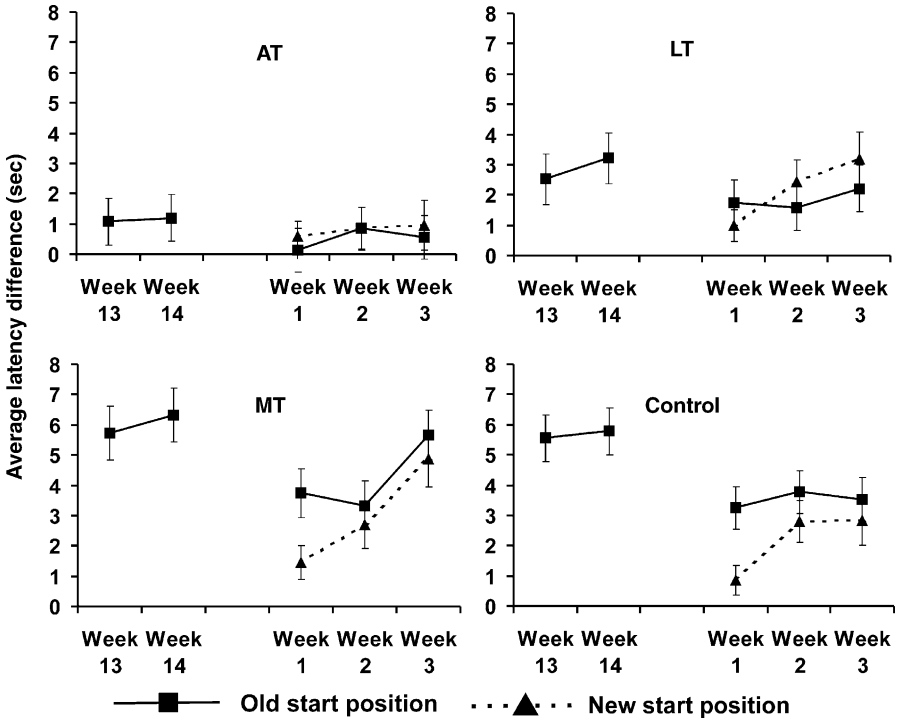


Fig. 6. Mean latency differences (s) for the AT (anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei), LT (lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei), MT (posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus) and control groups for the final 2 weeks of the odour–place paired-associate task and the 3 weeks of the spatial probe task. Data for both old and new start positions are shown for the spatial probe task. Vertical bars are ±S.E.M.

both the old ($F(1, 29) = 26.4$, $p < 0.0001$) and, especially, the new start position ($F(1, 29) = 65.08$, $p < 0.0001$). For the new start position, this decline differed as a function of group ($F(3, 29) = 7.69$, $p < 0.001$), probably due to a combination of a floor effects in the AT group and because the other three groups all showed a particularly marked drop in performance in week 1 of probe testing.

Turning to performance across the 3 weeks of probe testing, the LT, MT and control groups gradually improved over these 3 weeks, but there was little improvement in performance for the AT group. A 4 (group) × 3 (probe week) × 2 (start position) ANOVA revealed significant effects for group ($F(3, 29) = 4.14$, $p < 0.02$), probe week ($F(2, 58) = 6.71$, $p < 0.01$) and start position ($F(1, 29) = 23.55$, $p < 0.0001$). In addition to significant interactions for group × start position ($F(3, 29) = 2.96$, $p < 0.05$) and probe week × start position ($F(2, 58) = 11.43$, $p < 0.0001$), there was also a highly significant group × probe week × start position interaction ($F(6, 58) = 5.72$, $p < 0.001$). Our interpretation of these interaction effects is that the initial poorer performance when tested from the new start position (B) was most clearly evident in the control and MT rats and that only MT and LT groups showed progressive improvements with continued training with the new start position.

### 3.4. Simple discrimination tasks

These tasks were performed at the conclusion of odour–place testing to check that any impairment on the paired-associate task was not due to an inability to distinguish between the specific odours or places used previously or an inability to withhold a digging response. One group of rats (Ns: AT = 5, LT = 4, MT = 4, control = 5) completed the simple odour discrimination task and another group (Ns: AT = 4, LT = 4, MT = 3, control = 4) completed the simple spatial discrimination task. There was no significant difference in lesion size (bilateral percent damage to target aggregate) between the odour discrimination group and the spatial discrimination group for AT lesions ($t(7) = 2.11$, $p < 0.10$) or LT lesions ($t(6) = 0.07$, $p > 0.95$), but the amount of MT damage was higher in the odour group (mean = 70.0%) than the spatial group (mean = 56.0%, $t(5) = 7.00$, $p < 0.001$). Once a rat had reached the criterion of 10/12 correct responses on each of two consecutive days, the mean latency difference on the final 2 days of testing was used for subsequent scores for the analysis of acquisition rates across groups.

In contrast to the odour–place paired-associate task, all rats in all four groups were able to show rapid acquisition in the simple spatial and simple odour discrimination tasks (Fig. 7). Although the AT subgroups were generally slower to acquire these odour and spatial discrimination tasks, their final level of performance was similar to the other three groups. ANOVA for the odour discrimination task revealed a significant effect for group ($F(3, 14) = 4.87$, $p < 0.02$) and a significant group × week interaction ($F(15, 70) = 6.27$, $p < 0.0001$), with lower performance during acquisition for the AT group than for the MT ($p < 0.04$), LT ($p < 0.05$) and control groups ($p < 0.02$), which did not differ significantly. The mean values suggested more evidence of slower

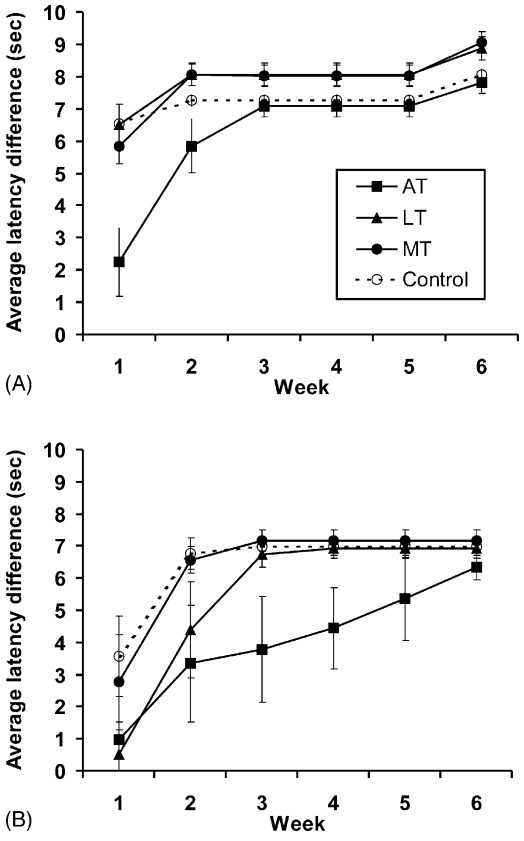


Fig. 7. Mean latency differences (s) on the simple odour (A) and place (B) discrimination tasks for acquisition in the AT (anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei), LT (lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei), MT (posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus) and control groups. Vertical bars are ±S.E.M.

mean rate of acquisition in the AT group on the spatial discrimination task, but neither the group main effect ($F(3, 13) = 2.67$, $p < 0.10$) nor the group × week interaction ($F(15, 65) = 1.67$, $p < 0.10$) was significant. The same conclusions were evident when the mean number of days required to reach criterion on the discrimination tasks were analysed. For the AT, LT, MT and control groups, the respective mean days to criterion were 7.20 (S.D.: 3.03), 4.25 (1.26), 3.75 (0.96) and 2.80 (1.30) for the odour task and 16.00 (10.23), 5.60 (2.88), 9.25 (2.99) and 5.50 (2.65) for the spatial location task. A one-way ANOVA showed no significant difference between the four subgroups trained on the simple spatial discrimination ($F(3, 11) = 2.47$, $p > 0.10$). A one-way ANOVA on the odour discrimination data revealed a significant effect for Lesion ($F(3, 14) = 4.87$, $p < 0.02$), with a significantly higher number of days to criterion for the AT group than for the MT ($p < 0.04$), LT ($p < 0.05$) and control ($p < 0.02$) groups, which did not differ significantly.

### 3.5. Activity level

At the conclusion of testing, rats' activity levels were measured on an empty, but now walled, board. Fig. 8 shows the

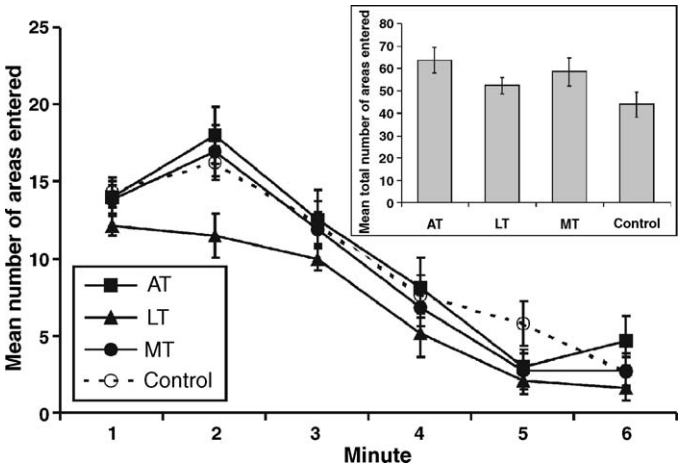


Fig. 8. Mean number of areas entered per minute (main figure) and total mean number of areas entered (inset) during the 6-min activity level test period for the AT (anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei), LT (lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei), MT (posteromedial thalamic aggregate comprising the central and medial mediodorsal nuclei and the intermediodorsal nucleus) and control groups. Vertical bars are ±S.E.M.

mean number of areas entered per minute and the total number of areas entered overall. The number of areas entered per minute declined markedly after the first few minutes in all groups ($F(5, 145) = 102.56$, $p < 0.0001$), but there was no group × week interaction ($F(15, 145) = 1.01$, $p > 0.44$). Although the total number of areas entered was slightly lower in the LT group than the three other groups, there was no group main effect ($F(3, 29) = 2.25$, $p > 0.10$).

## 4. Discussion

The current study examined the comparative effects of lesions to three different regions of the limbic thalamus in the rat on the ability to learn an arbitrary association, as defined by Gilbert and Kesner's [30,31] odour–place paired-associate task. Principally, the findings provide convincing first evidence that damage to the LT region, which includes the rostral ILn and the lateral MDn, causes a severe deficit in spatial associative memory. Second, this study provides additional evidence that the MT region, which includes the key medial aspects of the mediodorsal region, appears to have little or no influence on memory tasks that model the more conventional aspects of diencephalic amnesia. Third, the findings demonstrate that the AT region is also highly important for the integration of odour–place cues and confirms an earlier report that the AT plays an important critical role in spatial associative memory [68]. These results provide new evidence on the influence of the limbic thalamus on memory processes, particularly as the lesions were made by neurotoxin, and thus would have minimal impact on fibres of passage, were highly selective, and thus had minimal overlap across these three key thalamic regions, and involved the acquisition of new long-term memory rather than working memory processes, which has been the usual focus of previous work on selective thalamic lesions. At

least in terms of the processes required to learn arbitrary associations based on odour and spatial attributes [40], the thalamic damage associated with either AT or LT lesions, but not MT lesions, is thus sufficient to cause a substantial learning deficit. Acquisition of arbitrary associations is regarded as an important measure of declarative memory [23,64], but may have closer ties to semantic rather than episodic memory when prolonged training is necessary [58]. Taken together with evidence from similar selective lesions, the current findings reinforce the view that the manifestation of diencephalic amnesia may vary as a function of the nature and extent of thalamic injury and the specific memory task examined [6,7,45,47,48].

It is unlikely that the impairment in the odour–place paired-associate task after AT and LT lesions was due to any fundamental sensory or discrimination deficits or a simple inability to inhibit responding. All rats were able to acquire the simple odour and simple spatial discrimination tasks, using the same locations, odours and successive go/no-go procedure, in markedly shorter time than that provided for acquisition of the initial odour–place paired-associate task. Only the AT group showed evidence of slowed acquisition on the non-associative discrimination tasks, but all the AT rats achieved these feats in 1–4 weeks, and the LT rats accomplished these discriminations in 1–2 weeks, despite deficits in both groups on the associative odour–place task after 14 weeks of training and the fact that this prior testing might be expected to interfere with subsequent acquisition of the simpler tasks. The ability to perform consistently and reach criterion on the simple discriminations is similar to previous studies showing that rats with thalamic lesions can readily acquire the basic procedures for go/no-go discrimination tasks and have preserved memory capacity for unambiguous stimuli based on a consistent rule or strategy [12,42,87]. Neither running times for rewarded cues during training nor general exploratory activity at the end of testing differed across groups, so it is also unlikely that basic response or motivational factors played a part in the group differences observed on the odour–place task.

One of the two dominant lines of thought with respect to the thalamic basis of diencephalic amnesia in the recent rat literature has emphasised the importance of the ILn (and to a lesser extent, the MD nuclei), but minimized the importance of the AT nuclei [6,12,43,44,59,87]. Mair's research group has provided evidence that the effects of ILn lesions are generally more comparable to that of dorsal prefrontal cortex and ventral striatum lesions than that of hippocampal system lesions [13,86]. The dorsal prefrontal cortex represents an important terminal field for projections from both the rostral ILn and the lateral MDn, as well as the AT [62], but the ventral striatum may be more involved in neural circuits that include the MT and related midline structures [9,32,33,56,71]. The full nature of the effects of previous ILn lesions, however, at least in terms of delayed-independent deficits on matching to sample with retractable levers in an operant chamber, was reported in one study to be associated with extensive damage to the midline nuclei and the MDn, but not the AT [6], yet in another to be associated with lesions that largely avoided the midline thalamus and much of the MT and instead included the posterior AT region [12]. Similarly, anterior and ventromedial extensions of the ILn lesions are more likely to produce poorer olfactory delayed nonmatching to sample performance [87]. In sum, the recent perspective associated with the ILn is thus far one in which substantial deficits associated with rostral ILn lesions seem to require damage that encroaches substantially on other thalamic nuclei. The current study provides new evidence of the importance of the ILn, in terms of a severe deficit in the odour–place paired-associate memory task, at least to the extent that the Iln lesions extended to the lateral and central MDn but had minimal damage to other adjacent midline or anterior thalamic regions. There was mild to modest MT damage in our LT cases (16–38%), particularly to the central MDn (37–74%), but both MT and LT lesions produced equivalent overall damage to the traditional MD region (combined medial, central and lateral MDn). Hence it is possible that the effects of ILn lesions depend on an inclusion of the more lateral aspects of the MDn, but MD lesions by themselves clearly do not impair acquisition of arbitrary associations of odour–place information. The specific contribution of the ILn or the lateral MD awaits evidence from yet more localised lesions, but a specific role for the central MDn is unlikely because neither the size of the MT lesion nor the corresponding central or medial MDn damage was associated with impaired acquisition.

The absence of any impairment on the odour–place task after MT lesions, defined by the inclusion of the anterior and medial MDn, the central MDn and the intermediodorsal nucleus, adds weight to previous evidence that relatively mild deficits, if any, are often associated with selective MD lesions, at least in terms of hippocampal-sensitive spatial tasks in the rat. It is now acknowledged that previous evidence of severe deficits found in hippocampal-dependent maze learning tasks with large MD lesions [41,65,66,85], and indeed ILn lesions [44,59,85], was primarily due to associated damage to the AT [3,15,37,47,48]. When delay-dependent deficits have been found after selective neurotoxic MD lesions, such as working memory for a lever or olfactory stimulus, performance has declined to about only 80% correct at the longest, 13–20 s, delay used [6,12,87]. One domain in which MT or MD lesions appear to play a more marked influence, whereas AT or LT lesions appear to be without effect, is in terms of memory for reward value and the anticipation of rewarding or reinforcing events [18,26,47,51]. These latter effects may have as their basis a ventro-lateral prefrontal, ventral basal ganglia, MT neuroanatomical circuit [47]. In addition, there is some evidence that disruption to the MD specifically influences flexible responding in delayed radial maze foraging and disrupts the ability to switch from a preferred response rule or strategy to a new strategy [25,37,38], even with localized lesions [17]. We conjecture that these latter effects may be associated with a midline prefrontal cortex, dorsomedial basal ganglia, MD circuit.

The second dominant line of thought on the thalamic basis of diencephalic amnesia has emphasised the AT region (and to a lesser extent the MD) and minimised the role of the ILn [1,2,15,49,68,73]. The current study adds to the growing list of impairments on hippocampal-sensitive spatial learning and memory tasks found after AT lesions (for examples, see [3,6,15,47,73,78,82]). Previous evidence of a complete inability by rats with AT lesions to learn an associative memory task, in which the rats had to choose a visual object based on

its general spatial context, employed large electrolytic lesions [68]. The current study used a different associative memory task, in which the pairing of spatial location and a specific cue (odour) rather than the spatial context of two objects formed the arbitrary association, but it is perhaps the use of selective neurotoxic AT lesions that is of greater importance in confirming the role of this region for associative memory with spatial cues. Non-neurotoxic lesions disrupt fibres of passage, which in this instance may be a particularly relevant confound because large electrolytic AT lesions will disrupt fibres from the centrolateral nuclei and (especially) paracentral nuclei that course through the AT region and its adjacent structures [71] and the current study has shown that severe deficits in associative memory can occur after selective LT lesions that include these intralaminar nuclei. Indeed, as it is clear that both AT and LT lesions can separately impair associative memory, at least when spatial cues form part of the conditional context, it is perhaps premature to overemphasise only one region as the primary basis for diencephalic amnesia.

The period of probe testing in the current study suggested that the rats did not rely on an allocentric strategy at the end of the initial period of training, because performance on the probe trials when the start box was placed on the opposite side of the field fell to minimal levels in the control and MT groups in the first week of testing. However, a degree of general disruption was apparent because performance from the original start position was also reduced in these groups during this first week, although to a lesser extent. These observations and the indication of at least partial recovery on continued testing from the opposite start position suggest that the rats relied on a combination of place, direction or response cues to solve the location component of the odour–place paired-associate task. This possibility is consistent with previous evidence that animals may learn one or more type of cue in parallel and that performance on spatial tasks may rely on interactions between these cues [19,29,63]. One implication of our findings is that other studies attempting to measure 'spatial' memory in this or similar paired-associate tasks may need to discourage the use of non-spatial strategies, for example by introducing more than one start position early in training. Gilbert and Kesner's odour–place paired-associate learning studies on which the current study was based did not employ probe testing [30,31], so it is possible that the rats in those experiments were also relying partly or fully on strategies other than allocentric spatial memory. However, the (female) rats used here took far longer than the (male) rats in these earlier studies to acquire the odour–place task. On average, their controls reached high levels of performance in about 5–6 weeks, whereas the control and MT rats in the current study required about twice as long. Indeed, one control rat in the current study never acquired the task (Fig. 5). Lengthier training schedules are generally believed to discourage allocentric spatial strategies in favour of response strategies in rats and the latter strategies may actually interfere with place learning [29,52,57].

The precise explanation for the AT and LT lesion impairments in odour–place learning awaits further study and it is possible that these deficits arose for different reasons. A failure to process allocentric and related spatial information may be the primary reason for the disrupted acquisition in AT rats, whereas problems in response or directional learning may have retarded acquisition in the LT rats. AT lesions, but not LT lesions, impair spatial memory in hippocampal lesion-sensitive tasks, such as classic versions of the varying choice delayed nonmatching version of the radial-arm maze task, whereas LT (or similar) lesions impair matching to sample working memory for an egocentric (body turn) response or for one of two retractable levers [6,44,47,48]. These double dissociations dovetail with the predominant neural connections associated with the AT and LT regions, respectively the hippocampal system and the striatum. Given that ILn lesion effects may be more similar to those of prefrontal cortex lesions than hippocampal lesions [6], but both LT and AT regions have reciprocal prefrontal cortex connections that are most prominent at the level of the dorsal prefrontal cortex [9,62,71], disruption of prefrontal cortex activity may also provide a basis for the current lesion effects. One problem with this assumption, however, is that medial rather than dorsal prefrontal cortex lesions impair arbitrary association learning involving spatial cues, at least when the association is between location and objects [39]. While the available evidence suggests that the current AT lesion effects derive from their prominent connections with the hippocampal, rather than the prefrontal systems [62], it is also possible that there is a role for the relatively weak connections between the ILn and the retrohippocampal region, especially the perirhinal cortex [71]. The reason for the latter suggestion is that an interesting parallel exists between the effects of LT lesions and that of perirhinal lesions. Both of these lesions seem to have little, if any, effect on standard hippocampal-dependent spatial memory tasks yet, like the current study with LT lesions, perirhinal cortex lesions have a profound effect on associative memory when a spatial component provides one of the arbitrary cues [14]. The current data, especially the uncertainty associated with the performance of the control and MT rats, do not enable clarification of these possibilities but raise a number of possible options for further study. Perhaps the most immediate question, however, is the generality of the effects of AT and LT, and indeed MT, lesions on different associative memory tasks. For example, hippocampal lesions, but not AT lesions, impair egocentric conditional associative learning [69], so it would be informative to know whether LT or MT lesions impair such tasks. Conversely, large hippocampal lesions do not impair learning of an object–odour paired-association [30] and it remains to be determined whether any of the current limbic thalamic lesions influence acquisition of this task also.

While evidence from human clinical cases suggests an important role for the thalamus in amnesia the non-specific damage typically observed in these cases means that there is little consensus over the specific roles of individual thalamic nuclei [1,20,35,44,46,72]. The current study supports the view that amnesia may be caused by limited damage to any of a number of diencephalic structures, each contributing differently to particular aspects of the overall memory impairment. Such findings encourage traditional models of memory function [40,83] to place a greater emphasis on the important role of the limbic thalamus in the brain's memory systems.

## Acknowledgements

Our research has been supported by University of Canterbury and the Neurological Foundation of New Zealand. Sheree Gibb has been supported by a University of Canterbury Masters Scholarship and a Tertiary Education Commission Top Achiever Doctoral Scholarship.

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