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Dissociable memory effects after medial thalamus lesions in the rat

Anna S. Mitchell* and John C. Dalrymple-Alford
Van der Veer Institute for Parkinson's and Brain Research, and Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch 8001, New Zealand

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Abstract

Variable neuropathology in cases of diencephalic amnesia has led to uncertainty in identifying key thalamic nuclei and their potential role in learning and memory. Based on the principal neural connections of the medial thalamus, the current study tested the hypothesis that different aggregates of thalamic nuclei contribute to separate memory systems. Lesions of the anterior thalamic aggregate (AT), which comprises the anterodorsal, anteromedial and anteroventral nuclei produced substantial deficits in both working and reference spatial memory in a radial arm maze task in rats, supporting the view that the AT is an integral part of a hippocampal memory system. Lesions to the lateral thalamic aggregate (LT), which comprises the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei) produced a mild working memory impairment only, while lesions to the posteromedial thalamic aggregate (MT), which comprises the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus had no effect on radial arm maze performance. In contrast, only MT lesions impaired learning associated with memory for reward value, consistent with the idea that the MT contributes to an amygdala memory system. Compared with chance discrimination, the control and AT groups, but not MT or LT groups, showed evidence for temporal order memory for two recently presented objects; all groups showed intact object recognition for novel vs. familiar objects. These new dissociations show that different medial thalamic aggregates participate in multiple memory systems and reinforce the idea that memory deficits in diencephalic amnesics may vary as a function of the relative involvement of different thalamic regions.

Introduction

Damage to the limbic thalamus produces profound amnesia but the specific contribution of structures within this region is contentious (Kopelman, 2002; Schmahmann, 2003). Lesions affecting the intralaminar thalamic nuclei (ILn) or anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei (AT) are currently the two most frequently stated sources of this amnesic syndrome. AT lesions are of interest because they mirror some effects of hippocampal system damage but the range of deficits associated with ILn lesions suggests that the latter are more essential to thalamic amnesia (Aggleton & Brown, 1999; Mair *et al.*, 2003). The mediodorsal thalamic nuclei (MD) have also been regarded as critical (Victor *et al.*, 1989), with more recent interpretations suggesting a general influence on prefrontal cortex (PFC) function or in support of recognition memory (Aggleton & Brown, 1999; Gaffan & Parker, 2000; Van der Werf *et al.*, 2003a). It has been surprisingly difficult to resolve these conflicting views because the anatomical proximity of these three thalamic structures has often compromised lesion specificity and few studies have directly compared different thalamic lesions. The current study explicitly addressed the issue of lesion specificity and provides the first comparison of the behavioral effects of lesions to all three thalamic regions.

Correspondence: Dr J. C. Dalrymple-Alford, as above.
E-mail: john.dalrymple-alford@canterbury.ac.nz

**Present address*: Department of Experimental Psychology, Oxford University, Oxford, OX1 3UD, UK.

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Accounts of the relevant neuroanatomical connections, and suggestions that the MD region itself should be subdivided, guided the three lesion targets examined here (Fig. 1). The AT target primarily has strong reciprocal connections with the hippocampus via the retrohippocampal region. The lateral thalamic aggregate (LT) target comprised the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei), which have overlapping connections in a circuit with the anterior cingulate, precentral cortex, caudate-putamen and globus pallidus. The third target, the posteromedial thalamic aggregate (MT) comprised the central MD, medial MD and the intermediodorsal nucleus. The MT has prominent reciprocal connections with the ventral and lateral PFC, amygdala and ventral basal ganglia.

Comparison of these lesions addressed the idea that the thalamic regions express markedly different function in concert with their respective anatomical connections, consistent with the speculation that different thalamic regions contribute to the brain's multiple memory systems (Bentivoglio *et al.*, 1997). An alternative view is that ILn lesions produce severe memory deficits and that modest or more selective effects, if any, occur after localized AT or MD lesions (Mair *et al.*, 2003). If the first idea is correct, then selective AT, rather than MT or even LT, lesions should impair spatial memory in the radial maze because this task is highly sensitive to hippocampal system damage. Lesions to the agranular-insular PFC and amygdala produce deficits in working memory for reward value (Kesner & Williams, 1995; DeCoteau *et al.*, 1997; Ragozzino & Kesner, 1999), providing a task that may therefore be preferentially associated with the MT

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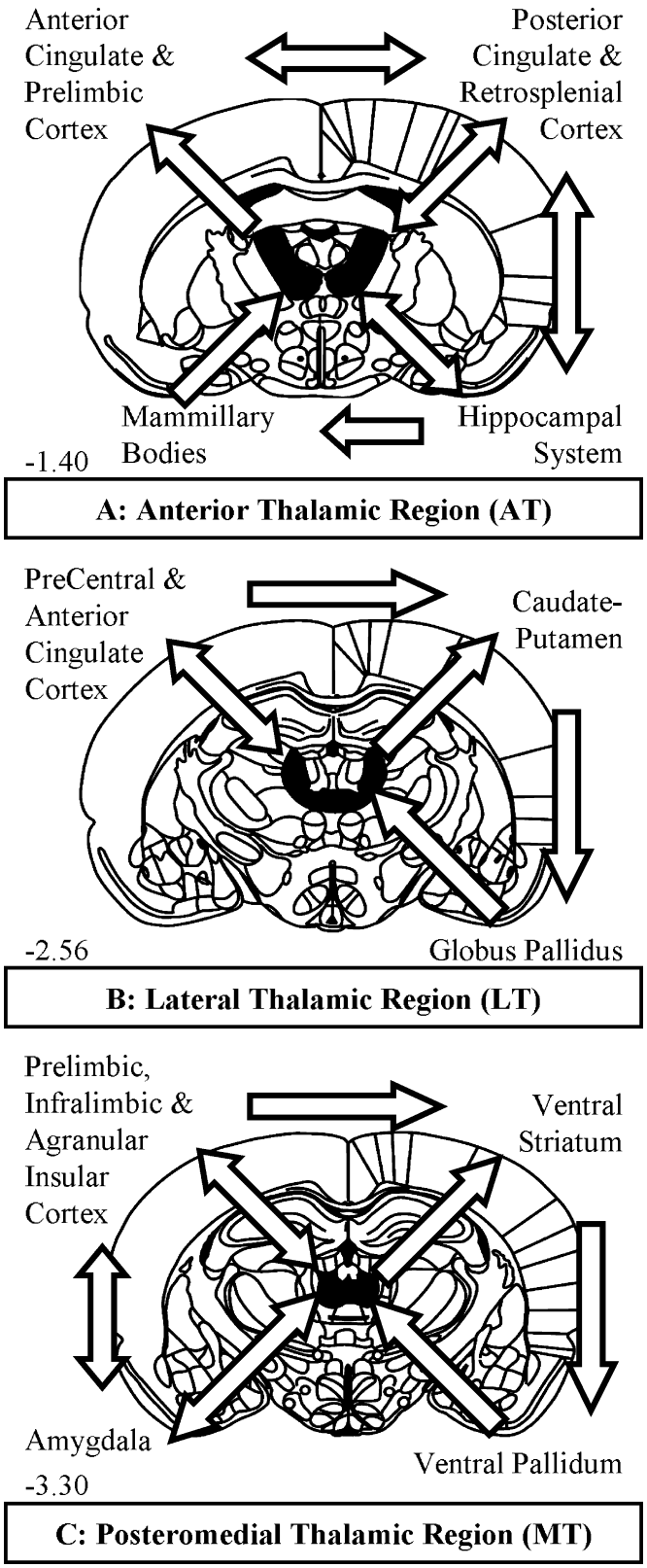

FIG. 1. Schematic diagrams of the prominent neural connections of three aggregates of medial thalamic nuclei. (A) Anterior thalamic region (summarized from: Shibata, 1992; van Groen & Wyss, 1995; Shibata, 1998; van Groen *et al.*, 1999). (B) Lateral thalamic region (Berendse & Groenewegen, 1991; Van der Werf *et al.*, 2002). (C) Posteromedial thalamic region (Groenewegen, 1988; Groenewegen *et al.*, 1990). Numbers refer to distance from bregma (Paxinos & Watson, 1998).

region. Another view is that some tasks may be influenced by all three thalamic regions, given their partially overlapping connections in the PFC. This third alternative was tested using a recency discrimination task to assess temporal order memory for objects, which is reliably impaired by PFC lesions (Mitchell & Laiacona, 1998; Hannesson *et al.*, 2004a,b).

Materials and methods

Subjects

Groups of four PVGc female hooded rats (initial weight 180–220 g) were housed in opaque plastic cages (27 × 45 × 22 cm high) under a reversed light schedule (off 08:00–20:00 h). Rats had free access to water and were maintained at 80–85% of *ad libitum* weight, bar free food access just before and after surgery to facilitate postoperative recovery. Testing occurred between 08:30 and 19:30 h at a rate of five to six daily sessions per week. All protocols conformed to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of the University of Canterbury.

Surgery

Anesthetized rats (50 mg/mL pentobarbitone at 1.65 mL/kg 20 min after 0.13 mg/mL atropine at 1.5 mL/kg, i.p.) were placed in a stereotaxic apparatus with the incisor bar set 7.5 mm below the intra-aural line to minimize or avoid fornix injury. After craniotomy, microinfusions of 0.12 M *N*-methyl-D-aspartate (Sigma Chemicals, Australia) dissolved in phosphate buffer, pH 7.20, were made via a 1-μL Hamilton syringe connected to a motorized infusion pump using 3 min for diffusion after the infusion at each site (see Table 1 for details and coordinates). Three groups of rats received either AT, LT or MT lesions. To maximize lesion accuracy, anterior–posterior coordinates in the horizontal plane were varied according to the bregma–lambda distance in each rat. A fourth group of rats (controls) received sham lesion surgery but no infusion; the same anterior–posterior and

TABLE 1. Methodology for *N*-methyl-d-aspartate lesions of the three medial thalamic aggregates; coordinates (cm) for various bregma–lambda (B–L) measurements, infusion volumes and rates

	AT		LT			MT	
	Anterior	Posterior	Anterior	Anterior	Posterior	Anterior	Posterior
AP coordinates for B–L distances (cm)							
0.60–0.61	−0.245	−0.255	−0.345	−0.345	−0.385	−0.365	−0.405
0.62–0.63	−0.255	−0.265	−0.355	−0.355	−0.395	−0.375	−0.415
0.64–0.66	−0.265	−0.275	−0.365	−0.365	−0.405	−0.385	−0.425
0.67–0.68	−0.275	−0.285	−0.375	−0.375	−0.415	−0.395	−0.435
ML	±0.120	±0.146	±0.130	±0.130	±0.130	±0.0	±0.0
DV	−0.58	−0.556	−0.56	−0.60	−0.56	−0.56	−0.57
Volume (μL, 0.12 M)	0.12	0.12	−0.60	0.08	0.06	0.20	0.18
Infusion rate (min)	4	4	2	2	2	4	4

Ant, anterior AP site; AP, anterior–posterior distance from bregma; AT, anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; DV, dorsal–ventral distance from dura; LT, lateral medial thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei; see Van der Werf *et al.*, 2002) 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.

ML coordinates were used from the three lesion groups spread evenly across controls, −0.25 cm dorsal–ventral at the corresponding sites.

Behavioral testing

Apparatus and testing environment for the spatial memory task

Spatial memory was tested using an elevated (85 cm above floor) 12-arm radial maze with a 35-cm-wide central wooden hub, painted black, and equally spaced aluminum arms (9 cm wide × 65 cm long). Each arm had 3-cm-high borders and a single Perspex barrier (25 × 20 cm) adjacent to the hub. A black wooden insert (8.5 × 5 × 3 cm) at the end of each arm incorporated a food well (2 cm diameter, 1 cm deep) with two 0.1-g pieces of chocolate when baited and with food odours provided by inaccessible chocolate underneath the well at all times. Clear Perspex guillotine doors that could be raised singly or as one unit via overhead cables governed access to the arms. The maze was located in a windowless rectangular light-gray-colored room with numerous spatial cues (high contrast posters hung on the walls, a door, computer, desk, chair and experimenter).

Behavioral paradigm for spatial memory

The rats were preoperatively trained on the task and then tested postoperatively. After maze familiarization, using methods previously described in Mitchell *et al.* (2002), rats received training on one of three different configurations of eight baited/two never-baited arms, counterbalanced across rats (the additional two arms always remained blocked for any given rat but all 12 arms were used across configurations). For the initial preoperative daily trials, the rat was placed in the central hub and, 5 s later, the 10 appropriate doors were opened allowing the rat to make a free choice of any arm. All doors were lowered as the rat proceeded to the food well at the end of the selected arm; the door of this arm was then opened and lowered behind the rat to allow it to access the central hub. After a 5-s interval, the same 10 arms were re-opened to allow the rat to make its next choice (the use of doors was to minimize the adoption of response strategies). The trial continued until all eight of the baited arms had been visited, 24 entries had been made or 10 min had elapsed. The whole maze was always wiped clean with a weak detergent solution between rats. After 25 preoperative trials, the doors were left open (no longer opened and closed) after the first arm choice. Preoperatively, working memory errors occurred infrequently but training continued until a criterion was reached in which there was no more than an average of one reference memory error across three consecutive trials (about 90 trials). Rats were matched for accuracy in avoiding the never-baited arms across the last three preoperative trials and randomly assigned to one of four groups for surgery. After 10 days of postoperative recovery, retesting in the eight baited/two never-baited radial-arm maze task continued for 15 daily trials (again, doors were only closed when the rat was initially placed in the maze hub).

Apparatus and testing environment for the memory for reward magnitude task

The memory for reward magnitude task was conducted in a different room to that used for spatial memory. The apparatus and procedure were modelled on those described by Kesner & Williams (1995). A small rectangular wooden platform painted black was divided into two 65-cm-long halves by a 50-cm-tall black wooden door which was the same width (35 cm) as the platform and operated by an overhead pulley. Centred 6 cm from each end of the platform was a recessed 2.6-cm diameter food well (flanked by two unused wells) which was covered by a small object (weighted plastic bottles, 120–150 cm high). The long edge of the platform on one side was positioned against the light-gray wall of the room, while a sheet of red Plexiglas (88 cm high, ending 15 cm from each end of the platform) on the opposite length provided a semiopaque wall that obscured the rat's view of the experimenter, seated in front of this Plexiglas.

Behavioral paradigm for memory for reward magnitude

Rats received familiarization with the reward magnitude apparatus at a break mid-way through presurgery radial maze training. They were shaped to displace an object that covered one of the food wells and were habituated to three brand cereals: Maximize (20% sugar), Froot Loops (40% sugar) and Cocoa Pops (40% sugar). After the postoperative object exploration tests (see below), rats were given a brief re-familiarization with the apparatus before acquisition training began. In each session, rats remained on the platform throughout 12 go/no-go working memory trials (six positive and six negative trials), counterbalanced by using pseudo-random sequences (Fellows, 1967). Each trial always began with the rat situated on the same side of the platform (left, relative to the experimenter). For the sample run of a trial, the rat ran from the left side of the platform to the food well on the right side where it dislodged the object to eat either a ½ piece of Maximize (20% sugar) or a ½ piece of Froot Loops (40% sugar). These two reward-value conditional stimuli were of equal size and similar texture. After the rat had eaten the cereal (minimum delay of 1–4 s), the test run of the trial began by raising the central door to allow the rat to cross back to the left side of the platform where the rat was able to dislodge the object covering the central food well where additional or no additional food reward (two Cocoa Pops) could be found. Half of the rats had to learn that Maximize cereal on the sample run was associated with additional food reward on the test run (i.e. go, positive trial) and that Froot Loops cereal on the sample run signaled no reward on the test run (i.e. no-go, negative trial). This magnitude of reward-dependent contingency was reversed for the other half of the rats (counterbalanced across groups). The trial was terminated when the rat displaced the object on the test run or 10 s had elapsed; the inter-trial interval was15 s. Rats had to learn to run quickly across the platform to dislodge the object on the test run if the reward value stimulus which they ate on the sample run signaled the availability of an additional reward and to refrain from dislodging the object on the test run when the alternate reward-value stimulus which was eaten in the sample run signaled no additional reward. Kesner and colleagues (e.g. Ragozzino & Kesner, 1999) have shown that intact rats respond to the reward value of the cereals in the sample run and not to other stimulus characteristics (e.g. texture). Postoperative training was conducted until 24 sessions were completed followed by a 4-week break before further sessions were conducted to assess retention and reacquisition of the reward-value association.

Apparatus and testing environment for the temporal order memory task

Testing took place in one of two similar windowless rooms, which were different to those used for the spatial memory and reward magnitude tasks. Two small rectangular test boxes were used for all behavioral testing (36 cm wide × 63 cm long × 34 cm high), with an equal light level at the floor of each box (34 lux). The ample sawdust that covered the floor of the boxes in all sessions was thoroughly mixed before each study and test trial (any faecal boli were removed). One of the longer walls of the box was made of clear Perspex and the remaining walls and floor were wooden and painted gray. The boxes

were placed on tables in the center of the room with the clear Perspex wall always facing away from the door so that the rat was not distracted while the experimenter exited the room. Each rat was only ever exposed to one room and box for testing, randomized across groups. A camera mounted above each box relayed recorded images to the adjacent control room. The objects used in this task were triplicates of two weighted objects: a glass bottle (210 cm high) and an aluminum can (130 cm high). When present, an object was fixed to the floor with Velcro and centred 1 cm away from a midway point along each short-end wall so that the rat could not circle them.

Behavioral paradigm for temporal order memory

Temporal order memory was based on a previously reported study that used a recency discrimination task requiring the spontaneous (non-rewarded) exploration of objects (Mitchell & Laiacona, 1998). Immediately after postoperative radial maze testing, single rats were familiarized in four daily 1-h trials with the empty test box (sawdust on floor only), starting each trial by being placed in the center of the box facing the longer wooden wall. On the fifth day, rats received a new (procedural) familiarization session of 5 min in the empty test box, 1 h in a clean opaque-covered holding cage located in the test room and a further 5 min back in the empty box. On the next day, the rat received a 5-min study trial to explore a pair of identical objects (A) followed by placement in the holding cage for a 1-h interval and then a second 5-min study trial to explore a second pair of identical objects (B; order of objects counterbalanced across rats). On completion of the second study trial, the rat was returned to the holding cage for a second 1-h delay, after which the test trial began. For the test trial, the rat was placed back in the box for 5 min, with a triplicate of object A and a triplicate of object B (positions counterbalanced across rats). The time spent exploring each object was recorded when the rat was 2 cm or closer and facing the object (climbing not counted). The amount of time spent exploring each object during this test trial is equated with preference for the object (dependent measure). During this test trial, intact rats normally show greater exploration of the familiar object presented earlier in time than the familiar object presented more recently (Mitchell & Laiacona, 1998). Furthermore, Hannesson *et al.* (2004b) have shown that this task assesses the relative recency of two familiar objects, not simply the relative familiarity of a recently explored object vs. a novel (i.e. 'forgotten') object.

Behavioral paradigm for familiar vs. novel object recognition

Rats received a familiar vs. novel object recognition test 48 h after the temporal order memory task, with each rat tested in its familiar exploration box. This test was adapted from the widely used spontaneous (non-rewarded) object recognition task developed by Ennaceur & Delacour (1988), which normally uses a large open field and a 15-min delay between study and test trials (Ennaceur & Aggleton, 1997). Individual rats were given a 5-min study trial to explore a new pair of identical objects (C) before being placed in separate holding cages for a 2-h delay before the object recognition test. The 2-h delay equated the initial study trial vs. test trial used in the temporal order memory task and thus equates the critical delay of memory for the initial object across the two tasks. For the object recognition task, individual rats were returned to the box for 5 min to explore a triplicate of object C and a novel object (D). The two objects, a weighted plastic bottle (170 cm high) and a conical light bulb (110 cm high), were counterbalanced across study and test trials and for position in the test trial. The time spent exploring each object was recorded when the rat was 2 cm or closer and facing the object (climbing not counted). During the test trial, intact rats normally spend more time exploring the novel object than the familiar object and this preference is taken as a relative measure of recognition of the previously explored familiar object and recognition of a new object (Ennaceur & Aggleton, 1997).

Histology

On completion of behavioral testing, rats were given an overdose of pentobarbital and transcardially perfused with 0.9% saline followed by 4% formalin. Brains were stored in 4% formalin for 24 h and transferred to a long-term sucrose solution. Serial frozen 50-μm sections were taken throughout the medial thalamus and stained with cresyl violet.

Results

Histological analyses

Both authors independently estimated the thalamic damage using the relevant plates from a standard atlas (Paxinos & Watson, 1998) and differences were resolved by consensus (J.C.D.-A. was blind to the individual behavioral data). Lesions to individual regions were expressed as a percent reduction on each relevant atlas plate and the volume of damage relative to the intact region estimated by factoring in the distances provided in the atlas (Table 2). Figure 2A–C shows the minimum and maximum extent of successful bilateral lesions for all groups. Such lesions met the inclusion criterion of clear evidence on visual inspection of bilateral damage to the intended target region and a minimum of 50% damage overall in that target. Exclusion of any rat in a lesion group was based on damage of more than 40% overall to either alternate thalamic target. As Table 2 shows, these criteria provided groups with highly accurate lesions, including moderate to substantial damage in the specified target while minimizing the amount of unintended damage to the adjacent thalamic regions. Acceptable AT lesions received a median of 90.7% bilateral damage (combined across the anteroventral, anteromedial and anterodorsal thalamic nuclei, treated as a single region) with minor damage to the MT region (median 4.8%) and modest damage to the LT region overall (median 21.8%) although the rostral central medial thalamic nuclei received moderate damage (median 47.2%). There was generally substantial damage to the interanteromedial nucleus (median 80.4%), moderate damage to the parataenial nucleus (median 61.5%) but little damage to the laterodorsal nucleus (median 2.4%) in these AT lesion rats. Acceptable LT lesions produced moderate overall damage on average (65.1%), evenly spread across the centrolateral and paracentral intralaminar nuclei and the lateral segments of the MD but with relatively little damage to the rostral central medial thalamic nuclei (21.0%). There was almost no damage to the AT region (1.1%) and only modest damage in the MT region (20.3%) in these LT rats. Acceptable MT lesions produced moderate to substantial overall damage (71.1%) to the central and medial segments of the MD and the intermediodorsal nucleus, with minor damage on average to the LT region (6.1%; the greatest damage occurred in the rostral region of central medial nucleus, 13.5%) and no damage to the AT region in all but two MT rats. The paraventricular nucleus also sustained moderate injury (66.7%) in the MT group.

Eight rats were excluded from the main behavioral analyses as they did not meet the inclusion and exclusion criteria (Table 2). Four AT rats sustained substantial damage to the MT and LT regions, with one AT rat sustaining insufficient AT damage. Two LT rats had excessive damage to the MT region. Two MT rats sustained insufficient damage to the intended target.

TABLE 2. Details of medial thalamus lesions in all rats, expressed as percentages of bilateral volumes

	AT				MT				LT										
Inclusions/ exclusions*	AD	AM	AV	Whole region	IMD	MDc	MDm	Whole region	CL	MD1/ MDp1	PC	rCeM	Whole region	IAM	LD	PT	PVA	PV/ PVP	Re/ Rh
AT inclusions ($n = 8$)																			
AT132	86.1	93.6	59.8	75.9	0.0	0.0	3.1	2.0	11.7	2.2	28.0	26.0	15.1	66.3	0.6	27.9	2.6	0.0	0.3
AT133	99.9	96.3	81.6	89.8	0.0	0.0	4.0	2.6	13.8	5.3	28.2	13.8	16.8	64.8	4.3	24.2	1.6	0.0	1.0
AT134	99.8	99.3	63.2	82.0	0.0	0.1	9.0	5.8	12.4	12.5	31.0	54.9	22.8	89.3	2.4	33.6	19.3	0.0	0.6
AT145	99.9	99.9	90.0	95.1	0.4	6.9	16.6	12.6	13.6	14.1	32.3	13.6	25.2	90.0	1.6	59.7	4.2	0.0	25.1
AT146	98.5	98.0	83.7	91.2	0.0	3.7	9.8	7.4	31.9	34.0	47.5	53.5	39.2	76.7	3.0	19.4	0.4	0.0	0.2
AT147	97.1	97.3	93.7	95.5	0.0	0.0	5.2	3.3	10.0	9.0	31.0	53.8	20.8	85.1	2.1	24.9	1.5	0.0	0.9
AT163	99.9	97.5	94.0	96.3	0.0	5.0	13.2	9.9	17.0	16.5	27.8	60.4	25.4	84.1	6.7	47.9	19.9	0.0	0.6
AT166	99.7	83.9	90.6	90.1	0.0	0.0	5.8	3.7	6.6	6.3	23.5	40.9	15.3	62.0	2.3	57.3	0.6	0.0	0.6
AT median	99.8	97.4	86.9	90.7	0.0	0.1	7.4	4.8	13.0	10.8	29.6	47.2	21.8	80.4	2.4	61.5	4.2	0.0	0.6
AT exclusions																			
AT129	51.5	64.3	36.4	48.4	54.9	99.5	57.2	69.0	81.1	78.2	77.4	83.2	79.7	73.4	6.6	22.7	0.1	2.1	4.7
AT169	99.8	100	88.9	94.6	38.7	47.2	43.2	44.0	30.6	41.1	42.9	99.9	45.9	100	4.7	60.0	22.5	0.5	44.9
AT171	67.4	82.4	59.3	68.4	49.5	98.8	54.7	66.8	80.5	80.7	77.7	91.3	81.4	86.3	13.5	72.1	29.8	0.5	8.2
AT173	51.9	71.5	38.5	51.8	35.4	98.1	44.3	58.9	70.4	62.3	78.5	89.9	72.8	90.9	1.9	20.2	0.3	0.0	7.8
LT inclusions ($n = 10$)																			
LT126	1.0	2.7	1.2	1.6	0.0	41.6	12.7	20.0	85.4	71.5	63.5	8.9	65.9	0.0	0.8	0.0	0.0	0.0	0.0
LT135	0.0	1.3	0.2	0.5	0.0	43.5	28.3	30.5	76.3	61.7	72.3	24.0	64.2	0.3	1.5	0.0	0.0	0.0	0.0
LT136	38.7	38.0	12.1	25.6	0.0	25.9	32.5	28.2	72.6	69.3	74.4	18.2	64.8	20.4	0.5	38.7	21.9	0.0	0.0
LT137	0.0	0.0	0.0	0.0	0.0	19.0	15.1	15.1	90.8	71.8	72.8	20.8	71.7	0.0	0.2	0.0	0.0	0.0	0.0
LT142	0.0	0.4	0.3	0.3	0.0	22.9	17.1	17.5	74.8	70.4	69.9	23.4	65.4	0.0	2.3	0.0	0.0	0.6	0.4
LT153	4.1	17.2	1.4	7.1	0.0	11.7	15.0	13.0	71.0	65.1	71.5	24.3	63.2	0.6	1.5	0.2	0.0	0.0	0.0
LT158	5.7	4.1	1.1	3.0	0.0	85.4	20.8	37.6	97.6	92.7	66.0	24.6	78.6	0.3	2.9	2.8	0.0	0.0	0.0
LT164	6.2	23.8	3.1	10.5	0.0	29.3	19.0	20.5	70.4	67.5	75.3	21.1	64.1	5.3	0.2	2.0	0.0	0.0	0.0
LT167	0.0	0.3	0.0	0.1	0.0	44.6	30.5	32.2	78.6	72.8	66.8	5.3	64.2	0.0	0.4	0.0	0.0	0.1	0.0
LT174	0.0	0.5	0.3	0.3	0.0	31.7	10.2	15.5	83.2	73.7	70.0	18.5	68.6	0.1	0.6	0.0	0.0	0.0	0.1
LT median	0.5	2.0	0.7	1.1	0.0	30.5	18.1	20.3	77.5	71.0	70.8	21.0	65.1	0.2	0.7	0.0	0.0	0.0	0.0
LT exclusions																			
LT125	2.0	5.1	4.2	4.1	2.2	63.0	38.8	43.0	96.7	88.8	78.8	20.6	79.8	0.0	1.8	0.0	0.0	4.9	0.0
LT154	5.9	7.2	6.1	6.4	8.1	89.3	51.7	59.2	99.8	99.8	79.5	41.2	86.9	3.6	2.6	0.0	0.0	1.9	0.3
MT inclusions ($n = 10$)																			
MT138	0.0	0.0	0.0	0.0	97.9	51.8	65.8	64.2	0.0	0.6	3.2	7.6	2.0	0.0	0.0	0.0	4.4	55.5	0.0
MT139	0.0	0.0	0.0	0.0	100	68.7	74.9	75.0	0.0	8.8	10.8	21.5	8.0	0.0	0.0	5.1	4.3	69.3	0.0
MT149	0.0	0.0	0.0	0.0	93.9	44.1	57.0	56.1	0.0	1.7	1.1	2.2	1.0	0.0	0.0	0.0	0.0	53.5	0.0
MT155	0.0	0.0	0.0	0.0	99.8	70.1	81.6	79.7	0.2	5.4	8.8	19.0	6.3	0.0	0.0	9.5	2.7	39.0	0.0
MT156	0.0	0.0	0.0	0.0	99.7	52.4	70.0	67.2	0.0	2.0	0.8	2.0	1.0	0.0	0.0	0.0	0.2	77.1	0.0
MT157	0.0	0.0	0.0	0.0	69.6	41.8	67.8	60.6	0.3	2.8	13.4	7.6	5.2	0.0	0.0	0.0	0.0	64.1	0.0
MT161	0.0	0.0	0.0	0.0	99.8	87.5	83.6	85.9	0.0	9.5	4.3	15.6	5.8	0.0	0.0	0.0	0.6	88.3	0.0
MT162	1.0	6.7	0.0	2.4	100	94.3	86.6	89.8	1.6	13.6	6.6	82.5	17.1	30.8	0.0	15.6	61.6	99.8	0.0
MT168	0.0	0.0	0.0	0.0	93.6	58.8	58.9	61.5	0.0	6.9	0.8	11.3	3.6	0.0	0.0	0.0	0.0	43.1	0.0
MT172	1.1	3.6	0.0	1.4	100	94.7	83.2	87.7	0.0	9.5	9.0	76.7	15.2	38.6	0.0	22.8	19.2	76.6	0.2
MT median	0.0	0.0	0.0	0.0	99.8	63.8	72.5	71.1	0.0	6.2	5.5	13.5	6.1	0.0	0.0	0.0	1.7	66.7	0.0
MT exclusions																			
MT127	0.0	0.0	0.0	0.0	5.2	0.7	3.1	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
MT128	0.0	0.0	0.0	0.0	56.1	22.7	29.0	29.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	26.2	0.0

*See text for inclusion/exclusion criteria. AD, anterodorsal nucleus; AM, anteromedial nucleus; AT, anterior thalamic aggregate comprising the AD, AM, and anteroventral (AV) thalamic nuclei; AT median, median percentage damage to the individual thalamic nuclei/region of all rats with acceptable AT lesions (AT inclusions); AT Whole region, percentage damage to the AD, AM and AV combined as a single area; CL, centrolateral nucleus; IAM, interanteromedial nucleus; IMD, intermediodorsal nucleus; LD, laterodorsal nucleus; LT, lateral thalamic aggregate comprising the intralaminar (CL, paracentral nucleus, rostral central medial nucleus) and lateral mediodorsal nucleus (MDl) / paralamellar mediodorsal nucleus (MDpl); LT median, median percentage damage to the individual thalamic nuclei/ region of all rats with acceptable LT lesions (LT inclusions); LT 'Whole region', percentage damage to the CL, paracentral nucleus (PC), rostral central medial nucleus (rCeM) and MDl/MDpl, combined as a single area; MDc, central mediodorsal nucleus; MDm, medial mediodorsal nucleus; MT, posteromedial thalamic aggregate comprising the IMD, MDc and MDm; MT median, median percentage damage to the individual thalamic nuclei/region of all rats with acceptable MT lesions (MT inclusions). MT Whole region, damage to the IMD, MDc and MDm combined as a single area; PT, parataenial nucleus; PV/PVP, paraventricular nucleus/posterior paraventricular nucleus; PVA, anterior paraventricular nucleus; Re/Rh, reunions nucleus/rhomboid nucleus combined as a single area.

Behavioral tests

Spatial memory

Figure 3 shows the pre- and postoperative errors in the radial-arm maze task for the four groups of rats. Preoperative performance was equivalent across all groups. A 4 (between-group) by 5 (repeated measure of postoperative blocks of three trials) ANOVA for working memory errors (revisit errors to the eight baited arms) produced a highly significant effect of group ($F_{3,35} = 91.99$, $P < 0.0001$), a significant effect of trial block ($F_{4,140} = 3.86$, $P < 0.01$) but no group × trial block interaction ($F < 1.0$) despite the reduction in errors across blocks in the AT and LT groups. Newman-Keuls posthoc tests of the group differences confirmed that the AT group made substantially more working memory errors compared with each of

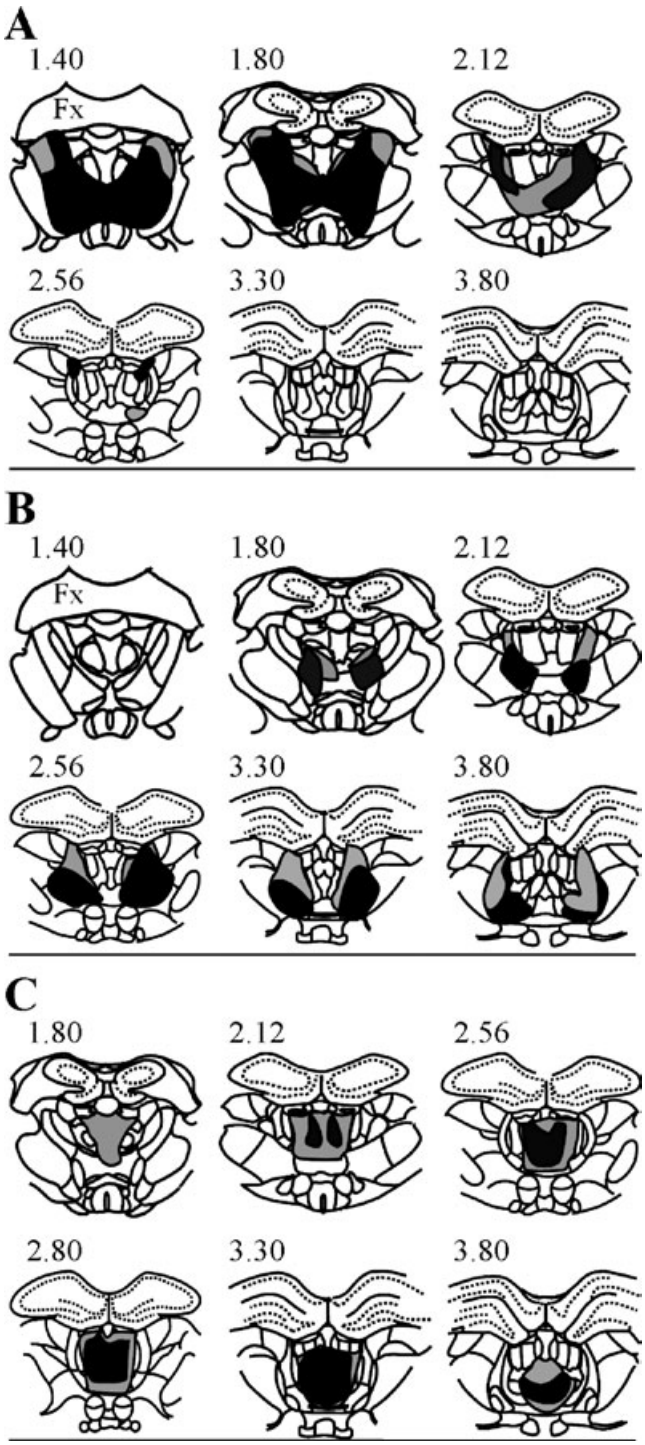

FIG. 2. A series of coronal schematics throughout the medial thalamus showing the area of cell loss in the smallest (black) and largest (gray) thalamic lesions in the each lesion group. (A) Group with lesions to the anterior thalamic aggregate (AT) comprising the anterodorsal, anteromedial and anteroventral 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. Dotted lines represent cell layers in the hippocampus. Numbers refer to the distance from bregma (Paxinos & Watson, 1998).

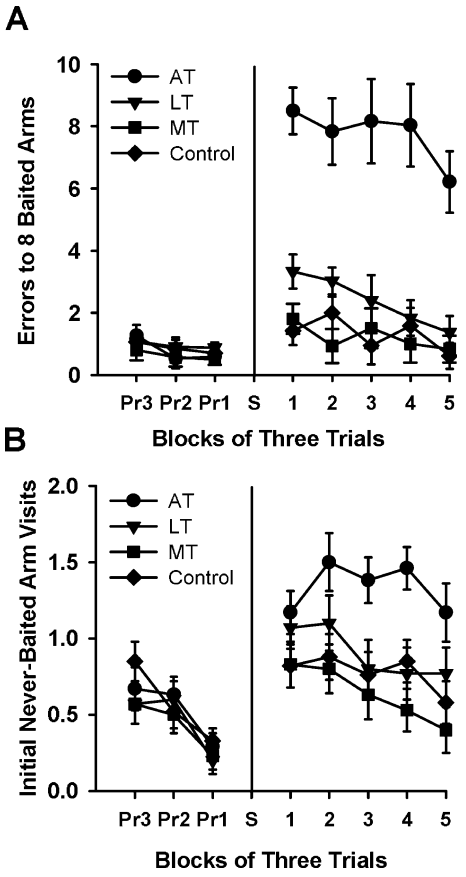

FIG. 3. Spatial memory. Mean (± SEM) number of errors for all groups pre- and postoperatively in the radial-arm maze. (A) Revisit errors to the eight baited arms (working memory errors). The group with lesions to the anterior thalamic aggregate (AT) comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei was different from all other groups ($P < 0.0001$); the 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) was different from the group with lesions to the posteromedial thalamic aggregate (MT) comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus ($P < 0.01$) and controls ($P < 0.02$). (B) Initial visits to the two never-baited arms (reference memory errors). The AT group was different to all other groups ($P < 0.01$). Pr3, Pr2, Pr1, last three blocks of preoperative sessions; S, surgery.

the other three groups ($P < 0.0001$). The LT group showed a relatively mild impairment on this measure by comparison to both the MT ($P < 0.01$) and control ($P < 0.02$) groups but the MT and control groups did not differ ($P > 0.8$). A similar repeated measures ANOVA for reference memory errors (initial visit errors to the two never-baited arms) also produced a significant effect of group ($F_{3,35} = 8.22$, $P < 0.0001$), a significant effect of trial block ($F_{4,140} = 3.33$, $P < 0.02$) but no group × trial block interaction ($F < 1.0$). Posthoc analysis revealed that only the AT group was significantly impaired, making more reference memory errors than each of the other three lesion groups ($P < 0.01$), which did not differ significantly (LT vs. MT, $P = 0.07$; LT vs. control, $P > 0.3$; MT vs. control, $P > 0.2$). Across the five blocks of postoperative testing, the AT group also made more revisit errors to never-baited arms than each of the other three groups (median and range for each group: AT, 0.33, 0.00–1.33; LT, 0.00, 0.00–0.67; MT, 0.00, 0.00–0.00; control, 0.00, 0.00–0.33). Kruskall-Wallis tests confirmed significant group differences on this measure for each trial block (block 1, χ^2 (3) = 14.63, $P < 0.002$; block 2, χ^2 (3) = 13.13, $P < 0.01$; block 3, χ^2 (3) = 15.00, $P < 0.002$; block 4, χ^2 (3) = 12.25, $P < 0.01$; block 5, χ^2 (3) = 16.83, $P < 0.001$).

Choice latencies

The latency to enter an arm was similar across groups for correct visits ($F_{1,35} = 2.09$, $P > 0.12$) but differences were apparent for incorrect choices. As the number of rats in each group that made any error varied across trial block, the available data for each trial block were analysed separately. Despite the clear group differences in the number of working memory errors (revisit errors to baited arms) in the first postoperative trial block, a one-way ANOVA found no significant choice latency differences across groups on this trial block ($F_{3,32} = 1.47$, $P > 0.2$). The mean choice latency for block 1 for revisit errors to baited arms was: AT, 5.11 s (SD 5.63); LT, 5.79 s (3.95); MT, 6.66 s (4.85) and control, 2.87 s (1.34). There were, however, significant group effects for latency for revisit errors to baited arms in blocks 2 ($F_{3,34} = 2.91$, $P < 0.05$) and 4 ($F_{3,34} = 3.16$, $P < 0.04$) with the AT group taking significantly less time to make choices than the LT, MT and control groups. Latencies for blocks 3 and 5 just failed to reach significance ($F_{3,35} = 2.40$, $P < 0.09$ and $F_{3,30} = 2.79$, $P < 0.06$, respectively). The combined mean choice latency across blocks 2–5 for revisit errors to baited arms was: AT, 1.69 s (SD 0.80); LT, 4.45 s (2.52); MT, 4.69 s (3.02) and control, 4.05 s (2.63). Choice latencies to a never-baited arm (both initial visits and revisits) were analysed as a single measure as there were very few such errors in some groups. The mean choice latency for block 1 for entries to never-baited arms was: AT, 2.61 s (SD 0.99); LT, 3.04 s (1.89); MT, 6.06 s (4.36) and control, 6.86 s (10.26), which was not significant across groups ($F_{3,32} = 1.22$, $P > 0.3$). The subsequent four blocks of testing showed that there was also no significant effect of group for latencies to never-baited arms: block 2 ($F_{3,36} = 1.65$, $P > 0.2$), block 3 ($F_{3,35} = 1.76$, $P > 0.2$), block 4 ($F_{3,34} = 2.15$, $P > 0.12$) and block 5 ($F_{3,27} = 1.15$, $P > 0.35$). The combined mean choice latency across blocks 2–5 for visit and revisit errors to never-baited arms was: AT, 1.66 s (SD 1.07); LT, 3.31 s (2.23); MT, 4.52 s (3.55) and control, 3.86 s (3.15).

Memory for reward magnitude

Figure 4 shows the postoperative acquisition and later retention and re-acquisition of the reward magnitude task by the four groups. Each two-session block represents responding in 12 trials of rewarded and 12 trials of non-rewarded discrimination stimuli. Within four to six sessions of testing (i.e. two to three blocks), all rats rapidly learned to dislodge the object covering the food well in about 2 s when the reward-value stimulus on the sample run signaled an additional reward on the test run (i.e. the positive trials). The between-group by blocks of sessions (4 × 12) repeated measures ANOVA for latencies on these positive-trial ('go') test runs produced a highly significant effect of trial block ($F_{11,385} = 42.96$, $P < 0.0001$) but no significant effect of group ($F < 1.0$) or group × trial block interaction ($F < 1.0$). Increased latencies to displace the object during negative-trial ('no-go') test runs began to emerge after about 10–12 sessions (i.e. five to six blocks). The corresponding ANOVA on these negative trials revealed highly significant effects of group ($F_{1,35} = 8.81$, $P < 0.0001$), trial block ($F_{11,385} = 122.45$, $P < 0.0001$) and a group × trial block interaction ($F_{33,385} = 5.24$, $P < 0.0001$). These effects were due to the fact that the MT group was slower to learn not to respond on the no-go trials than all of the other three groups ($P < 0.001$), which did not differ.

After the 4-week break, all groups showed diminished retention of performance on the negative ('no-go') trials. A group by trial block ANOVA to compare negative-trial latency in the last acquisition block (block 12) vs. the first retention block (block 13) revealed a significant effect of group ($F_{1,35} = 6.71$, $P < 0.001$), a significant effect of trial block ($F_{1,35} = 111.64$, $P < 0.0001$) but no group × trial block interaction ($F < 1.0$). Further analysis, using a repeated measures ANOVA for re-acquisition (no-go trial blocks 13–15), confirmed a significant effect of group ($F_{1,35} = 6.24$, $P < 0.002$). The MT group continued to perform more poorly than the other three groups, which did not differ. There was also a significant effect of reacquisition trial block ($F_{2,70} = 50.62$, $P < 0.0001$), reflecting the rapid performance

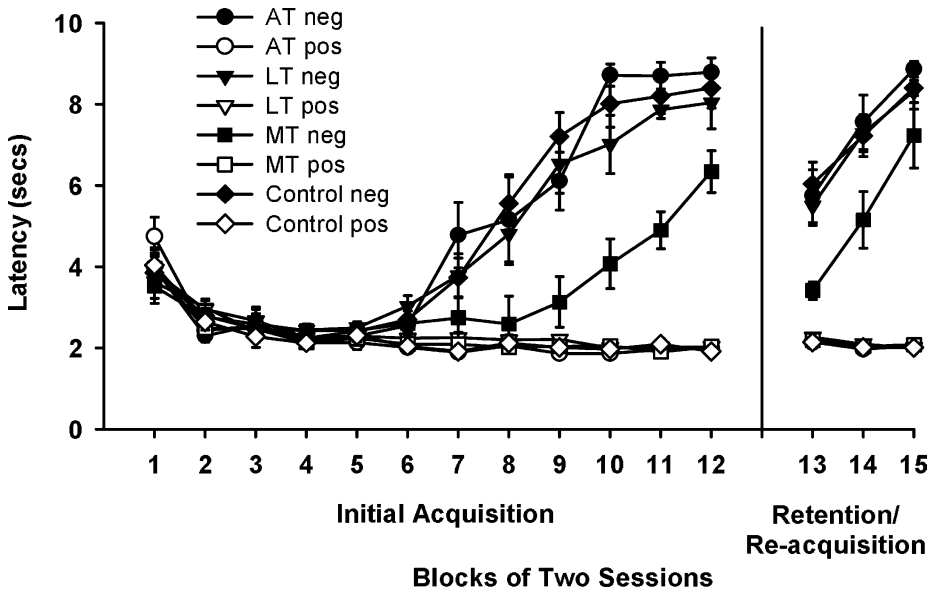

FIG. 4. Memory for reward magnitude. Mean (± SEM) latencies for postsurgery acquisition grouped into blocks of two sessions (six positive and six non-rewarded trials per session) using a conditional go (pos, positive: additional reward available)/no-go (neg, negative: no reward) procedure. All groups exhibited shorter latencies for positive trials and longer latencies for negative trials. The group with lesions to the posteromedial thalamic aggregate (MT) comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus showed poorer acquisition than all other groups for no-go trials during the latter half of training ($P < 0.001$) and during retention/re-acquisition ($P < 0.01$). AT, group with lesions to the anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; LT, group with lesions to the lateral thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei).

improvements across these final trial blocks, but no significant group × trial block interaction ($F < 1.0$).

Temporal order memory for familiar objects

For the test trial, the relative preference of the two objects was examined using a discrimination ratio index (Ennaceur & Aggleton, 1997). The discrimination ratio index reflects the preference for the older of the two objects in the test trial as a ratio of the total exploration time and consequently controls for individual variability in exploratory behavior. Hence, for exploration in the test trial, the time spent exploring object (A), which had been presented during the first study trial, was subtracted from the time spent exploring object (B), which had been presented in the second study trial, and this difference was divided by the total exploration time of both objects in the test trial [(A − B)/(A + B)]. One rat from the control group was excluded from the data analysis as it climbed onto the ledge of the box during the test trial. Perhaps due to highly variable performance across the groups, the one-way between-group ANOVA of the discrimination ratio produced a non-significant effect of group ($F_{3,37} = 1.58$, $P = 0.213$; Fig. 5A). However, additional analyses of the discrimination ratio within each group relative to chance preference (Student's single sample *t*-test; significance set at $P < 0.05$) revealed some evidence of impaired temporal order memory in the LT and MT groups. This alternative method of analysis is frequently employed in object preference tasks (e.g. Ennaceur & Aggleton, 1997; Hunt & Aggleton, 1998; Mitchell & Laiacona, 1998; Hannesson *et al.*, 2004a,b). The AT and control groups demonstrated a clear preference for the first of the two familiar objects (object A; AT, $t_7 = 4.81$, $P < 0.002$; control, $t_9 = 3.24$, $P < 0.01$), which indicates that these two groups showed temporal order memory for the objects presented. By contrast, the preference level shown by the LT and MT groups was not different to chance (LT, $t_9 = 1.81$, $P > 0.11$; MT, $t_9 = 0.83$, $P > 0.40$).

The mean exploration time for the first identical pair of objects (A) in the study trial 2 h before the test trial (87.30 s) was equivalent to that for the second identical pair of objects (B) in the study trial 1 h before the test trial (85.75 s), indicating no overall bias for either object. These exploration times in the study trials did not differ across groups ($F_{1,35} = 1.42$, $P = 0.26$). While the group × study trial interaction approached significance ($F_{3,35} = 2.57$, $P < 0.07$), no consistent pattern emerged for mean exploration to the first or second object across groups (object A: AT, 96.49 s, LT, 86.40 s, MT, 93.62 s, control, 75.80 s; object B: AT, 95.32 s, LT, 79.30 s, MT, 80.59 s, control, 89.85 s).

Recognition of familiar vs. novel objects

For the test trial, the relative preference of the two objects was also examined using a discrimination ratio index. In this case, the time spent exploring the novel object (D) in the test trial was subtracted from the time spent exploring the familiar object (C), which had been presented in the study trial, and this difference was divided by the total exploration time of both objects in the test trial [(D − C)/(D + C)]. Two rats were excluded from this analysis (one control and one MT rat) as they climbed onto the ledge of the box during the test trial. In contrast to temporal order memory, the within-group analyses (relative to chance preference; Student's single sample *t*-test, significance set at $P < 0.05$) confirmed that object recognition memory was evident in all four groups (AT, $t_7 = 2.42$, $P < 0.05$; LT, $t_9 = 3.27$, $P < 0.01$; MT, $t_8 = 5.07$, $P < 0.001$; control, $t_9 = 7.01$, $P < 0.0001$; Fig. 5B).

The mean total amount of exploration time during the 5-min study trial of the two identical objects (C) was 94.10 s. One-way ANOVA revealed no effect of group in terms of these exploration times ($F < 1.0$).

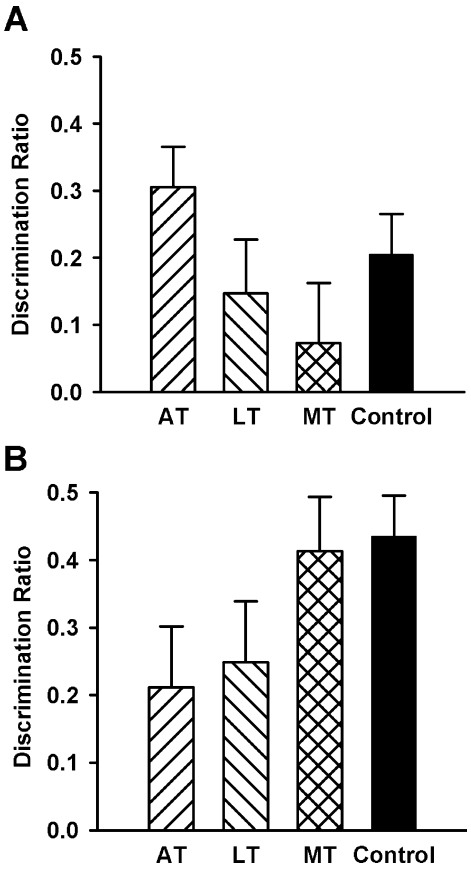

FIG. 5. (A) Temporal order memory of two objects. Only controls and the group with lesions to the anterior thalamic aggregate (AT) comprising the anterodorsal, anteromedial and anteroventral thalami nuclei preferred the earlier versus more recent object presented ($P < 0.01$ and $P < 0.001$, respectively) compared with chance discrimination. (B) Object recognition (2-h retention delay). All groups preferred the novel vs. familiar object ($P < 0.05$). Values show mean (± SEM) discrimination ratios during a test trial for each task. LT, group with lesions to the lateral thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei); MT, group with lesions to the posteromedial thalamic aggregate comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus.

Lesion–behavior correlations

Given the clear lesion–behavior dissociations found across tasks and to improve variance for damage to any given region, we considered it appropriate to examine the association between the extent of lesion in each target and a corresponding behavioral measure for all rats that had received a thalamic lesion (but not the control group). For example, we examined the correlation between spatial memory performance and the percent of AT damage in all of the AT, LT and MT rats, including those AT, LT and MT rats that had been excluded from the main behavioral analyses. There were no significant correlations between brain damage sustained to the medial thalamic target regions and performance in either the temporal order memory or familiarity vs. novelty detection tasks but two interesting lesion–behavior associations were found. First, the extent of damage in the AT aggregate revealed a strong relationship with errors in the radial maze, including errors to the eight baited arms ($r = 0.89$, d.f. = 35, $P < 0.0001$; Fig. 6A) and initial

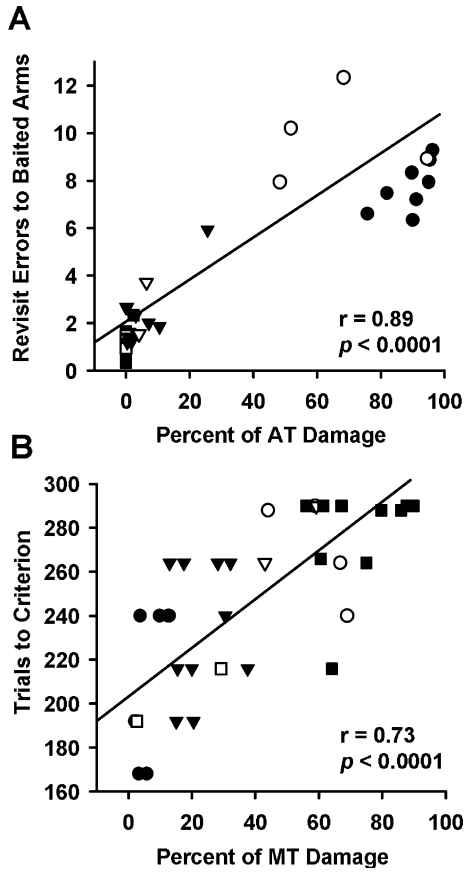

FIG. 6. Scattergrams of mean percent damage for all lesion rats ($n = 36$) and performance on two memory tasks. (A) Correlation between extent of lesions to the anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei and mean revisit errors to baited arms (working memory errors) in the radial arm maze task. (B) Correlation between extent of lesions to the posteromedial thalamic aggregate comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus and trials to criterion on the reward magnitude task (crossing the platform for negative trials in >7 s per session across three consecutive sessions). ●, AT inclusions ($n = 8$); ○, AT exclusions ($n = 4$); ▼, lateral thalamic aggregate comprising the lateral and paralamellar segments of the mediodorsal thalamic nuclei and the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) (LT) inclusions ($n = 10$); ▽, LT exclusions ($n = 2$); ■, MT inclusions ($n = 10$); □, MT exclusions ($n = 2$). Individual cases are plotted; some symbols overlap. AT, cases with lesions intended for the anterior thalamic aggregate; MT, cases with lesions intended for the posteromedial thalamic aggregate; LT, cases with lesions intended for the lateral thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral mediodorsal thalamic nuclei (lateral and paralamellar nuclei). See text and Table 2 for inclusion / exclusion details.

visits to the two never-baited arms ($r = 0.73$, d.f. $= 35$, $P < 0.0001$). Even small amounts of AT damage appeared to increase errors beyond that shown by controls (e.g. mean working memory errors in the control group, 1.31, SD 1.82). Rat LT 136, which showed the highest number of spatial memory errors in the LT group, also had a large amount of MT and (mostly unilateral) AT damage (Table 2). Damage to the LT and MT aggregates was not correlated with spatial memory errors ($r = 0.23$ and $r = -0.18$, respectively). Consistent with previous evidence, however, there was also a suggestion that substantial LT or MT damage exacerbated the effect of AT lesions on the spatial memory task (Warburton *et al.*, 1999).

The second lesion–behavior association was that the extent of brain damage in the MT aggregate correlated with the number of trials required to reach the acquisition criterion in the reward magnitude task during the main period of testing ($r = 0.73$, d.f. $= 35$, $P < 0.0001$, Fig. 6B) (criterion set at crossing the platform on no-go trials in >7 s per session across three consecutive sessions). In general, relatively large MT damage was required to produce impaired acquisition on this task (control mean trials to criterion, 208.36, SD 28.03). Damage to the AT and LT aggregates did not correlate with trials to criterion ($r = -0.31$ and $r = -0.01$, respectively).

Discussion

This study is the first to compare directly the effects of bilateral lesions to the anterior (anterodorsal, anteromedial and anteroventral nuclei), lateral (ILn and the lateral segments of the MD) and posteromedial (medial and central segments of the MD and the intermediodorsal nucleus) regions of the limbic thalamus. The traditional aggregates, AT, ILn and MD, have each been proposed as the main or critical substrate of memory loss after thalamic injury. However, these thalamic regions may all contribute to the neural basis of diencephalic amnesia in line with their different primary neural connections with other key brain regions or because of partially overlapping connections at the level of the PFC. Taken together, this neuroanatomical evidence suggests both differential and coincidental effects across tasks. To examine these questions, contrasting memory tasks were employed with selective neurotoxin lesions that resulted in minimal overlap across these three adjacent thalamic regions.

The current study has provided evidence of new behavioral dissociations across the AT, LT and MT aggregates, which presumably reflects the different memory attributes required in each task. AT lesions produced marked deficits in spatial memory in the radial-arm maze task throughout postoperative testing. LT lesions produced a far smaller and transient increase in working memory errors only and MT lesions had no effect on radial maze performance. By contrast, only MT lesions impaired acquisition of the reward magnitude task. There was also some evidence that both LT and MT lesions impaired recency judgements of the temporal order of two familiar objects, whereas the AT lesion group performed extremely well on this task. None of the medial thalamic lesions impaired performance in the fourth task, object recognition memory. These findings provide clear support for the idea that different thalamic regions participate in independent brain circuits associated with processing different memory attributes (Bentivoglio *et al.*, 1997). Problems with the specificity of thalamic damage have often led to the view that multiple sites of injury and widespread effects on the related functional systems may be responsible for severe amnesia in human cases (Della Sala *et al.*, 1997). Even when one region is emphasized, such as the AT or its connections via the mammillothalamic tract, the influence of additional damage remains uncertain (Harding *et al.*, 2000; Van der Werf *et al.*, 2000). The current findings suggest that the contribution of thalamic injury to diencephalic amnesia may vary with the extent of damage to one or more medial thalamic aggregate or that such injury influences potential interactions amongst multiple memory systems (Kim & Baxter, 2001).

The severe impairment in radial-arm maze performance after AT lesions is consistent with previous evidence that the AT is required for spatial memory. Like previous studies, these spatial memory deficits occurred despite preoperative training and selective AT lesions (Aggleton *et al.*, 1996; Byatt & Dalrymple-Alford, 1996; Warburton *et al.*, 1999; Alexinsky, 2001; van Groen *et al.*, 2002). Here, additional evidence suggests that this impairment increases with increasing lesion size and is not dependent on damage to the adjacent LT and MT regions but may be exacerbated by additional damage to these

adjacent neural structures. AT lesions that satisfied our inclusion criteria produced only 15–39% damage to the LT region, 2–13% damage to the MT region and virtually no damage to the laterodorsal nucleus (0.6–7%) but there was notable damage to the rostral central medial thalamic nuclei (median, 47%; part of the ILn/midline complex) and the interanteromedial nucleus (median, 80%; usually included as part of the AT complex; also see Warburton *et al.*, 1999). These findings reinforce the proposal of Aggleton & Brown (1999) that the AT region is a key component of an extended hippocampal system, although there is uncertainty whether the various components of this extended system equally influence spatial memory, especially both working and reference spatial memory after preoperative training (Olton & Papas, 1979; Bolhuis *et al.*, 1994; Hunt *et al.*, 1994; Hannesson & Skelton, 1998; Kesner & Giles, 1998; Santin *et al.*, 1999; Eichenbaum & Cohen, 2001; Vann *et al.*, 2003; Jarrard *et al.*, 2004; Pothuizen *et al.*, 2004). Evidence for an interdependence of the AT and hippocampal system is reinforced by marked deficits on tests of spatial memory, including the radial-arm maze, after crossed unilateral lesions of these two regions (Warburton *et al.*, 2001). Thus, the retention deficits displayed by the AT lesion group in the current study for both the working and reference memory components of spatial memory further support the notion that the AT nuclei are critical for the expression and storage of previously acquired spatial information, in addition to on-line encoding of new spatial information (Warburton *et al.*, 1999; Alexinsky, 2001).

To the extent that spatial memory tasks provide an animal analog of human episodic memory, disruption to the AT may play an important role in the memory features associated with diencephalic amnesia (Gaffan, 1992; Aggleton & Brown, 1999; Aggleton & Pearce, 2001). The current study was not designed to test the exact nature of this spatial memory impairment or its mechanisms. Other evidence suggests that allocentric, rather than egocentric, spatial memory underpins the effects of AT lesions on spatial tasks (Warburton *et al.*, 1997; Sziklas & Petrides, 1999) and deficits in processing extra-maze cues seem likely in the current study. For example, simple response strategies would be of little value in discriminating baited/never-baited arms. Another likely factor concerns potential deficits in processing directional information, which might be affected throughout the extended hippocampal system after AT lesions and which have been reported after lesions centred on the anterodorsal thalamic nucleus and adjacent regions that contain cells sensitive to head direction (Wilton *et al.*, 2001). AT lesions may also disrupt 'theta activity' in the proposed extended hippocampal system (Vann & Aggleton, 2004; Vertes *et al.*, 2004). In addition, AT lesions result in c-*fos* hypoactivity in the retrosplenial cortex and hippocampal system and there is evidence that inhibited c-*fos* expression in the hippocampus disrupts both working and reference memory in the radial-arm maze (He *et al.*, 2002; Jenkins *et al.*, 2002).

The current findings provide little support for the alternative to an AT-based account of diencephalic amnesia, which suggests that damage to the ILn and related midline nuclei has a substantial influence on memory and that the severity of the AT lesion effects critically depends on damage to these adjacent thalamic regions (Mair *et al.*, 2003). In this alternative account, the rostral ILn and striatum are emphasized in functional circuits with the frontal cortex and their disruption explains the neural basis of diencephalic amnesia (Burk & Mair, 1999; Mair *et al.*, 2002, 2003). Support for this view comes from reports of substantial delay-independent deficits in radial maze, operant and olfactory recognition memory tasks after large ILn/midline nuclei lesions and related striatal lesions (Young *et al.*, 1996; Burk & Mair, 1998, 1999, 2001; Mair *et al.*, 1998, 2002, 2003; Zhang *et al.*, 1998; Porter *et al.*, 2001). These studies also often report that ILn lesions produce markedly slowed response latencies (e.g. Burk & Mair, 2001). Choice latencies in the radial-arm maze and reward magnitude tasks were, however, not affected by LT lesions in our study. It is possible that, like previous reports in the human and animal literature (Mair *et al.*, 1998; Van der Werf *et al.*, 2002, 2003a,b; Schmahmann, 2003), non-specific dysfunction during the first few weeks of postoperative recovery contributed to the very mild impairment in working memory in the radial-arm maze task after lesions to the LT region. This mild deficit may also have been due to the subtotal status of the LT lesions (63–78%) or the relatively minor damage to the rostral central medial thalamic nuclei (5–24%). In line with the previous discussion, it is also possible that the working memory impairment was instead the result of associated AT damage (see Fig. 6A). It is important to note that the lesion–behavior correlations, particularly for spatial memory, may have been inflated due to the influence of extreme values and the relatively reduced spread of error scores and lesion size. Although more work that intentionally varies the degree of thalamic damage is required to confirm the brain–behavior associations observed, these correlations suggest that relatively small amounts of damage to the AT may markedly increase the number of spatial memory errors, at least in the radial maze. The current study reinforces the idea that, rather than inadvertent ILn lesions adding to the effects of large AT lesions, unintended encroachment into the AT nuclei by lesions that target adjacent medial thalamic nuclei may contribute to the spatial memory impairments reported after ILn and MD thalamic lesions (Mair *et al.*, 1992; Aggleton *et al.*, 1996; Byatt & Dalrymple-Alford, 1996; Hunt & Aggleton, 1998; Savage *et al.*, 1998).

While it appears that the LT aggregate may not be specifically involved in either allocentric spatial memory or memory for reward value, many of the prominent interconnections of this aggregate suggest instead a role in a dorsal striatum/caudate-putamen memory system, which predicts that LT lesions should be associated with stimulus–response-type memory deficits (Kesner, 1998; White & McDonald, 2002). There is already some evidence of deficits in response memory or related tasks after ILn lesions in rats, in human infarct cases with ILn damage and in Korsakoff's syndrome cases, although injury to other brain areas may also contribute to these effects (Mair *et al.*, 1998, 2002; Holdstock *et al.*, 1999; Exner *et al.*, 2001). Clearly, a greater variety of tasks and task conditions is required to compare the effects of AT, LT and MT lesions and their contributions to spatial and other forms of memory.

The last statement highlights the importance of differentiating a functional role for the MT aggregate. Intact spatial memory after MT lesions is consistent with most, but not all, studies of MD lesions in rats (Stokes & Best, 1990; Young *et al.*, 1996; Burk & Mair, 1998; Hunt & Aggleton, 1998; Aggleton & Brown, 1999; Floresco *et al.*, 1999; Alexinsky, 2001). Our study indicates that MT lesions with minimal or no damage to key adjacent regions, but not AT or LT lesions, cause deficits in the acquisition of memory for reward value (affect). It is possible that MT lesions impair conditional discriminations or inhibition *per se* or a switch in performance from a spatial to a non-spatial task instead of producing a specific reward magnitude deficit. The first two factors are unlikely to be distinguishing features of MT lesions. Deficits in conditional discrimination are not a general characteristic resulting from MD lesions (Chudasama *et al.*, 2001). The radial maze task that was used requires a conditional discrimination between rewarded vs. non-rewarded arms and MT rats were readily able to inhibit responding to non-rewarded arms, including slowed latencies when making such errors, unlike their performance on the conditional reward magnitude discrimination task. One effect of

MD lesions is to impair reversal learning and perhaps responses to other changes in task requirements (McBride & Slotnick, 1997; Chudasama *et al.*, 2001) but the transfer from spatial memory to reward magnitude also seems an unlikely explanation for the performance deficit in the latter task. The two tasks were separated by object recognition tests and completely different rooms were used for all of the tasks, with different rewards and apparatus, so that none of the relevant cues were the same. Previous studies reported that intact rats and those with hippocampal lesions, but not those with amygdala or agranular insular PFC lesions, transfer to other cereals of similar sugar content in the go/no-go reward magnitude task and that all rats readily discriminate low and high sugar rewards (Kesner & Williams, 1995; DeCoteau *et al.*, 1997; Ragozzino & Kesner, 1999). Thus, the hedonic difference in the sugar content of stimuli predominately influences unimpaired rats' responses on the reward magnitude task, rather than the conditional nature of the task or other factors such as size, texture or shape of the reward. Transfer tests were not used here but we were careful to ensure that all pieces of the two sample cereals were of roughly equal size on visual inspection and the textures of the two cereals appeared to be similar.

It would be useful to have additional information on the effects of MT lesions on the reward magnitude task, including the effects of preoperative training, intratrial delays, evidence of perceptual discrimination between the relevant stimuli and transfer to new rewards of equal sugar content. Such evidence would reinforce the conclusion that MT lesions impair memory for reward value. This conclusion resonates, however, with several existing lines of evidence. The reward magnitude task was chosen as it is susceptible to lesions to the amygdala and agranular-insular (lateral) PFC but not to the hippocampus, medial PFC or dorsal PFC (Kesner & Williams, 1995; DeCoteau *et al.*, 1997; Ragozzino & Kesner, 1999). The reward magnitude deficit is thus consistent with the anatomical connections of the MT and suggests a role for this aggregate, but not the AT or LT, within an amygdala-based stimulus–reward memory system (Baxter & Murray, 2002; White & McDonald, 2002). This relationship is reinforced by neurophysiological evidence that the amygdala, medial MD and lateral PFC process stimulus–reward information (Oyoshi *et al.*, 1996), evidence of a severe deficit in stimulus–reward associative memory in non-human primates, when a unilateral lesion of the amygdala in one hemisphere is crossed with medial MD and ventromedial PFC lesions in the opposite hemisphere (Gaffan *et al.*, 1993) and other deficits in related stimulus–reward paradigms after MD lesions in animals (Gaffan & Murray, 1990; Gaffan & Watkins, 1991; Chudasama *et al.*, 2001; Corbitt *et al.*, 2003). In humans, the impairment in affective judgements in Korsakoff's syndrome patients (Brand *et al.*, 2003) is perhaps related to deficits in recognition memory for affective stimuli after damage to the MT and disruption to an extended amygdala system (Adolphs *et al.*, 2000).

Comparison of each individual group's discrimination ratio compared with chance preference showed that, unlike the controls and the AT group, both the LT and MT groups failed to show a clear preference for the earlier of two presented objects. This analysis provides some evidence to suggest that LT and MT lesions impair temporal order memory. However, perhaps due to the inherent variability evident in spontaneous object recognition tasks, there was no significant effect when the four groups were compared directly with each other. Both patients with MD infarcts and Korsakoff's syndrome show problems with temporal memory, which is usually attributed to direct or indirect changes in frontal circuitry (Shuren *et al.*, 1997; Kopelman, 2002). To the extent that LT and MT lesions may impair temporal order memory for objects, this is not due to an inability to recall objects *per se* given that 1-h delays occurred between successive object presentations and the subsequent probe test and all groups showed intact object recognition memory despite a 2-h delay. Object recognition after LT/ILn lesions has not been reported previously. Intact object recognition after AT or MD lesions replicates similar findings after shorter delays (Aggleton *et al.*, 1995; Hunt & Aggleton, 1998; Moran & Dalrymple-Alford, 2003). Poor temporal order memory, but intact recognition memory, is reminiscent of medial and dorsal PFC lesions in rats (Mitchell & Laiacona, 1998; Hannesson *et al.*, 2004a,b). Therefore, the LT and MT regions, via their connections with the medial PFC, may have a role in establishing memory for temporal order but not for detecting object familiarity. The possibility that LT and MT lesions, but not AT lesions, impair temporal order memory is an important outcome that warrants further study.

There is a need for additional work on AT lesions and temporal order memory. There are significant neural connections between the anteromedial nucleus of the AT and the dorsal medial PFC and prominent direct and indirect connections between the AT and hippocampal regions (Aggleton & Brown, 1999; van Groen *et al.*, 1999). The hippocampus has recently been implicated in temporal order memory in spatial, olfactory and object preference tasks (Kesner, 1998; Fortin *et al.*, 2002; Kesner *et al.*, 2002; Jobson *et al.*, 2003) so the lack of an AT lesion effect on memory for temporal order suggests an intriguing dissociation between the AT and both the hippocampal and PFC regions. It is possible that the functional overlap between the AT aggregate and hippocampal system function is restricted to spatial memory. Alternatively, the reciprocal connections between the hippocampal region and the medial PFC (Witter *et al.*, 1989; Jay & Witter, 1991) may be sufficient to support temporal but not spatial memory after AT damage.

Conclusions

Although diencephalic amnesics with thalamic injury are by definition impaired in their capacity for new learning, they display substantial variability across a variety of memory and behavioral tasks. They may demonstrate deficits in recall, recognition, autobiographical memory and retrograde amnesia (Miller *et al.*, 2001; Kopelman, 2002; Schmahmann, 2003) as well as deficits in planning, inhibition, attention, memory for temporal order and emotional responding (Shuren *et al.*, 1997; Benke *et al.*, 2002; Brand *et al.*, 2003; Van der Werf *et al.*, 2003b). Thus, it is unlikely that one specific region, fiber pathway or neural circuit is responsible for the degree or range of memory and other cognitive deficits observed after medial thalamic damage in humans or animals. The comparative lesion effects described in the current report provide convincing new evidence that aggregates of medial thalamic nuclei, in line with their significant neural connections, are functional components of multiple parallel memory systems in the brain. In the case of AT and MT lesions, the severity of the core deficits appears sensitive to the extent of injury, which may also explain some of the variability in both human cases and across animal studies. Accumulating evidence on the differential effects of selective damage to thalamic regions in animal models signals the need to identify a wider range of deficits and their brain injury correlates in clinical cases.

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Abbreviations

AT, anterior thalamic aggregate comprising the anterodorsal, anteromedial and anteroventral thalamic nuclei; ILn, intralaminar thalamic nuclei; LT, lateral thalamic aggregate comprising the intralaminar nuclei (centrolateral, paracentral and rostral central medial nuclei) and lateral and paralamellar mediodorsal nuclei; MD, mediodorsal thalamic nuclei; MT, posteromedial thalamic aggregate comprising the central and medial mediodorsal thalamic nuclei and the intermediodorsal nucleus; PFC, prefrontal cortex.

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