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Memory Impairments Following Restricted Medial Thalamic Lesions in Monkeys

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Summary. Thalamic contributions to memory were assessed in monkeys with lesions placed in the medial portions of either the anterior or posterior thalamus (AMT and PMT, respectively). Both lesions produced a moderate impairment in a test of object recognition memory. Furthermore, all three animals in the PMT group and two out of the three in the AMT group were moderately impaired on a test of object-reward associative memory. Comparison of these results with those of a previous study in which the AMT and PMT regions were removed jointly (Aggleton and Mishkin 1983) suggests that damage in either region can induce a memory loss but that combined damage to both is required to produce a full-blown amnesia.

Key words: Monkey – Amnesia – Thalamus

Introduction

For nearly a century, lesions in the medial diencephalon have been recognized as the cause of profound disturbances in new learning and memory in man (Gudden 1896). Postmortem examinations have indicated repeatedly that neuropathological changes in the mamillary bodies and in various nuclei within the medial portions of the thalamus are associated with this syndrome of global anterograde amnesia (Angerlegues 1969; Victor et al. 1971; Brierly 1977). Nevertheless, the paucity of patients with sufficiently focal lesions has made it difficult to determine which area or areas of pathology are central in the syndrome.

With the recent introduction of tests sensitive to memory losses in monkeys (Gaffan 1974; Mishkin and Delacour 1975; Squire and Zola-Morgan 1983) it may now have become possible to resolve this question experimentally. As a first step toward this goal, we previously investigated whether or not medial thalamic lesions alone would be sufficient to induce amnesia (Aggleton and Mishkin 1983). The results showed that animals with diencephalic lesions involving the medial aspects of both the anterior and medial thalamic nuclei were impaired in the relearning of a one-trial object recognition task, delayed nonmatching-to-sample. In addition, their poor performance at long delays, after they had relearned the nonmatching principle with short delays, gave further indication of a memory deficit. Yet, the same lesion had no effect on the animal's ability to learn pattern discriminations or spatial delayed response, abilities that have been found to be spared also in monkeys rendered severely amnesic by medial temporal-lobe damage (Mishkin 1978; Orbach et al. 1960; Squire and Zola-Morgan 1983). The pattern of deficits exhibited by the monkeys with medial thalamic lesions was thus consistent with an experimentally induced amnesia. Nevertheless, this preliminary study did not demonstrate that the thalamic lesions alone were sufficient to induce global amnesia, since all animals sustained retrograde degeneration in the mamillary bodies as a result of damage to the anterior nuclei, the mamillothalamic tract, or both. Also, the study did not assess whether the memory loss extended beyond recognition ability. In the current experiment we tried to address both of these shortcomings and at the same time determine which part of the original lesion was mainly responsible for its effect.

For this purpose, the original medial thalamic (MT) lesion was divided into an anterior component, centered on the medial portions of the anterior

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thalamic nuclei, and a posterior component, centered on the magnocellular portion of nucleus medialis dorsalis (MDmc). The rationale for this division was twofold. First, there is some neuropathological evidence that damage limited to either the anterior or posterior medial thalamic regions may induce amnesia in humans (Delay and Brion 1969; McEntee et al. 1976; Mills and Swanson 1978; Markowitsch 1982). Second, each of these two regions receives projections from a different one of the temporal-lobe limbic structures that have been implicated in memory, the anterior nuclei receiving inputs from the hippocampus (Rosene and Van Hoesen 1977), and magnocellular MD receiving them from the amygdala (Nauta 1961). In addition to the monkeys given anterior and posterior medial thalamic lesions, others were prepared in order to examine the effects of (a) damage restricted to midline (as distinguished from medial) thalamic nuclei and (b) interruption of the mamillothalamic tract, the large fiber bundle which connects the mamillary bodies with the anterior thalamic nuclei.

The operated monkeys and normal controls were tested on the same object recognition task, delayed nonmatching-to-sample, that had been used previously with the MT animals. In addition, the two main operated groups were compared with normal controls on a one-trial test of associative memory in order to assess the generality of any mnemonic disturbances.

Materials and Methods

Surgical Groups

Fourteen experimentally naive cynomolgus monkeys (*Macaca fascicularis*) weighing from 3.0–7.5 kg were used in this study. All but one were male. The animals were housed individually and maintained on a diet of Purina Monkey Chow and fruit.

Surgery was performed aseptically while the animal was anesthetized with Ketamine (10 mg/kg) and Nembutal (35 mg/kg). Two groups of three animals each received bilateral, one-stage lesions of the anterior and posterior halves, respectively, of the medial portions of the thalamus (Groups AMT and PMT). Unilateral, dorsomedial bone and dural flaps were made to allow retraction of the medial wall of the left hemisphere. A portion of the body of the corpus callosum was then split sagittally to reveal the dorsal thalamus. The exposed descending limbs of the third ventricle at the anterior and posterior limits of the thalamic midline served as landmarks to guide the placement of the lesions. In the PMT surgeries, the caudalmost 4 mm of the thalamic midline, or massa intermedia, was split with a glass sucker, and a parasagittal strip of tissue approximately 2 mm wide was then removed from each side of the midline with a 22-gauge sucker. In the AMT surgeries, the anterior 3.5–4.0 mm of the thalamic midline was split sagittally, and a 1-mm-wide parasagittal strip of tissue was then removed from each side of this transection. Together, the AMT and PMT lesions summed to the original MT lesions.

In an additional monkey an attempt was made to sever the mamillothalamic tract (TMT) with minimal damage to the thalamus itself. In this case, the anterior thalamic midline was transected for a distance of 2 mm from the rostral end of the massa intermedia. Then a glass sucker with a right-angled tip was lowered into the midline split and rotated through the tissue to a depth of approximately 2 mm on either side of the midline. In the final case, which had been prepared as an operated control (Ct) in the earlier study, the entire length of the massa intermedia was transected, but no additional thalamic tissue was removed.

At the completion of the surgery the bone and dural flaps were replaced and the overlying anatomical layers sutured. All animals received Bicillin (600,000 U) to prevent infection.

Four control animals were used for the first experiment; these consisted of the one with a thalamic transection damaging the midline nuclei (Ct) and three that were unoperated (C1, C2, and C3). The data for these four monkeys were obtained from the previous study (Aggleton and Mishkin 1983). Three different unoperated monkeys (C4, C5, and C6), with matched training histories, were used as controls for the second experiment.

Histological Verification of Lesions

At the completion of the experiments the animals received a lethal dose of Nembutal and were perfused intracardially with a 10% solution of formol saline. The brains were removed, blocked, embedded in celloidin, and cut at 25 μm in the coronal plane. Every tenth section was stained with thionine. In order to quantify the extent of the AMT and PMT lesions, matched sections at seven different levels from each animal were enlarged, traced with a camera lucida, and measured. The percentages of the entire thalamus, of nucleus medialis dorsalis, and of the anterior nuclei that had either been removed or showed marked cell loss were then calculated. The thalamic nomenclature is taken from the work of Olszewski (1952).

Figures 1 and 2 depict the extent of each of the thalamic lesions. The AMT removals always included the full extent of the anterior midline nuclei, while the degree of damage to the anterior thalamic nuclei ranged from 30% (AMT 2) to 79% (AMT 3). Other thalamic damage included the medial edge of nucleus ventralis anterior and, in some cases, injury to nuclei paracentralis, reticularis, and ventralis posterior lateralis (Fig. 1). Although the AMT surgeries did not directly involve either the

Fig. 1. Coronal sections depicting the medial, anterior thalamic lesions (AMT) and the mamillothalamic tract transection (TMT). Areas in black were removed, those with cross-hatching showed gliosis and cell loss, and those with diagonal lines showed gliosis only. *Abbreviations: AD,* nucleus anterior dorsalis; *AM,* nucleus anterior medialis; *AV,* nucleus anterior ventralis; *C,* cingulate gyrus; *Cdc,* nucleus centralis densocellularis; *CL,* nucleus centralis lateralis; *Clc,* nucleus centralis latocellularis; *CnMd,* nucleus centrum medianum; *F,* fornix; *LD,* nucleus lateralis dorsalis; *MB,* mamillary bodies; *MD,* nucleus medialis dorsalis (*mc,* pars magnocellularis; *mf,* pars multiformis; *pc,* pars parvocellularis); *Pcn,* nucleus paracentralis; *Pf,* nucleus parafascicularis; *R,* nucleus reticularis; *Re,* nucleus reuniens; *SM,* stria medullaris; *TMT,* mamillothalamic tract; *VA,* nucleus ventralis anterior (*mc,* pars magnocellularis); *VLc,* nucleus ventralis lateralis pars caudalis; *VLm,* nucleus ventralis lateralis pars medialis; *X,* area X

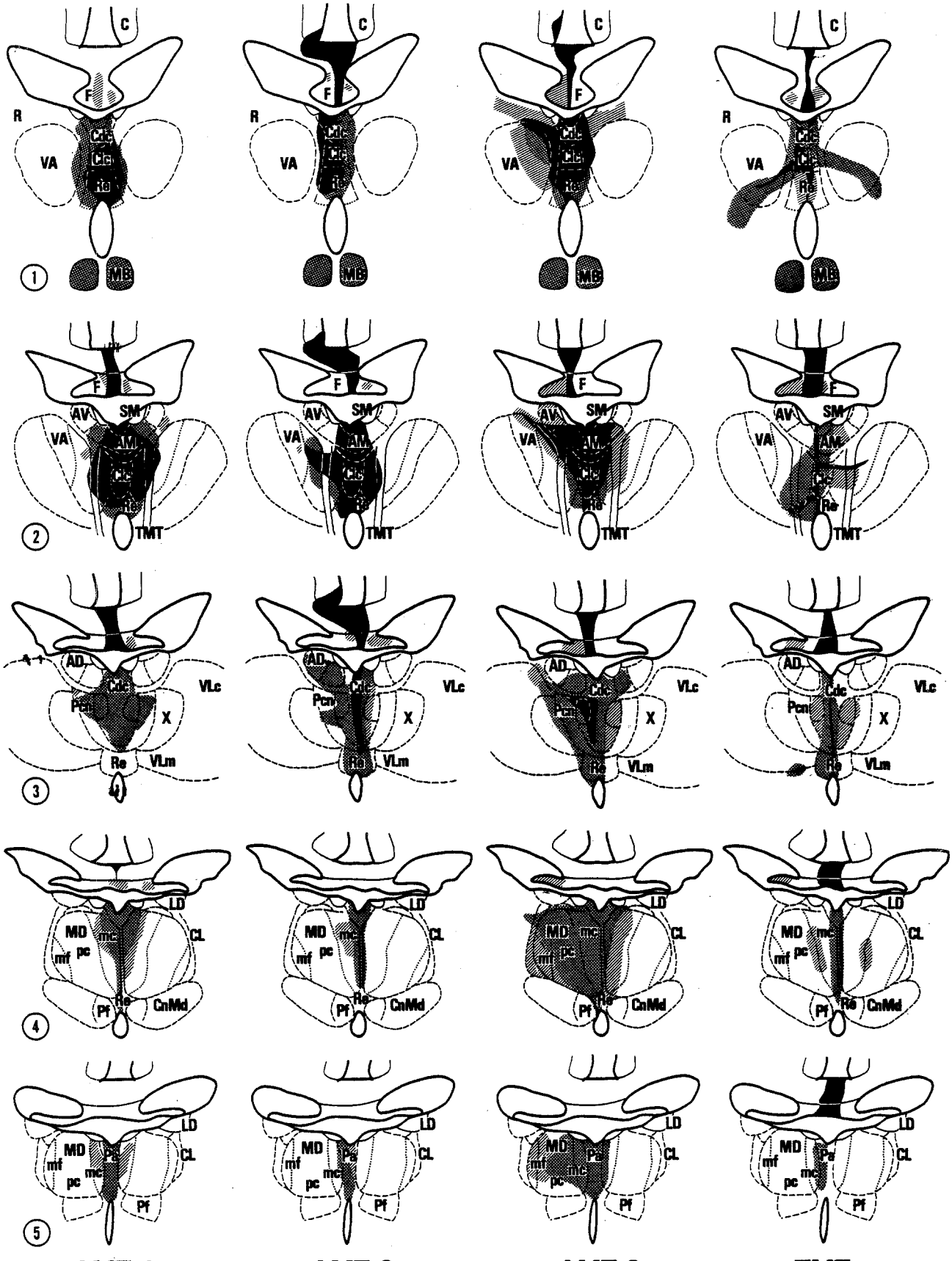
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Fig. 1

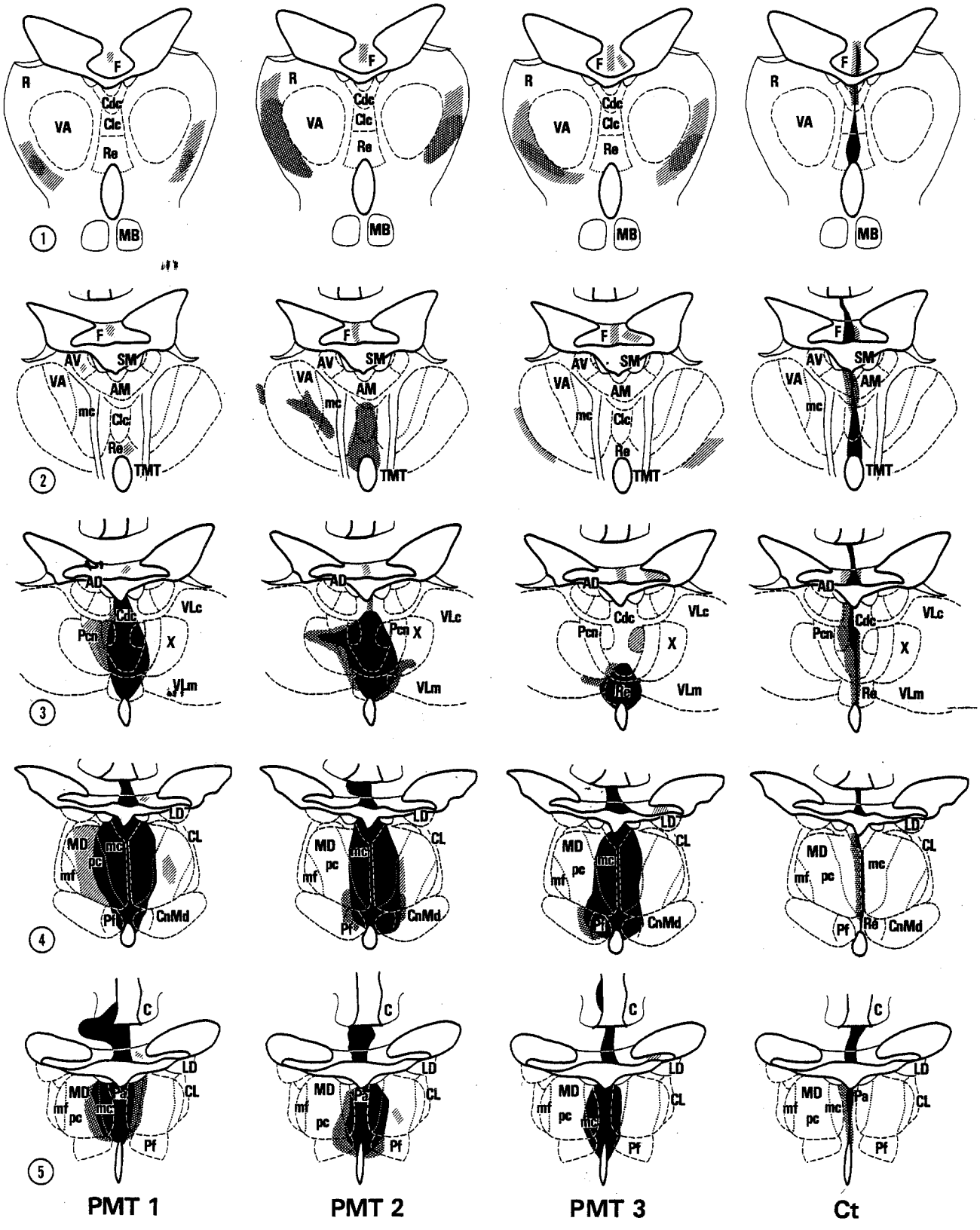

Fig. 2. Coronal sections depicting the medial, posterior thalamic lesions (*PMT*) and the midline thalamic control lesion (*Ct*). Abbreviations as in Fig. 1

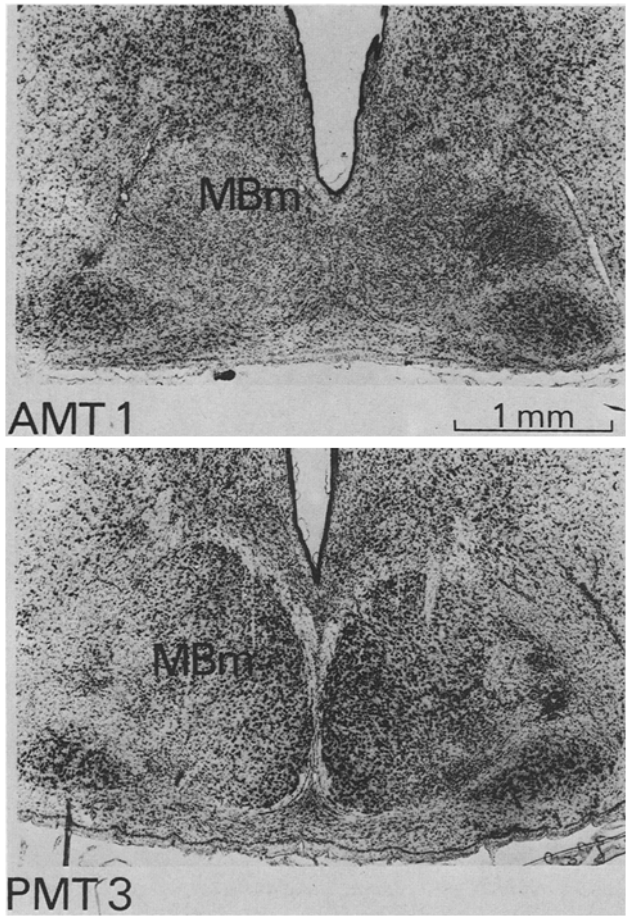

Fig. 3. Photomicrographs of mamillary bodies in monkeys AMT 1 and PMT 3 illustrating the cell loss and gliosis consequent to the AMT, but not PMT, lesions (thionine stain)

mamillary bodies or nucleus medialis dorsalis (MD), there was significant degeneration and gliosis in both structures. In all three monkeys the mamillothalamic tract was interrupted on both sides, resulting in conspicuous, bilateral retrograde degeneration and gliosis in the medial mamillary nuclei. The fornix, on the other hand, was usually damaged only unilaterally, and then only in part. Cell loss and gliosis were also found throughout the posterior midline nuclei and in the medial portions of MD, the proportion of MD involvement ranging from 10% (AMT 2) to 35% (AMT 3). This retrograde degeneration presumably arose from interruption of MD efferents to the prefrontal cortex.

The mamillothalamic tracts were successfully cut in monkey TMT, though at different depths in the two hemispheres (Fig. 1). Much of the anterior midline nuclei were removed in the course of the surgery, and retrograde degeneration resulted in an almost total cell loss in the more caudal midline nuclei. While the transection also produced damage to nuclei ventralis anterior, ventralis lateralis medialis, and the fornix, there was only slight unilateral damage to the anterior nuclei. There was, in addition, a loss of cells in the magnocellular portion of nucleus medialis dorsalis (MDmc) comparable to that seen in the smallest AMT lesion (Fig. 1).

The PMT removals (Fig. 2) included all of the posterior midline nuclei and much of MDmc. There was in addition some invasion of the lateral, parvocellular portion of nucleus medialis dorsalis, though such damage was minor in animals PMT 2 and PMT 3. The proportion of total MD damage ranged from 40% (PMT 3) to 50% (PMT 1). The lesions extended ventrally to include the medial edges of nuclei centrum medianum and parafascicularis, and rostrally to the caudal limit of either nucleus centralis densocellularis (PMT 1 and 2) or centralis latocellularis (PMT 3). The anterior thalamic nuclei and the mamillary bodies appeared normal in all three cases (Fig. 3). Also, the fornix suffered only slight midline damage, though there was evidence of additional unilateral damage to this tract in monkey PMT 3.

In monkey Ct, in which the thalamus was transected sagittally (Fig. 2), a thin line of cell loss and gliosis could be traced along the entire thalamic midline. This lesion resulted in a loss of approximately 60% of the midline cell bodies, with only slight additional damage in MDmc and in nuclei anterior medialis, centrum medianum, parafascicularis, and paracentralis.

Apparatus and Procedures

All experiments were carried out in a Wisconsin General Testing Apparatus (WGTA) inside a darkened, sound-shielded room. Additional sound masking was provided by background white noise. The test tray had three wells spaced 18 cm apart and located 18 cm from the front of the testing cage. Banana pellets (P.J. Noyes Co., 300 mg) or raisins concealed in the wells served as rewards. Both the testing compartment and the animal's compartment were illuminated in Experiment 1, while only the testing compartment was illuminated in Experiment 2. The unoperated control monkeys in Experiment 2 (C4, C5, and C6), unlike the other monkeys, had been trained in Experiment 1 with illumination in the testing compartment only, and so their data for that experiment are not included here.

Experiment 1 Recognition Memory

The testing procedure, delayed nonmatching-to-sample with trial-unique objects, was identical to that used in the study on the effects of combined AMT and PMT lesions (Aggleton and Mishkin 1983). After the animals were taught to push aside objects from the wells of the test tray to obtain the concealed food reward, formal training began. In the first part of each trial the monkey displaced a baited, novel sample object which overlay the central well. A 10 s delay followed during which the opaque screen of the WGTA was interposed between the animal and the test tray. In the second part of each trial the screen was raised to reveal both the previously presented sample and a new object, each of which covered a lateral well. The animal was rewarded for avoiding the sample and displacing the new object. The left-right position of the sample and the novel object followed a pseudorandom order. Twenty trials, separated by 30 s intervals, were given daily. Each trial utilized a new pair of objects taken from a pool of 1,300 objects, thereby ensuring that no test item was repeated within a month. Thus, the test required the monkey to distinguish between a familiar and an unfamiliar object based on a single exposure to the 'familiar' object 10 s earlier. The monkeys were trained to a preoperative criterion of 90 correct choices in 100 trials before receiving surgery.

Training resumed two weeks after surgery, or after a two-week rest interval in the case of the unoperated controls, and was continued until the animals reattained the preoperative criterion. The monkeys' recognition memory was then taxed further through progressive increases of the delay between sample presentation and choice test from the 10 s delay to 30 s, 60 s, and, finally, 120 s. The animals received twenty trials a day for five days at each delay interval before progressing to the next interval.

Table 1. Effects of thalamic lesions on object recognition memory (delayed nonmatching-to-sample)

Groups		Delays (% Correct) 30s	60s	120s	Objects (% Correct) 3	5	10	Ave.
Normal Controls	C 1	94	89	89	89	89	71	87
	2	95	89	92	90	89	87	90
	3	91	92	91	92	93	81	90
Surgical Control	CT	93	95	97	98	96	90	95
Anterior Medial Thalamus	AMT 1	83	81	69	80	83	63	77
	2	87	85	80	80	80	71	81
	3	84	73	74	78	74	60	74
Posterior Medial Thalamus	PMT 1	90	86	90	86	80	69	84
	2	81	86	75	85	87	75	82
	3	89	85	77	79	75	61	78
Mamillo-thalamic tract	TMT	82	64	74	76	81	75	75

The effects of increased interference were then tested by requiring the animals to recognize lists of three, five, and then ten objects, with the nonmatching rule still in effect. In the first condition, the animal displaced three consecutive sample objects (A, B, C) overlying the central well, with 20 s intervals between object presentations. After a further 20 s delay, sample object A and novel object D were presented for choice over the lateral wells; this trial was followed 20 s later by presentation of sample object B coupled with novel object E, and 20 s after that by sample object C paired with novel object F. The next block of 3 trials was initiated after a 30 s interlist interval. Each monkey received ten such lists or thirty trials a day for five days. The same procedure was then used for list lengths of 5 objects and, finally, 10 objects.

Experiment 2 Associative Memory

The AMT and PMT groups were subsequently compared with three similarly trained but unoperated animals (C4, C5, and C6) for their ability to remember which of two equally familiar objects had been paired previously with a food reward (Gaffan 1979). Each trial consisted of two stages. First, two novel objects were presented successively, with an interval of 10 s, over the central well of the test tray. The monkey found a food reward under one of the two objects, determined randomly. After a further delay of 10 s, the same pair of objects was presented simultaneously over the lateral wells, and the monkey was rewarded for displacing the object that had covered a food reward in the first stage of the trial. Following a delay of 30 s, the next trial began with two new objects taken from the same pool of 1,300 objects used in Experiment 1. Each monkey received 20 such trials a day until it achieved the criterion of 90 correct choices in 100 trials.

If the monkey failed to learn after 800 trials the task was modified such that each of the objects was presented for acquisition twice (hereafter referred to as double presentation) before the choice test. Again, only one of the objects, A or B, covered a food reward, and it did so on both of its exposures. The sequence of object presentation varied equally between the two combinations ABAB and ABBA, with a 10 s interval between each presentation.

Once the animals reached criterion, or had received a maximum of 1,500 trials, they were tested for their ability to remember the object-reward associations for longer than 10 s. Each monkey received 200 trials, with double presentations, in which delays of 10, 30, 60, and 120 s following the last presentation were tested concurrently. Each daily session consisted of 20 trials, with 5 trials at each delay interval intermixed. The animals were then tested for an additional 200 trials with the same schedule of mixed delays but with each of the test objects presented for acquisition only once.

Results

Experiment 1 Recognition Memory

The animals with restricted medial thalamic lesions were compared both with the unoperated control monkeys and with the three animals given MT lesions (i.e. combined AMT and PMT lesions) described in the previous report (Aggleton and Mishkin 1983). Neither AMT nor PMT damage alone produced a reliable impairment in relearning the recognition task, although one animal with each lesion did require several hundred trials to reattain the criterion (Fig. 4). In contrast, the monkeys in the MT group had required from 640 to 1,720 trials to relearn the recognition task after surgery and hence were severely affected in comparison with both the AMT and PMT groups as well as the controls.

Consistent impairments emerged in both the AMT and PMT groups, however, when either the delays or list lengths were increased. Statistical comparison of the mean performance scores of the AMT, PMT, MT, and Control animals (Fig. 5, Table 1) over the three delay periods confirmed the differences among the groups (Kruskall-Wallis test: $H = 9.46$, $p < 0.005$). Subsequent comparisons revealed that although the AMT and PMT groups did not differ from each other, both were significantly worse than the control animals ($U = 0$, $p = 0.05$ in each

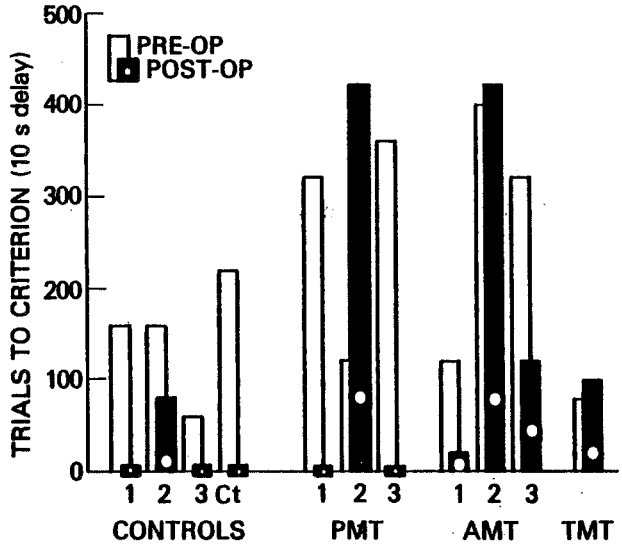

Fig. 4. Trials to learn the recognition task (delayed nonmatching-to-sample); white circles represent error scores

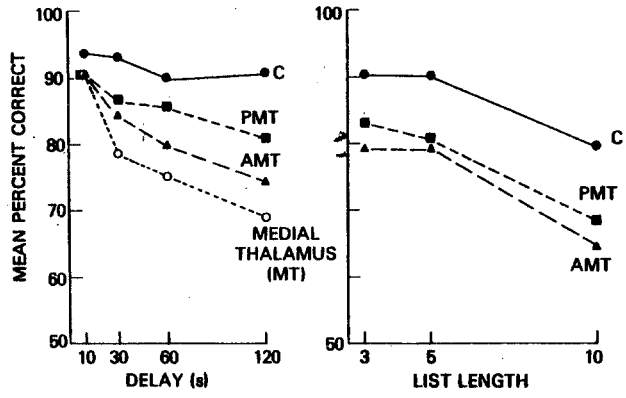

Fig. 5. Mean performance of unoperated control monkeys (C) and monkeys with either anterior (AMT) or posterior (PMT) medial thalamic lesions on the recognition task (delayed nonmatching-to-sample). *Left:* Performance with increasing delays between sample presentation and choice test. *Open circles* show mean scores of animals with medial thalamic (MT) lesions from previous study (Aggleton and Mishkin 1983). *Right:* Performance with increasing list lengths of objects

case) but significantly better than the MT group ($U = 0, p = 0.05$ in each case). In addition, it should be noted that two of the three animals in the MT group had required double presentation of each sample object in order to regain the criterion and that subsequent testing of these animals on the progressively increasing delay intervals was carried out with the same double presentation of samples. In view of this facilitation of their performance, comparisons between the MT group, on the one hand, and the AMT and the PMT groups on the other, clearly underestimate the actual differences.

Because of their poor performance, as evidenced particularly by their need for double sample presentations, the animals in the MT group had not been tested on the next phase of the performance test – list lengths of 3, 5, and 10 objects. Comparisons among the mean scores of the three remaining groups (Fig. 5 and Table 1) indicated a significant effect of the partial lesions ($H = 5.6$, $p = 0.05$). Subsequent comparisons indicated once again that there were no differences between the AMT and PMT groups, but both were worse than the controls ($U = 0, p = 0.05$ in each case).

The animal in which the mamillothalamic tract had been severed (TMT) also displayed a clear, but moderate, impairment on the recognition task. This animal required 100 trials to relearn the nonmatching principle and then performed more poorly than all the unoperated controls throughout the test with increasing delays and list lengths (Table 1). The performance of this animal was comparable to that of the animals in the AMT group. By contrast, the surgical control animal (Ct), with the thalamic midline transection, relearned the basic object recognition task immediately and then surpassed the unoperated animals on the performance tests.

The overall scores of the monkeys in the AMT group on the various delays and list lengths (Table 1) correlated perfectly with both the total extent of thalamic damage and the extent of damage sustained separately by the anterior thalamic nuclei und nucleus medialis dorsalis. Thus, for example, the least impaired animal in the group, AMT 2, sustained the smallest thalamic lesion in all respects. No such correlations were apparent, however, between the extent of lesions and the performance of individual animals in the PMT group.

Experiment 2 Associative Memory

The control group learned the object-reward association task (Fig. 6) in fewer trials than all of the monkeys with thalamic lesions but one (AMT 2). In fact, none of the operated animals except AMT 2 showed any evidence of learning during the first 800 trials, when each object was presented once (Fig. 6); and two of the monkeys (AMT 3 and PMT 1) still failed to reach criterion in the next 700 trials despite double presentation of the objects, although they did achieve 72% and 68% correct responses, respectively.

Figure 7 illustrates the mean scores of the three groups across the delay intervals for both the single and double presentation conditions. The perform-

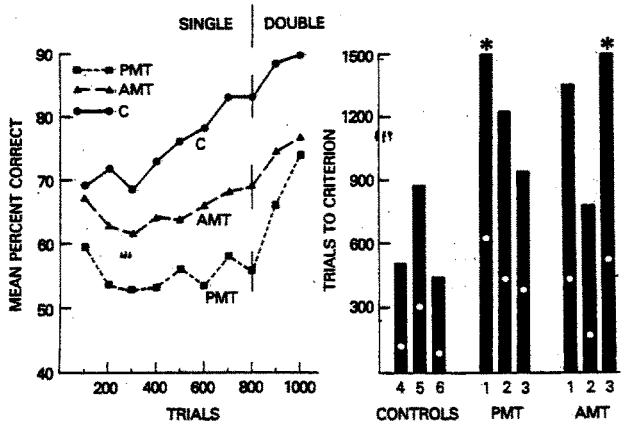

Fig. 6. Learning scores on the object-reward association task (win-stay, lose-shift). Left: Learning curves of groups over successive blocks of 100 trials. Animals reaching criterion in less than 1,000 trials were assigned scores of 90% for all trial-blocks beyond criterion. Right: Total trials and errors (white circles) to criterion. Asterisk denotes failure to attain criterion within maximum of 1,500 trials

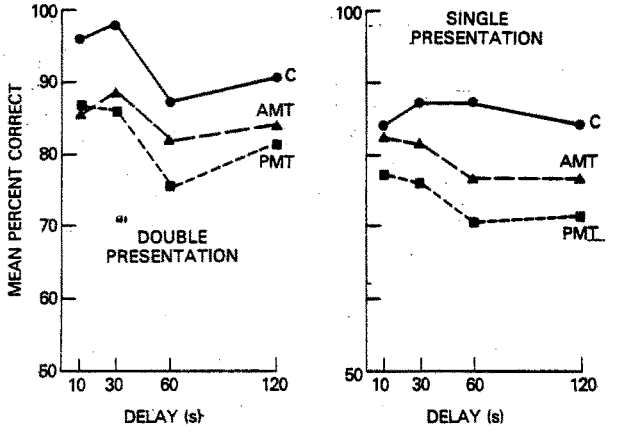

Fig. 7. Mean performances of groups on the object-reward association task (win-stay, lose-shift) over the four delay intervals, with both double and single object presentation

ance of the PMT group for the two conditions was impaired relative to that of the normal animals ($U = 0, p = 0.05$ in each case), but again, because of the high level of performance of AMT 2, which in this case was entirely normal, the scores of the AMT group did not differ significantly from that of the controls.

For purposes of correlation with extent of damage, the animal's scores on the associative memory task were assessed in terms of both the number of trials and errors to reach criterion and overall performance on the two sets of delay conditions. Both measures yielded the same ranking of animals. Within the AMT group this ranking correlated perfectly, as before, both with the overall extent of thalamic damage and with the extent of damage separately to the anterior thalamic nuclei and nucleus medialis dorsalis (MD). Within the PMT group the ranking correlated perfectly only with the proportion of MD damage.

Discussion

Lesions centered in the medial portions of either the anterior thalamus (AMT) or the posterior thalamus (PMT) produced impairments on tasks designed to assess both recognition and associative memory. These results extend those of an earlier study which examined the effects of combined (or MT) lesions on recognition memory. The present results, coupled with the finding that the more extensive MT lesions did not disrupt performance on either pattern discrimination or delayed response tasks (Aggleton and Mishkin 1983), indicate that thalamic lesions can disrupt more than one class of memory, yet leave other types of learning intact. This result strengthens the similarity between the effects produced by diencephalic damage in monkeys and the amnesic syndrome of diencephalic origin in humans, in whom it has also been found that a wide class of memory abilities may be severely affected even while other learning abilities are spared (Butters and Cermak 1980; Squire 1982).

'Diencephalic Amnesia' in Monkeys

The present results allow some tentative conclusions concerning the diencephalic damage responsible for the more severe memory impairment that followed the larger, MT ablations in the earlier study. The PMT lesions, which did not extend beyond the thalamus, produced small but consistent impairments on both memory tasks. This is the first evidence from nonhuman primates that thalamic damage alone may be sufficient to induce amnesia. Several nuclei within the PMT region were consistently involved in the lesions: The magnocellular portion of nucleus medialis dorsalis (MDmc), the posterior midline nuclei, and parts of nuclei parafascicularis, centrum medianum, paracentralis, and parvocellular MD. The small and variable involvement of the latter group of nuclei make it unlikely that these were the critical loci of damage for the behavioral effects; and the excellent performance of monkey Ct, in which the thalamic midline was split, suggests that removal

of the posterior midline nuclei adjacent to MD is also unlikely to have been responsible for the deficits. It seems most likely then that the memory impairments reflect damage to the magnocellular division of MD. Evidence that MDmc is the major thalamic target of the amygdala (Nauta 1961; Aggleton and Mishkin 1982) strengthens the link between this thalamic subdivision and memory, inasmuch as the amygdala too has been implicated in memory functions (Mishkin 1978; 1982).

It is more difficult to identify the critical neuropathology in the AMT lesions, since these lesions were associated with both retrograde degeneration in MD and extrathalamic damage to the mamillary bodies and fornix. Necrosis in MD presumably contributed to the impairments of the AMT group, but it cannot have been the sole cause. Otherwise, the PMT lesions should have been just as disruptive as the MT lesions, since the damage to nucleus medialis dorsalis in the two groups was the same; and the AMT lesions should have been less disruptive than the PMT lesions, since the former involved less damage to nucleus medialis dorsalis. Neither of these results was obtained. Hence, damage in either the anterior medial thalamus, the mamillary bodies, or the fornix must have also been partly responsible for the impairment.

There is ample neuropathological evidence that mamillary body damage is involved in many human cases with amnesias of diencephalic origin (Angelergues 1969; Brierly 1977), and so it is reasonable to suppose that the necrosis within the medial mamillary bodies of the AMT group contributed to their poor performance. This conclusion is supported by the finding that animal TMT, in which the mamillothalamic tracts were cut and the mamillary bodies degenerated, performed just as poorly as the AMT animals on the recognition task (Table 1), even though this animal sustained little damage to the anterior thalamic nuclei. Since the anterior thalamic nuclei and the mamillary bodies are interconnected, however, and since both receive substantial projections from the hippocampus via the fornix (Poletti and Cresswell 1977; Rosene and Van Hoesen 1977; Veazey et al. 1982), it may be more accurate to regard these two diencephalic regions as forming a single functional system, damage to either part of which will disrupt the whole.

There was some evidence that the two memory tasks were sensitive to different patterns of diencephalic damage. First, no correlation was found between the scores on the two tasks across all operated animals; in particular, animal AMT 2 was unimpaired on the associative task despite having a greater impairment on the object recognition test than that of two of the three animals in the PMT group. Second, within both the AMT and PMT groups, performance on the associative task correlated with the degree of MD damage, whereas performance on the recognition task did not. A specific link between MDmc and object-reward associative memory is supported by the finding that removal of the amygdala, which, as already indicated, projects to MDmc, has a particularly disruptive effect on this form of memory (Spiegler and Mishkin 1981).

Implications for 'Diencephalic Amnesia' in Humans

The results from the object recognition task indicate that combined damage to both the anterior and posterior thalamic regions in the monkey produces a far greater memory impairment than damage restricted to either region alone. This finding suggests that the severe memory losses seen in human cases with diencephalic pathology is likewise the consequence of a combination of damage in the posterior medial thalamic region and either the anterior medial thalamic region, the mamillary bodies, or both. The corollary of this suggestion is that patients with necrosis restricted to a particular diencephalic nucleus will display either mild or negligible amnesia.

The extensive studies of Victor et al. (1971) on the neuropathology of Korsakoff's syndrome provide strong support for both suggestions. In a series of 43 autopsied patients in whom the mamillary bodies were found to be necrotic, nucleus medialis dorsalis appeared to be normal in five of them. These same five patients were the only ones whose memory also appeared to be intact. Thus, in this series, only a combination of dorsomedial thalamic and mamillary body damage was consistently associated with amnesia. Although other studies of Korsakoff patients have failed to find the same perfect correlation between amnesia and necrosis in nucleus medialis dorsalis, there is general consensus that amnesic Korsakoff patients always suffer some periventricular thalamic damage in addition to the nearly universal mamillary body pathology (Rigges and Boles 1944; Malamud and Skillicorn 1956; Mair et al. 1979). Additional support for the proposal that combined damage to MD and to structures fed by the fornix is necessary for the amnesic syndrome to appear is provided by the frequent failure of fornix transection alone to disrupt memory in man (Woolsey and Nelson 1975; Squire and Zola-Morgan 1983).

The converse of the latter finding also appears to

be true. That is, although there are a number of reports of amnesics with diencephalic damage in which the necrosis is apparently restricted to the dorsomedial portion of the thalamus, the lesions are never confined to one nucleus (Smythe and Stern 1938; McEntee et al. 1976; Mills and Swanson 1978; Schott et al. 1980). Furthermore, when selective surgical lesions have been placed in nucleus medialis dorsalis (Spiegel et al. 1955; Orchinik 1960; Hassler and Dieckmann 1967) or, for that matter, in the anterior thalamic nuclei (Hassler 1962), only occasional, transient disruptions of memory have been observed. A recent exhaustive review of the role of MD in memory concluded that "the clear majority of the reports on human cases with lesions involving MD suggest a role of this nucleus in memory related processes. However, there apparently exists no report of a lesion confined exclusively to MD combined with behavioural measures of memory deterioration" (Markowitsch 1982).

The proposal that has been outlined here is not meant to imply that the syndrome of diencephalic amnesia is an all-or-none phenomenon which occurs only with combined damage to two or more diencephalic sites. Indeed, the evidence from our studies in monkeys suggests that there may be both mild and severe degrees of amnesia associated, respectively, with focal and more widespread diencephalic lesions. Unfortunately, there have been only very few attempts to quantify the memory disorders in amnesic patients with confirmed pathologies (Mair et al. 1979). Clearly, more such quantitative studies are needed before it can be concluded with certainty that amnesias are indeed graded in relation to the amount of involvement of the different diencephalic nuclei that have now been implicated in memory.

Two Parallel Limbo-diencephalic Pathways for Memory

The notion that combined damage to two or more specific diencephalic sites is necessary to induce a full-blown anterograde amnesia closely parallels the recent proposal that combined damage to the amygdala and hippocampus is responsible for the profound anterograde amnesia associated with temporal-lobe pathology (Mishkin 1982). This conclusion was derived, in part, from the finding that whereas removal of either the hippocampus or the amygdala alone yielded only a mild impairment of recognition memory in the monkey, a combination of the two lesions had a profound effect (Mishkin 1978). That finding, together with the knowledge that the hippocampus projects via the fornix to both the anterior thalamic nuclei and the mamillary bodies (Rosene and Van Hoesen 1977) and that the amygdala projects via the ventral amygdalofugal pathway and stria terminalis to MDmc (Nauta 1961), first suggested the existence of two parallel limbo-diencephalic pathways for memory, either of which can help support the function in the absence of the other (Mishkin 1982). Additional evidence for this proposal was provided by the recent finding that whereas disconnection of either the amygdala or the hippocampus alone from the diencephalon had little effect on recognition memory in monkeys, their combined disconnection produced a severe impairment (Bachevalier et al. 1982). The present results complete the circle of supporting evidence by showing that separate damage to the diencephalic targets of the amygdala and hippocampus yielded a less severe memory loss than that caused by combined damage to both of their targets.

It must be noted, however, that the support provided by the present study is derived from diencephalic ablations which, though selective, did extend beyond the projection targets of the amygdala and hippocampus and also necessarily interrupted fibers of passage originating outside the lesion sites. These considerations prevent any final conclusions regarding the exact loci of damage responsible for the memory losses that were found. More precise identification of these loci will require study of the effects of still more selective diencephalic lesions and ones made with neurotoxins that destroy nerve cells but spare axons (Coyle 1982).

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