

DIENCEPHALIC AMNESIA

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SUMMARY

The anatomical basis and cognitive profile of diencephalic amnesia remain unclear. We report a two-part study. First, we studied 4 patients with bilateral medial thalamic infarctions using magnetic resonance imaging and comprehensive neuropsychological testing. All patients were followed for more than 1 year. Using a stereotactic method, we plotted the lesions in an atlas delineating the probable structure involved. Secondly, in 2 monkeys, using autoradiography, we traced the pathway from the amygdala to the dorsomedial nucleus, paying particular attention to the intrathalamic course of the amygdalothalamic projections.

Our findings were (1) patients develop amnesia when infarctions are located anteriorly; (2) in patients with amnesia, the lesions can be small and strategically located, probably interfering with both hippocampal-related neural structures such as the mamillothalamic tract, and amygdala-related neural structures such as the ventroamygdalofugal pathway; and (3) a specific component of the latter is situated lateral but immediately adjacent to the mamillothalamic tract in the monkey, enabling both structures to be damaged bilaterally by small mirror image lesions. The amnesia is characterized by deficits in anterograde verbal and visual learning and in retrograde amnesia, but motor learning is preserved. We raise the possibility that bilateral diencephalic lesions may interfere particularly with temporal aspects of memory.

INTRODUCTION

The clearest examples of chronic anterograde amnesia in animal and man occur with lesions in either the medial temporal area (Scoville and Milner, 1957; Corkin, 1984) or the diencephalon (Victor *et al.*, 1971). For the medial temporal lobe, the evidence in the monkey indicates that amnesia is worse when both the hippocampal formation or its connections and the amygdala or its connections are damaged (Mishkin, 1982). Since the hippocampal formation and the amygdala have powerful connections with the diencephalon, an important question is, are the diencephalic nuclei and/or the connections of *both* these medial temporal structures affected when amnesia occurs with diencephalic damage? While this has been suggested (Aggleton and Mishkin, 1983*b*), the answer remains unclear for many reasons. (1) The diencephalon contains many nuclei and projections in a compact space so that lesions in this area that cause amnesia often damage several nuclei and/or their connections, making it difficult to determine the responsible structures. One of the ways of sorting this out is to have control cases with diencephalic damage but without amnesia. However, only a few such patients have been reported (Kritchevsky *et al.*, 1987). (2) Reports often have either good neuropsychological

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documentation of amnesia (Mills and Swanson, 1978; Schott *et al.*, 1980; Speedie and Heilman, 1982; Goldenberg *et al.*, 1983; Guberman and Stass, 1983; Winocur *et al.*, 1984; von Cramon *et al.*, 1985; Rousseaux *et al.*, 1986; Gentilini *et al.*, 1987) or good anatomical description of the lesions based on autopsy or stereotactic plottings (Castaigne *et al.*, 1981) but only a few studies have both (Mair *et al.*, 1979; Barbizet *et al.*, 1981; Mori *et al.*, 1986). Further, in some studies, memory is only tested acutely (Dehaene, 1982; Swanson and Schmidley, 1985; Bogousslavsky *et al.*, 1986; Meissner *et al.*, 1987), and thus a chronic amnesia has not been established.

The subicular cortex, which is the principal output sector of the hippocampal formation, has powerful projections to the mamillary bodies and anterior thalamic nuclei via the fimbria-fornix. The mamillothalamic tract connects the mamillary body to the anterior thalamic nuclei. While these are classic features of neuroanatomy, the linkage between the amygdala and dorsomedial thalamic nucleus, although known to exist experimentally, is more difficult to characterize. In particular, its spatial relationship to the mamillothalamic tract is unclear, although von Cramon *et al.* (1985) have speculated that it may course in the internal medullary lamina medial to the mamillothalamic tract.

In an attempt to focus on the anatomical questions that have been raised about diencephalic amnesia, we report a two-part study. First, we studied 4 patients with bilateral thalamic infarcts, all in the interpeduncular profundus arterial territory. All patients had magnetic resonance imaging (MRI) and comprehensive neuropsychological testing in the chronic stage. Using a technique first described by Archer *et al.*, (1981) and validated in a postmortem study by Graff-Radford *et al.* (1985a), we localized the lesions anatomically. We then attempted to relate the patients' performance on memory tests to the location of the lesions.

Secondly, because it was important to know as accurately as possible the course of the amygdalothalamic projections, we traced this pathway in the nonhuman primate. These monkeys received tritiated amino acid injections in the basolateral nuclei of the amygdala, and the pathway from the amygdala to the dorsomedial nucleus was studied using autoradiography. Of special interest was the intrathalamic course of this pathway relative to the mamillothalamic tract, that is, could both these pathways be damaged by small strategically located mirror image lesions?

Another important issue is the pattern of amnesia in patients with diencephalic infarcts. It has clearly been established that patients with medial thalamic infarcts may develop an anterograde verbal and visual amnesia (Winocur *et al.*, 1984; Graff-Radford *et al.*, 1985b; von Cramon *et al.*, 1985; Rousseaux *et al.*, 1986; Gentilini *et al.*, 1987). What is little explored is the pattern of retrograde amnesia and these patients' performance on motor learning tasks. In this paper we will attempt to address these issues and discuss the implications of our findings in relation to the possible role of the diencephalon in memory.

CASE REPORTS

Case 1

A 68-yr-old right-handed retired teacher was in excellent health until June 20, 1982 when she was suddenly found to be confused. She was admitted to hospital obtunded and remained somnolent for the first 10 days.

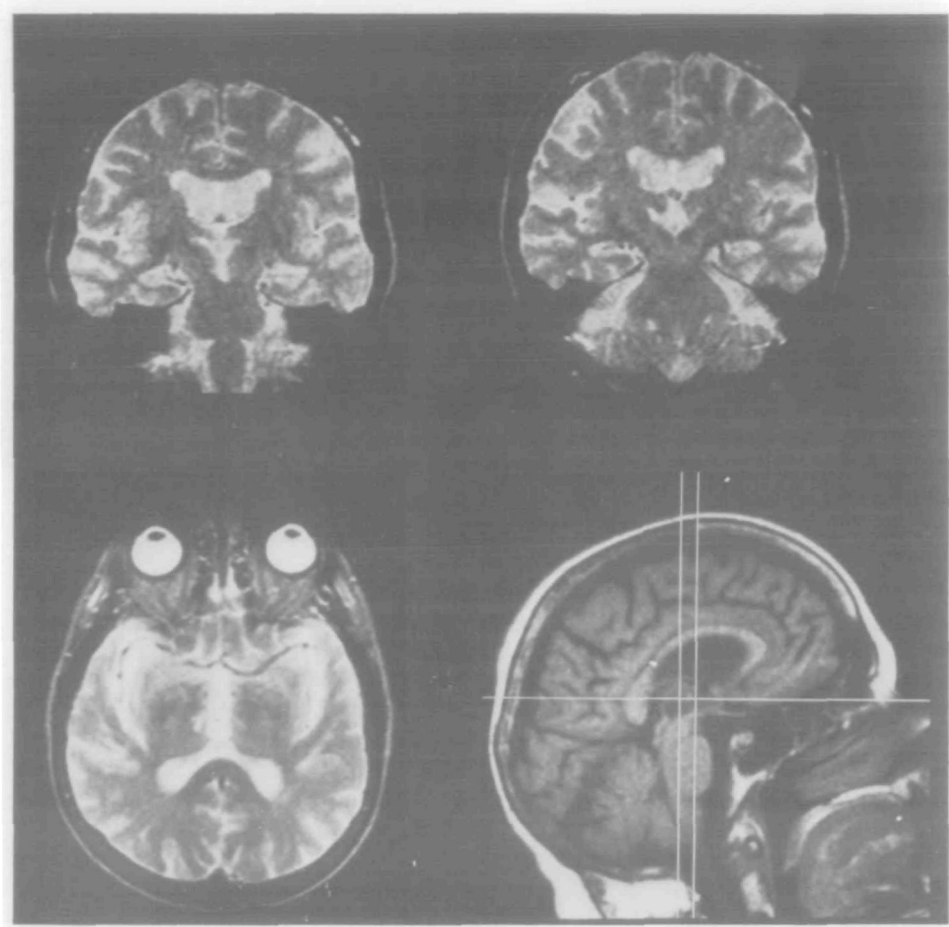


FIG. 1. Lesions in *Case 1* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

There was a past history of borderline diabetes, but no history of hypertension or smoking. Examination revealed a supranuclear vertical gaze paresis. A CT scan 10 days after admission showed bilateral enhancing medial thalamic infarctions.

The patient was discharged and lived in her own home with permanent live-in help because of a significant memory impairment. The family noted a personality change in that she was less inhibited. Over the next 5 yrs she was seen several times in the neurology clinic and underwent neuropsychological testing. Her memory deficits remained stable.

On September 25, 1987 she underwent MRI which confirmed the bilateral thalamic infarcts and no other lesions (fig. 1). She also had neuropsychological testing which revealed a stable pattern of amnesia.

Case 2

A 19-yr-old left-handed woman had the sudden onset of confusion in April 1986 and was admitted to the University of Iowa Hospitals. She had no previous illness but was on contraceptive pills. She was intermittently drowsy, had right emotional facial weakness, mild drift of the right arm, and normal sensation

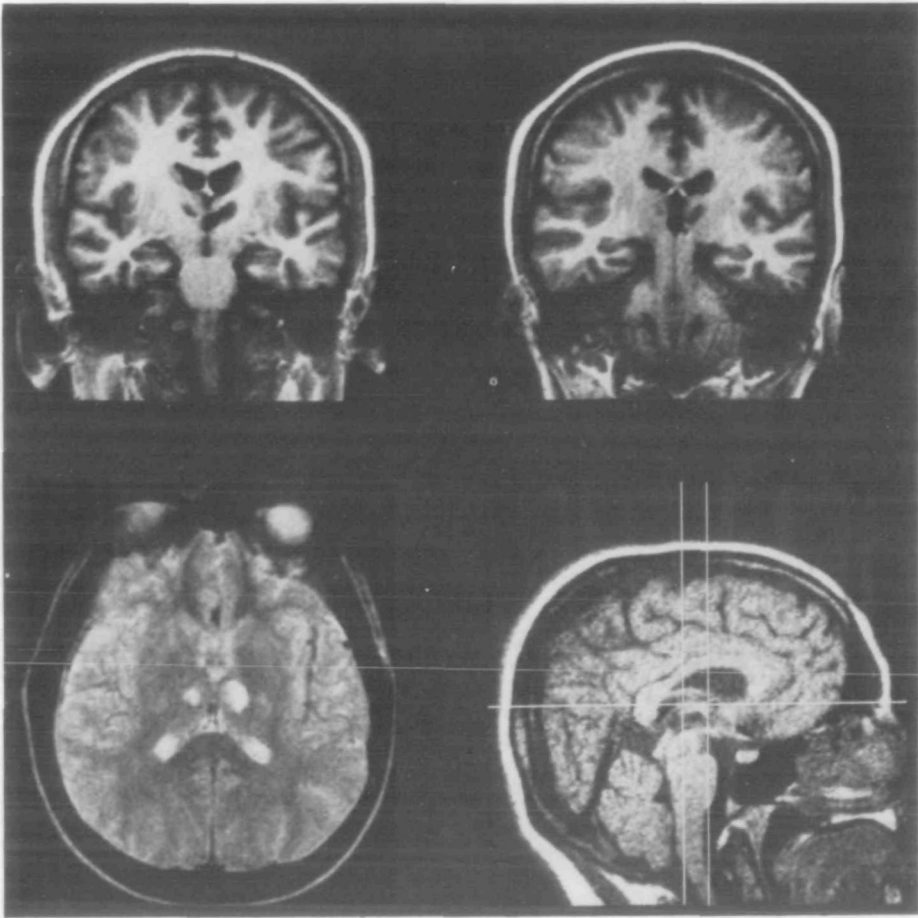


FIG. 2. Lesions in Case 2 shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

and reflexes. She remained confused and drowsy for the first week in hospital. CT showed bilateral medial thalamic infarctions. Echocardiography and arteriography were normal. MRI in October 1986 revealed bilateral thalamic infarcts without other lesions (fig. 2).

Over the next year she underwent neuropsychological evaluation three times, the last time in July 1987. Since her stroke her family have noticed that she is socially uninhibited and laughs inappropriately. Examination in July 1987 showed full eye movements, a decreased right nasolabial fold, and decreased swing of the right arm while walking. The patient's family noted that she had to be reminded many times to complete certain tasks.

Case 3

At the end of January 1987 a 57-yr-old right-handed farmer was found by his wife to be snoring and was difficult to arouse. For 2 h she tried to wake him and then called the ambulance. He awoke briefly some hours later in hospital but became somnolent again and remained so for several days. Two weeks later he was transferred to the University of Iowa Hospitals. There was no history of hypertension, diabetes,

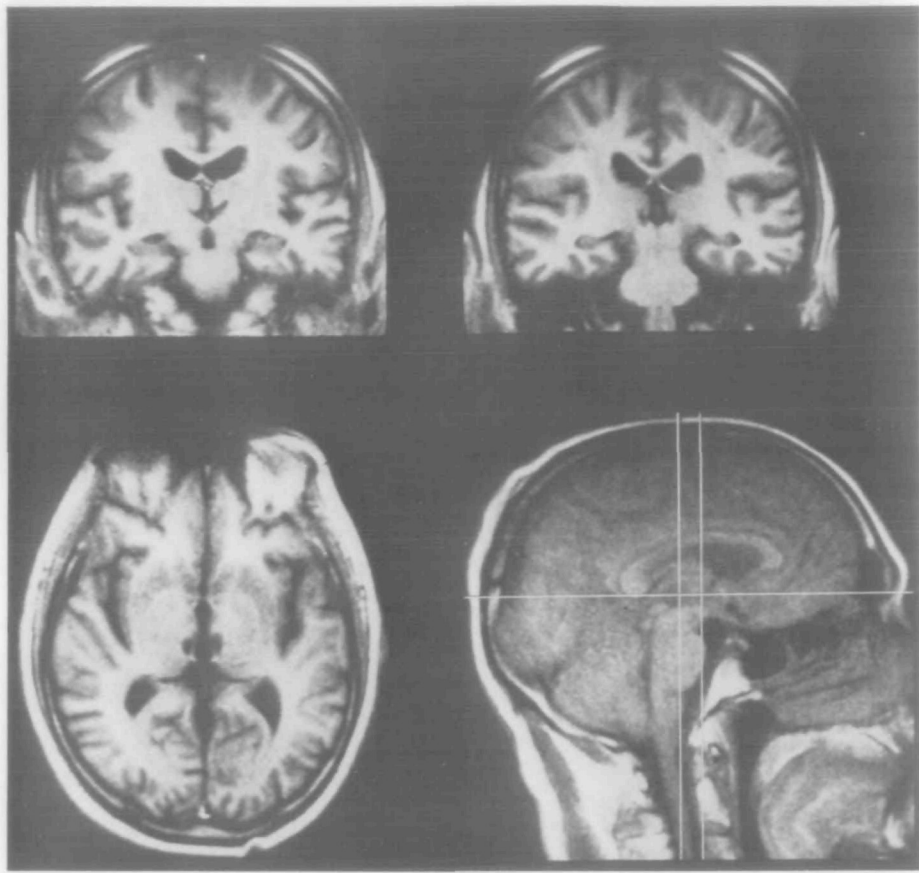


FIG. 3. Lesions in *Case 3* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

smoking, or alcohol abuse. Except for increased somnolence neurological examination was normal. MRI revealed bilateral medial thalamic infarctions (fig. 3). Echocardiography showed an atrial myxoma. Cerebral angiography was normal.

The patient underwent cardiac surgery and the atrial myxoma was successfully removed. He was seen in the neurology clinic in May and October 1987 and March 1988, and underwent neuropsychological evaluation and a repeat MRI of the head. The patient has returned to farming and he and his family deny any memory deficit.

Case 4

A 56-yr-old right-handed factory worker had a sudden onset of unresponsiveness, lasting 2 h, on February 5, 1987. He was taken to the local hospital, regained consciousness, and no focal neurological deficits were found. He had no history of hypertension, diabetes, smoking, or cardiac disease. There was a past history of bladder cancer resected in 1980 without recurrence. CT, EEG, ECG and cerebral angiography were normal. MRI showed a small left occipital and bilateral thalamic infarctions (fig. 4). On referral to the neurology clinic at the University of Iowa on March 4, 1987 he was found to have down and upbeat

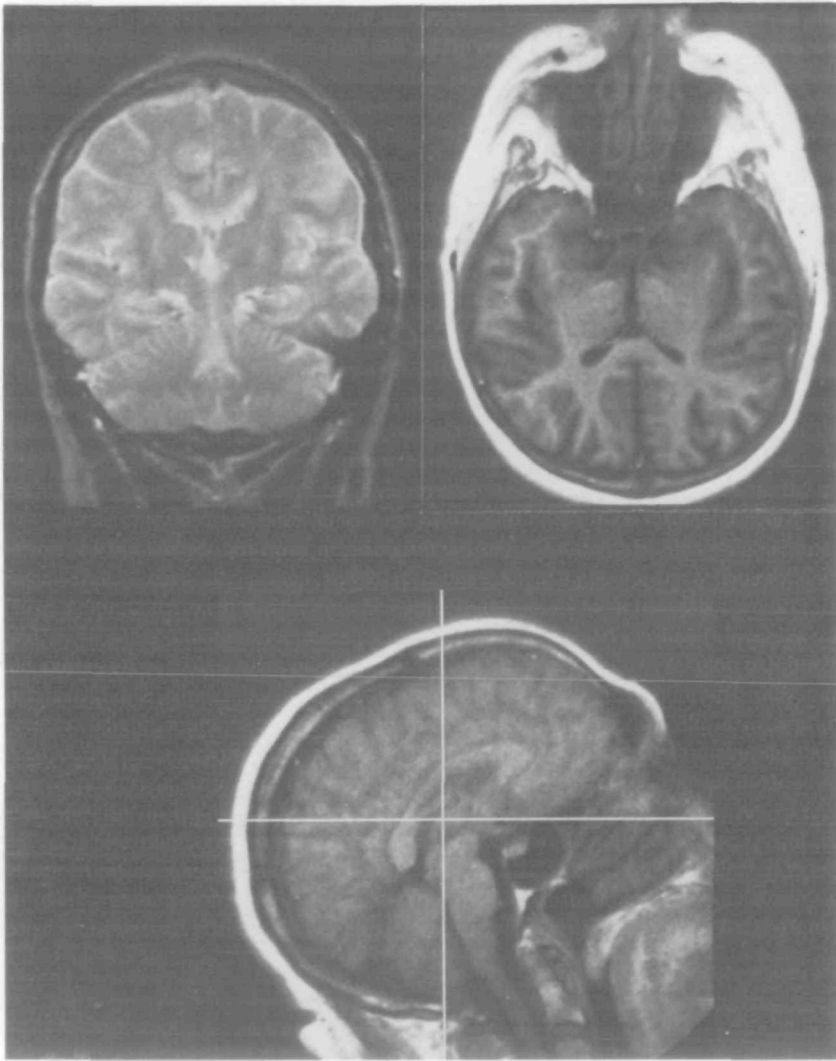


FIG. 4. Lesions in *Case 4* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

nystagmus and mild pronator drift on the right. He returned in May 1987 and March 1988, and underwent neuropsychological testing. Repeat MRI was performed in May 1987. The patient has returned to his usual activities and he and his family note no memory deficit.

METHODS

Neuroradiological study

All 4 patients underwent MRI in the chronic stage of the disease, coincident with neuropsychological testing. The scanner was a Picker International Superconductor with an 0.5 Tesla magnet. Images were obtained in sagittal, axial and coronal planes using both T1 and T2 weighted imaging methods. We have

previously described in detail the method of localizing the lesions (Kritchevsky *et al.*, 1987). Archer *et al.* (1981) originally described this method using CT and we confirmed its accuracy in a postmortem study (Graff-Radford *et al.*, 1985a). The method is based on the Schaltenbrand and Wahren Atlas (1977) and the rationale is to find the 3-dimensional location of the lesion in relation to the anteroposterior commissure line (AP line), i.e., how far is the lesion (1) ahead of or behind the commissures; (2) above or below the AP line; and (3) lateral to the midline.

In essence, the anterior and posterior commissures are identified on the midsagittal slice. (The anterior commissure is located below the juncture of the fornix and corpus callosum while the posterior commissure can be localized at the point where the cerebral aqueduct forms.) The anterior commissure/posterior commissure line (AC/PC line) is drawn between the commissures. Next, lines marking the centres of the horizontal and coronal slices containing the lesion are superimposed by the computer on this midsagittal slice and from where these lines intersect, a line perpendicular to the AC/PC line is drawn. Measuring the distance from the anterior commissure to where the perpendicular line intersects the AC/PC line gives the distance of the centre of the coronal slice to the anterior commissure. The distance above or below the AP line of the centre of the axial slice is obtained by measuring the perpendicular height above or below the AP line of intersection of the centres of the coronal and axial slices. The medial/lateral dimension of the lesion is measured on both the axial and coronal slices and the distances from the centre of the third ventricle to the most medial centre, and most lateral part of the lesion are noted. At these 3 distances the dimensions of the lesions are measured anterior/posterior in the axial slice(s) and superior/inferior on the coronal slice(s). The lesion is then plotted on the three sagittal plates in the Schaltenbrand and Wahren Atlas corresponding to the medial, middle, and lateral distances of the lesion from the midline. Note that the AP diameter is plotted in the same plane as the axial slice and the superior/inferior diameter the same plane as the coronal slice. The planes of the axial and coronal slices in relation to the AP line are obtained by measuring the angles these slices make when they intersect the AP line on the midsagittal view. In all instances the magnification factor of the MRI and magnification of the Atlas are taken into account. A way to check the accuracy of the above method is to take advantage of the fact that the MRI image is plotted on a grid system such that the location of anterior/posterior limits of the lesion on the axial slice, and the superior/inferior limits of the lesions on the coronal slice, can be transferred to the midsagittal slice on the anteroposterior and superoinferior grids, respectively. On the midsagittal slice, perpendicular lines are dropped from the top grid delineating the anteroposterior limits of the lesion and horizontal lines are drawn from the posterior grid delineating the superior/inferior limits of the lesion. The lesion is located where the perpendicular and horizontal lines intersect. This location in relation to the AP line can be measured and plotted in the Atlas.

Anatomical study

The basolateral nuclei of the amygdala in 2 monkeys were injected with tritiated amino acids and autoradiography was used to detect the anterograde axoplasmic transport.

TABLE I. NEUROPSYCHOLOGICAL TESTS

Orientation	Temporal Orientation Test ¹
Intelligence	Wechsler Adult Intelligence Scale-R ²
Language	Multilingual ³ and Boston Diagnostic Aphasia Examination ⁴ (selected subtests)
Visuospatial abilities	Copy of the Rey-Osterreith Complex Figure ⁵ Facial Discrimination Test ¹
Executive control	Judgement of Line Orientation Test ¹ Wisconsin Card Sorting Test ⁶ Controlled Oral Word Association Test ³

¹Benton *et al.* (1983). ²Wechsler (1981). ³Benton (1976). ⁴Goodglass and Kaplan (1983). ⁵Lezak (1983).

⁶Heaton (1981).

TABLE 2. MEMORY TESTS

Verbal memory	Rey Auditory Verbal Learning Test with 30 min delayed recall and recognition ¹ Wechsler Memory Scale (subtests logical memory, paired associates) and 30 min delayed recall ² Craik Tulving Encoding ³ Release from proactive interference ⁴ Warrington Recognition Memory Test (words) ⁵
Visual memory	Benton Visual Retention Test ⁶ Rey-Osterreith Figure Recall (30 min delay) ⁷ Warrington Recognition Memory Test (faces) ⁸
Retrograde memory	Autobiographical construction and interview Recall of US Presidents Boston Famous Faces Test ⁹ Boston Recognition of Events Test ⁹ Boston Recall of Events Test ⁹ Squire Recall and Recognition of Past Events ¹⁰ (Forms A and B)
Motor learning	Rotor Pursuit Learning (1 h delayed recall) ¹¹ Mirror Tracing (1 h delayed recall) ¹²

¹Lezak (1983), p. 422. ²Wechsler (1945). ³Craik and Tulving (1975). ⁴Wickens (1970). ⁵Warrington (1984). ⁶Benton (1974). ⁷Lezak (1983), p. 395. ⁸Warrington (1984). ⁹Albert *et al.* (1979). ¹⁰Squire *et al.* (1989). ¹¹Corkin (1968); Eslinger and Damasio (1986). ¹²Milner (1962).

Neuropsychological study

The first 3 patients were tested in the first month after onset and all 4 patients were tested in the chronic stage. In the chronic stage Case 1 was tested several times, finally 6 yrs after the stroke; Case 2 more than 1 yr after her stroke; Case 3 6 and 12 months after his stroke; and Case 4 3 and 12 months poststroke.

The neuropsychological examination probed the following: orientation, intellect, speech and language, visuospatial and visuoperceptual processing, 'executive control', and memory. With regard to memory, the following functions were tested: anterograde verbal, anterograde visual, retrograde memory and motor learning. A complete list of the neuropsychological tests is given in Tables 1 and 2.

RESULTS

Neuroradiological study

Axial and coronal slices showing the lesions, together with the centre of these slices drawn on the midsagittal view, are shown in figs 1–4. Fig. 5A (left side) and B (right side) show the results of plotting the lesions on the sagittal sections in the Atlas 5.15 mm from the centre of the third ventricle (Plate 39 in the Schaltenbrand and Wahren Atlas). The lesions in Cases 1 and 2 are situated more anteriorly and involve the mamillothalamic tract, and the pathway from the inferior thalamic peduncle to the dorsomedial nucleus. The latter is true on both sides for Case 1 and on the left for Case 2. Case 2 also has involvement of the anterior nuclei bilaterally. In Case 3 there are large lesions affecting mainly the dorsomedial nuclei bilaterally. Case 4 has small bilateral lesions in the lower part of the dorsomedial nuclei. In both Cases 3 and 4 the mamillothalamic tract is spared. Cases 1–3 involve the midline nuclei bilaterally.

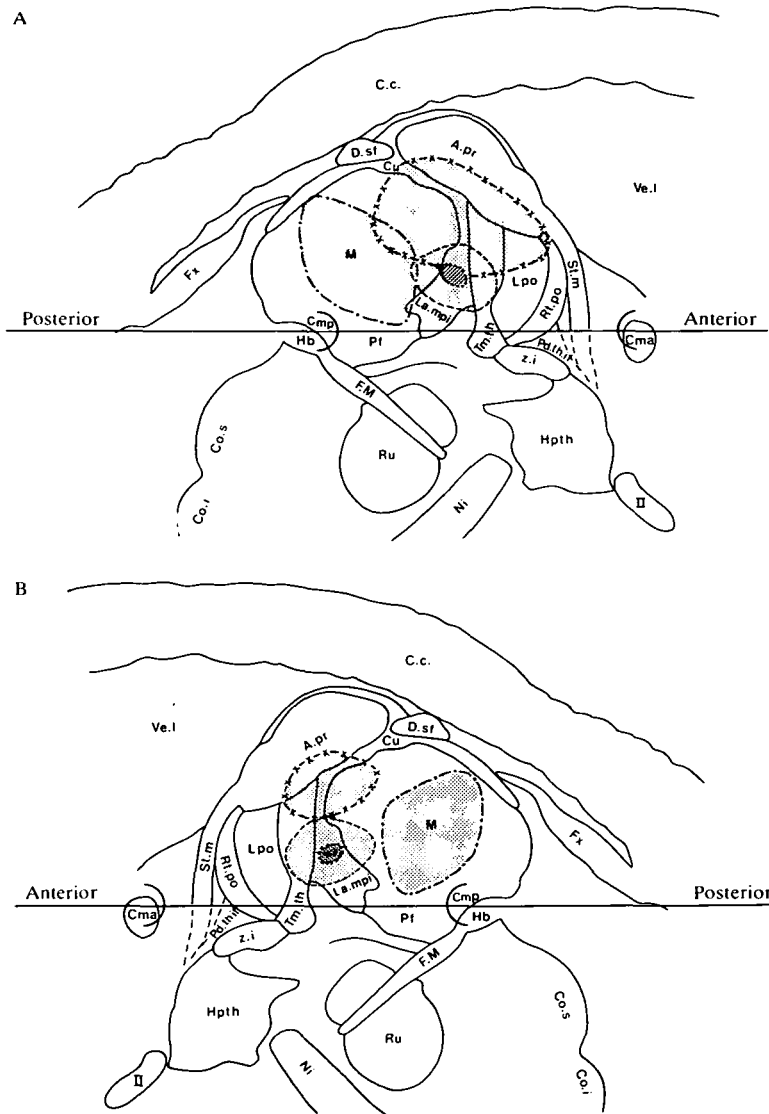


FIG. 5. A, left-sided lesions, B, right-sided lesions on the sagittal plates 5.5 mm from the midline in the Schaltenbrand and Wahren Atlas. The lesion in *Case 1* is small but strategically located, probably damaging the mamillothalamic tract (Tm.th) and interrupting fibres from the inferior thalamic peduncle (Pd.thif). In *Case 2* the lesion also damaged the mamillothalamic tract. In addition, the anterior nuclei are damaged. Fibres from the inferior thalamic peduncle are probably only partly interrupted as they head for the superior part of the dorsomedial nuclei. The anterior part of the dorsomedial nuclei is damaged. In *Case 3* the dorsomedial nuclei are damaged bilaterally but the mamillothalamic tract is preserved. The lesions in *Case 4* may have partially interrupted fibres coming from the inferior thalamic peduncle but the mamillothalamic tract probably was spared. Case 1 (---); Case 2 (-x-x); Case 3 (-·-·); Case 4 (····).

Abbreviations: A.pr = anterior nuclei; C.c. = corpus callosum; Co.i = inferior colliculus; Co.s = superior colliculus; Cma = anterior commissure; Cmp = posterior commissure; D.sf = lateral dorsal nucleus; F.m = fasciculus retroflexus; Fx = fornix; Hpth = hypothalamus; Hb = habenula; La.mpi = lamella medialis polaris; Lpo = lateral posterior nucleus; M = dorsomedial nucleus; Ni = substantia nigra; Pd.thif = inferior thalamic peduncle; Pf = parafascicular nucleus; Rt.po = reticular nucleus; Ru = red nucleus; St.m = stria habenularis; Tm.th = mamillothalamic tract; Ve.l = lateral ventricle; z.i. = zona incerta; II = second cranial nerve.

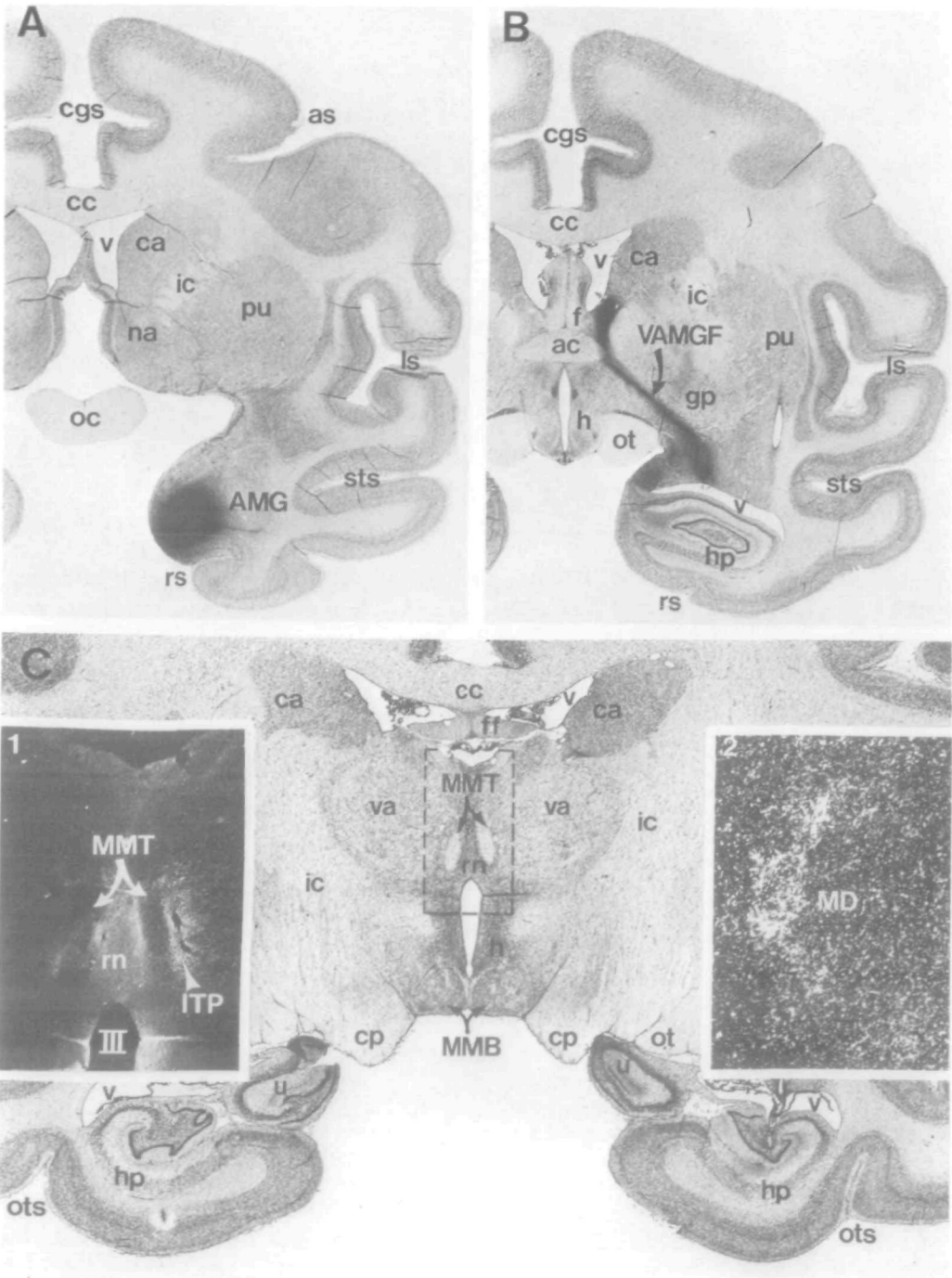


FIG. 6.

Anatomical study

Fig. 6A shows the injection site in the amygdala from 1 case. The injection in this case labelled the accessory basal and mediobasal nuclei of the amygdala, as well as the deep layers of the adjacent entorhinal cortex. Fig. 6B and C demonstrates the course of a major component of the ventroamygdalofugal pathway that links the amygdala to various basal forebrain structures such as the bed nucleus of the stria terminalis, nucleus accumbens, and nucleus basalis of Meynert. However, a significant portion of this large neural system turns caudally in the vicinity of the ventromedial part of the globus pallidus and enters the thalamus medial to the anterior limb of the internal capsule (fig. 6C1). These axons form a part of inferior thalamic peduncle and terminate in the dorsomedial nucleus of the thalamus (fig. 6C2). In passing through the ventral anterior nucleus they assume a position immediately lateral to the mamillothalamic tract.

Neuropsychological study

Table 3 presents the overall results of the neuropsychological tests and Tables 4 and 5 give the detailed scores of the memory testing. Figs 7 and 8 show the results on the remote memory tests and motor learning tests, respectively. None of the patients had a significant global decline in intellectual functioning or was aphasic, and in all patients visuospatial abilities were normal in the chronic stage. (The IQ scores for Case 2 were in the borderline range, but were considered to be normal given the patient's educational and occupational background.) In all patients 'executive control' function (as measured by the Controlled Oral Word Association Test and the Wisconsin Card Sorting Test) was mildly to moderately impaired. In addition, by family report and clinical observation, all patients demonstrated personality changes, characterized primarily by disinhibition and lack of motivation.

Tables 4 and 5 show that Cases 1 and 2 have severe anterograde verbal and visual memory deficits; Cases 3 and 4 have milder deficits evident only on delayed tasks. Case

FIG. 6. (Opposite) A, Nissl-stained transverse section from the Rhesus monkey brain developed for autoradiography showing the location of tritiated amino acids injected into the medial parts of the basolateral amygdaloid nuclei and the deep layers of the entorhinal cortex. B, transverse section from the same animal demonstrating the ventroamygdalofugal pathway (VAMGF) in its course from the posterior amygdala beneath the globus pallidus (gp) to the bed nucleus of the stria terminalis at the base of the body of the lateral ventricle (v). C, Nissl-stained transverse section from the same case at the level of the uncus (u) and mamillary bodies (MMB). Note the midline region of the thalamus (outlined rectangle) and the position of the mamillothalamic tracts (MMT). Inset 1 is a dark-field photomicrograph of the rectangular area that demonstrates tritium-labelled axons in the inferior thalamic peduncle (ITP) immediately lateral to the mamillothalamic tract ipsilateral to the amygdaloid injection. As shown in inset 2, these axons follow a posterior intrathalamic course where they terminate in the dorsomedial thalamic nucleus. Note that a selective vascular lesion at the level of inset 1 would disrupt both the mamillothalamic tract and the inferior thalamic peduncle. Other abbreviations: ac = anterior commissure; as = arcuate sulcus; ca = caudate nucleus; cc = corpus callosum; cgs = cingulate sulcus; cp = cerebral peduncle; h = hypothalamus; hp = hippocampal formation; ic = internal capsule; ls = lateral sulcus; na = nucleus accumbens; oc = optic chiasm; ot = optic tract; ots = occipitotemporal sulcus; pu = putamen; rn = nucleus reuniens; rs = rhinal sulcus; sts = superior temporal sulcus.

TABLE 3. RESULTS OF NEUROPSYCHOLOGICAL TESTING

Case no.	Age (yrs)/sex/ handedness	Yrs of education	Occupation	Stroke onset	Stage of testing	Temporal orientation	WAIS-R		Language	Visuospatial abilities*	Executive control*	Personality changes
							VIQ	PIQ				
1	68/F/R	16	Retired educator	20.6.82	Acute	Defective	99	79	Nonphasic	2	2	Marked
2	20/F/L	10	Homemaker	16.4.86	Acute	Defective	117	93	Nonphasic	1	2	Marked
3	57/M/R	12	Farmer	31.1.86	Acute	Intact	72	53	Nonphasic	3	2	Moderate
4	58/M/R	12	Retired factory employee	5.2.86	Chronic	Intact	96	117	Nonphasic	1	2	Moderate
						No data available from acute stage	93	119	Nonphasic	1	2	Moderate
					Chronic	Intact	88	88	Nonphasic	1	2	Moderate

* Interpretation scale: 1 = intact; 2 = mild to moderate impairment; 3 = severe impairment.

TABLE 4. VERBAL MEMORY

Case no.	Test stage	Rey Auditory Verbal Learning Test			Wechsler Memory Scale			Wechsler Memory Scale Paired Associates			Craik-Tulving Encoding			Warrington Recognition Memory Test Words	Scaled score
		Trial 1	Trial 5	Recall	30 min delay	Immediate	30 min delay	Immediate	30 min delay	Print	Rhyme	Semantic	Release from proactive interference		
1	Acute	0	4	0	25	25	14	14	14	14	14	20	20	20	5
2	Chronic	3	5	0	1	0	.2	3	2	0	0	0	0	0	6
	Acute	1	3	0	0	6	.5	6	6	4	4	0	0	0	
3	Chronic	4	6	3	1	0	1	0	2	2	2	1	0	0	8
	Acute	6	12	8	3	2	1	0	3	3	4	3	1	6	
4	Chronic	7	14	8	14	11	13	7	5	7	8	5	12	14	10
	Acute	No data available from acute stage.			9	11	8	10	12	14	10	4	4	15	
	Chronic	6	12	8	11	10	6	5	10	10	8	4	4	15	

Abnormal scores are underlined.

TABLE 5. VISUAL MEMORY

Case no.	Test stage	Benton Visual Retention Test		Rey Osterreith Complex Figure Test		Warrington Recognition Memory Test Faces Scaled score
		No. correct	No. of errors	Copy	30 min delay	
	Maximum score	10	>9	36	36	
1	Acute	<u>1</u>	<u>20</u>	<u>21</u>	<u>1</u>	
	Chronic	<u>4</u>	<u>11</u>	<u>36</u>	<u>5</u>	<u>4</u>
2	Acute	<u>1</u>	<u>21</u>	<u>9</u>	<u>0</u>	
	Chronic	<u>4</u>	<u>12</u>	<u>29</u>	<u>8</u>	7
3	Acute	<u>5</u>	<u>4</u>	36	<u>13</u>	9
	Chronic	7	5	35	<u>20.5</u>	<u>5</u>
4	Acute	No data available from the acute stage				
	Chronic	5	7	<u>29</u>	<u>10</u>	6

Abnormal scores are underlined.

1, despite having a college education and a high verbal IQ, scored worst on the Rey Auditory Verbal Learning Test and is the only patient to be defective in the recall *and* recognition components of this test. She is also defective on both the Warrington recognition tests. Case 2 scored normally on the recognition component of the Rey Auditory Verbal Learning Test. She also scored normally on the Warrington Recognition Memory Test for words and faces. In contrast, Cases 3 and 4 at the chronic stage scored in the normal range on all the verbal and visual memory tests except for those requiring delayed recall. The latter are the most difficult types of memory task, indicating that these 2 patients have a milder memory deficit than Cases 1 and 2. An exception to this general pattern is that Case 3 is defective on the Warrington Face Recognition Test.

All patients showed good motor learning (fig. 8).

Fig. 7 shows the scores on the remote memory test, 7A showing scores on the Boston Famous Faces test for spontaneous recall and 7B the scores using semantic and first name cues. Fig. 7C shows the results in recognition of recent events for Albert's test. Fig 7D and E show recall and recognition scores on Squire's test of famous events. All patients, but especially Case 1, benefited from cues on the Boston Famous Faces test and in the recognition format on the Squire's test. Only on this latter test on the recognition format does Case 1 show a temporal gradient scoring better in the 1950s compared with the 1980s.

These scores require qualification by the description of the performance of Case 1 on some of the tests as well as an analysis of 2 taped interviews, one in 1982 and another in 1988 and her answers in a written questionnaire about events in her personal biography.

First, on the recognition of famous faces it is noteworthy that the patient frequently was able to give the correct last name when given cues including the person's first name (fig. 7A, B). She also accurately identified by name all members of her family when shown pictures of them.

Secondly, in the interviews and biographical questionnaire the patient gave accurate information about her personal life, such as her date of birth, names of her schools

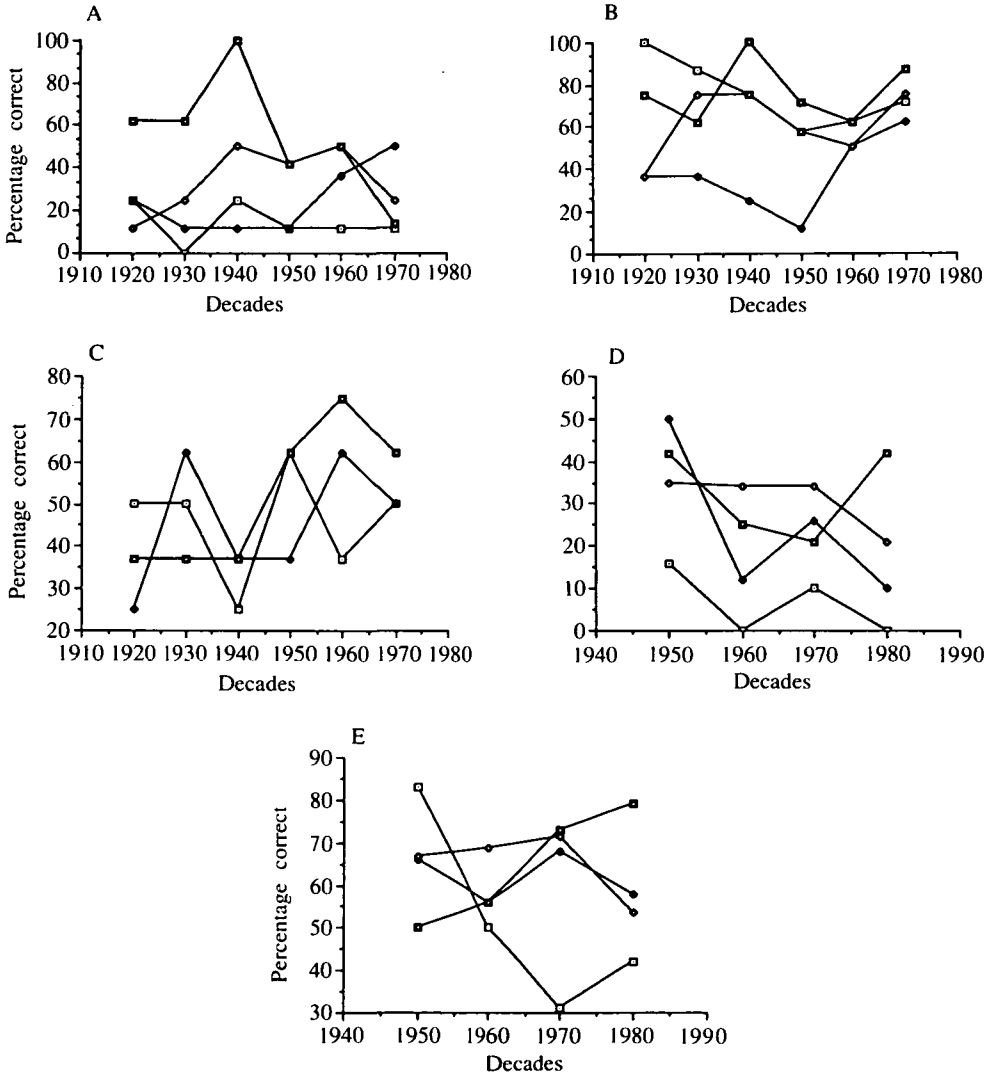


FIG. 7. A, scores by decade on recall of famous faces without cues (Boston Famous Faces Test, Albert *et al.*, 1979). B, scores by decade on recall of famous faces using both semantic and first name cues. C, scores on recognition of recent events by decade (Albert *et al.*, 1979). D, score on recall of recent events by decade (Squire *et al.*, 1989). This test was based on forms A and B and had 12 to 19 items per decade. The controls were 5 Iowans (3 females and 2 males) aged over 60 yrs. E, scores on recognition of recent events by decade (Squire, 1989). This test was based on a combination of forms A and B and had 12 to 19 items per decade. The controls were the same as for the recall component. In this test Case 1 shows a clear temporal gradient, scoring better in the 1950s than in the 1980s. Case 1 (□); Case 2 (◆); Case 3 (◇); Case 4 (○).

and colleges, names of people who influenced her, names of schools she taught at, age she started teaching, age and year she was married, date of death of her husband, names of her children and grandchildren, and acreage of her farm. An important characteristic of her performance was that she was greatly helped by the examiner orientating her,

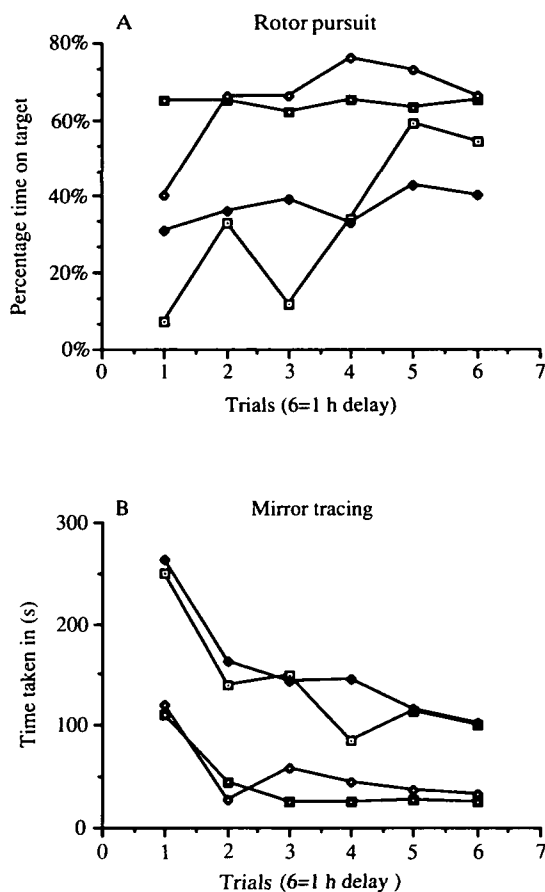


FIG. 8. A, motor learning in rotor pursuit. All patients except Case 3 showed improvement in the percentage of time on the target. Case 3 improved by having fewer episodes off target (not shown in graph). All patients maintained their improvement in the 1 h delay trial. B, motor learning on the mirror tracing test. All patients learned this task and maintained their learning at the 1 h delay trial. Case 1 (□); Case 2 (◆); Case 3 (◻); Case 4 (◇).

for example, in 1982 she was asked who was President of the US and she said 'Lyndon B. Johnson'. When the interviewer said, 'No, it's later than that' she then replied 'Oh, Ronald Reagan'. When asked what her daughter did, she said that her daughter was the head nurse in Orthopaedics in a specific hospital (which she named) in Des Moines. The examiner pointed out that it was after that and the daughter had moved. The patient then gave the correct name of the current hospital in California to which her daughter had moved. When asked to name her grandchildren, she named the first 4 and when prompted that there may be another, she named the youngest. Another important point is that she gave no indication of learning about new events since her stroke. For example, she could not recall undergoing a colonoscopy even when the examiner tried to prompt her about this.

Case 2 was too young for the standardized remote memory tests to be of significance,

but she performed well on a personal history questionnaire. Cases 3 and 4 performed normally on the remote memory tests and the personal history questionnaire.

In summary, Case 1 has a severe anterograde visual and verbal memory loss. Case 2 is also impaired but less so than Case 1. Cases 3 and 4 are only mildly impaired and not at all disabled by the deficits demonstrated in the laboratory. Motor learning was preserved in all patients. Remote memory loss was present in Case 1 as seen on spontaneous recall, probably normal in Case 2 (in view of her recall of biographical data), and normal in Cases 3 and 4. These findings on formal memory testing are in keeping with the observations of how the patients functioned in society after their stroke. Case 1 was completely disabled, Case 2 needed some supervision, and Cases 3 and 4 resumed their previous activities without any supervision.

DISCUSSION

Our findings support the notion that a significant anterograde amnesia resulted when there was damage to diencephalic neural systems related closely to both the hippocampus and amygdala, specifically the mamillothalamic tract and ventroamygdalofugal pathway to the dorsomedial nucleus (as in Case 1) and the mamillothalamic tract, anterior nuclei, anterior part of the dorsomedial nuclei, and superior part of the ventroamygdalofugal pathway (Case 2). (Note that the preservation of the ventral part of the ventroamygdalofugal pathway and most of the dorsomedial nuclei might account for this patient's better performance than that of Case 1.) When only one of these systems was damaged, a milder, clinically insignificant memory loss occurred (as in Cases 3 and 4). The role of damage to the midline nuclei or their medial temporal connections cannot be determined.

The second part of our study showed that the hippocampal and amygdala pathways are adjacent to each other anteriorly in the thalamus of the monkey (fig. 6c). Our plottings of the infarcts revealed that the lesions causing amnesia were also anteriorly located and involved the region where these pathways course adjacent to each other. In contrast, the lesions that did not cause a clinically significant amnesia were situated more posteriorly in the thalamus. It should be noted that the size of the infarct did not necessarily influence the occurrence of amnesia. Case 1 had the second smallest infarct and had the worst amnesia, whereas Case 3 had the second largest infarct and had a subclinical memory deficit. Furthermore, lesions involving dorsomedial nuclei alone did not cause a clinically significant amnesia.

CT findings in reported cases of infarction-related diencephalic amnesia

Von Cramon *et al.* (1985) summarized the CT findings of 11 diencephalon infarcts reported to cause amnesia; 6 were their own cases and 5 were from the literature. They noted that anteriorly located lesions cause amnesia, whereas posterior lesions do not, and concluded that the internal medullary lamina and the mamillothalamic tract were the critical sites of the lesions causing amnesia. Since then there have been several reports.

Gentilini *et al.* (1987) evaluated 8 cases with bilateral medial thalamic infarcts. All had acute CT scans between 4 days and 3 months, making it difficult to distinguish oedema from the chronic lesion. Case 5 could not be tested and Case 6 was an alcoholic. Case 2 had no acute verbal amnesia and the left-sided lesion was located posteriorly. Cases 4 and 8 recovered from their acute amnesia by 3 months; again the lesions were posterior. Case 1 had a documented amnesia at 3 months. The right lesion is clearly anterior but we are uncertain about the lesion on the left. Case 3 remained chronically amnesic according to the family and the lesions are probably anterior. Case 7 remained amnesic for several months in hospital; again the lesions are anterior. In essence it seems from the study that anteriorly located lesions are necessary for chronic amnesia. With posterior lesions, amnesia does not occur or the patients recover from it. This is in keeping with the authors' conclusion that the damage to the mamillothalamic tracts, anteriorly located structures, is related to the amnesia.

Mori *et al.* (1986) reported a case of left thalamic infarction and amnesia. Again the lesion was situated anteriorly and involved the mamillothalamic tract. Rousseaux *et al.* (1986) reported 5 cases of medial thalamic infarcts, 3 bilateral and 2 unilateral. They concluded that anterior medial thalamic lesions are more likely to cause amnesia than posterior lesions. Kritchevsky *et al.* (1987) reported 1 mainly left-sided and 1 right-sided thalamic infarct without chronic amnesia. The lesions were in the dorsomedial nucleus and did not involve the mamillothalamic tract, that is, they were posteriorly situated.

There are 2 relevant postmortem studies. Castaigne *et al.* (1981) reported the postmortem findings of 28 cases with paramedian thalamic infarction. Cases 2, 5, 7, and 13 had chronic amnesia and Cases 2, 5, and 7 had neuropsychological testing documenting this. Cases 5 and 7 had additional posterior cerebral territory infarctions which might have contributed to the memory deficit by involving the medial temporal area. The infarcts in Cases 2 and 13 involved the mamillothalamic tract (on the left in 2 and bilateral in 13). Again this suggested that anterior thalamic lesions are associated with amnesia. Bogousslavsky *et al.* (1986) reported a haemorrhagic thalamic infarct which did not involve the mamillothalamic tract and caused amnesia acutely. Because the amnesia was only noted acutely and the infarction was haemorrhagic, it is possible that there were pressure effects on anterior structures contributing to the deficits.

In summary, there are numerous reports of chronic amnesia from thalamic infarcts and the lesions are situated anteriorly. There are also several reports of thalamic infarcts without amnesia and the lesions are situated posteriorly. This is in keeping with the 4 patients we report here.

Primate studies

We will now review in the monkey the known afferent and efferent projections of the hippocampal formation and amygdala to selected diencephalic nuclei that have been thought to play a role in memory. Table 6 summarizes these projections as described in 6 studies. As can be seen, the anterior thalamic nuclei and mamillary bodies are strongly related to the hippocampal formation, whereas the dorsomedial nuclei are related to

TABLE 6. AFFERENT AND EFFERENT HIPPOCAMPAL AND AMYGDALA PATHWAYS TO AND FROM SELECTED DIENCEPHALIC NUCLEI IN THE NONHUMAN PRIMATE

	<i>Anterior nuclei</i>	<i>Mamillary bodies</i>	<i>Dorsomedial nuclei</i>	<i>Midline nuclei</i>
Hippocampal formation				
Afferent ^{1*}	+	0	0	+
Efferent ²	++	++	0	+
Amygdala				
Afferent ³	0	0***	0**	+
Efferent ⁴	0	0	++	+

0 = no projections; + = mild to moderate projections; ++ = strong projections.

¹Amaral and Cowan (1980); ²Rosene and Van Hoesen (1977); ³Mehler (1980); ⁴Nauta (1962); Aggleton and Mishkin (1984); Price (1986).

*Projections from the supramamillary nucleus to the hippocampus; **projections from dorsomedial nucleus to perirhinal cortex which then projects to amygdala; ***projections from supramamillary nucleus to amygdala.

the amygdala. The midline nuclei, including nucleus reuniens, are related to both hippocampal formation and the amygdala.

In summary, damage to the anterior thalamic nuclei, mamillary bodies and their connections is likely to impair a neural system related closely to the hippocampal formation, whereas damage to the dorsomedial nucleus or its connections is likely to impair neural systems related more intimately with the amygdala. At present, it is uncertain which system or systems that damage to the midline will affect.

Dense amnesia following lesions of the diencephalon and its connections

Lastly, we will summarize the occurrence of a dense amnesia in anatomically well documented lesions of the diencephalon and its connections, either in isolation or in combination. We will do this for man and monkey. Table 7 summarizes these findings. We should admit at the outset that whether there is a dense amnesia or not is a judgement we have made on the available data which is deficient in many instances; the patients with isolated fornix (Woolsey and Nelson, 1975), anterior thalamic (Mark *et al.*, 1970) and mamillary body lesions (Victor *et al.*, 1971), for example, had no formal neuropsychological testing but were all felt not to be amnesic. It would surprise us if on formal testing some deficit in memory functioning could not be documented in such cases. This is why we have used the term dense amnesia which we believe would be clinically obvious to the patients' families and their doctors. Furthermore, the monkeys with isolated lesions often showed mild impairment on memory tests compared with controls, but again these deficits were significantly less severe than monkeys with combined lesions.

Mair *et al.* (1979) and Mayes *et al.* (1988) carefully studied patients with Korsakoff's syndrome who came to postmortem and had only mamillary body and midline nuclei damage on gross inspection. As Table 5 shows, the midline nuclei have connections with both the hippocampus and the amygdala. Despite this, damage to this area alone, in the monkey, apparently does not cause severe amnesia (Aggleton and Mishkin, 1983b).

TABLE 7. AMNESIA IN ANATOMICALLY DOCUMENTED LESIONS INVOLVING THE DIENCEPHALON AND ITS MEDIAL TEMPORAL CONNECTIONS

Structures damaged	Presence or absence of dense amnesia	
	Human	Monkey
Isolated		
Fornix	No* ¹	No ^{2,3,4,5} /Yes ⁶
Mamillary bodies	No* ⁷	No ⁸
Anterior thalamic nuclei	No* ⁹	—
Ventroamygdalofugal pathway	—	No ⁵
Dorsomedial nuclei	No ¹⁰	—
Midline thalamic nuclei	—	No ¹¹
Combined		
Mamillary bodies, midline thalamic nuclei	Yes ^{12,13}	—
Dorsomedial nuclei, fornix	—	Yes ³
Fornix, ventroamygdalofugal pathway	—	Yes ⁵
Mamillothalamic tract, ventroamygdalofugal pathway	Yes ^{14,15}	Yes ¹⁷
Anterior, dorsomedial, midline nuclei and fornix	—	Yes ^{16,17}

*No formal neuropsychological testing.

¹Woolsey and Nelson (1975).

²Moss *et al.* (1981).

³Zola-Morgan and Squire (1985).

⁴Bachevalier *et al.* (1985a).

⁵Bachevalier *et al.* (1985b).

⁶Gaffan *et al.* (1984).

⁷Victor *et al.* (1971).

⁸Aggleton and Mishkin (1985).

⁹Mark *et al.* (1970).

¹⁰Kritchevsky *et al.* (1987).

¹¹Aggleton and Mishkin (1983b).

¹²Mair *et al.* (1979).

¹³Mayes *et al.* (1988).

¹⁴Mori *et al.* (1986).

¹⁵von Cramon *et al.* (1985).

¹⁶Aggleton (1986).

¹⁷Aggleton and Mishkin (1983a).

However, in the postmortem studies of the two groups of Korsakoff's patients quoted above, damage to midline nuclei *and* mamillary bodies may be sufficient to cause amnesia. Again hippocampal and amygdala pathways could be involved.

In summary, patients and monkeys with isolated damage to one of the nuclei in the thalamus, or one of the medial temporal connections to these nuclei, are usually reported not to have a dense amnesia. In contrast, combined lesions invariably cause significant amnesia.

The diencephalon and memory

Thus from an anatomical point of view, we can conclude that (1) lesions located anteriorly in the thalamus are more likely to cause amnesia; (2) our tracing the ventroamygdalofugal pathway to the dorsomedial nucleus in the monkey showed that this pathway is lateral and adjacent to the mamillothalamic tract; (3) the lesions causing amnesia in our patients are likely to have interfered with pathways to the diencephalon both from the hippocampal formation (mamillothalamic tract) and amygdala (ventroamygdalofugal pathway). In contrast, in the 2 patients without significant amnesia the mamillothalamic tract was spared. All these observations support the idea that simultaneous damage to diencephalic nuclei and/or their connections related both to the hippocampal and amygdala is likely to result in a dense amnesia.

Other structures, however, such as hypothalamus, basal forebrain and medial frontal area have strong connections both to the medial temporal area and the thalamus and it is possible that pathways from these structures to the thalamus may also have been

damaged by the infarctions and contributed to the amnesic state. In view of the experimental evidence in the monkey that damage to the ventroamygdalofugal pathway (at a site less likely to interfere with the above-mentioned pathways) and the fornix is sufficient to cause amnesia (Bachevalier *et al.*, 1985b), it is likely that interference in these two pathways by the lesions in our patients is also probably sufficient to cause amnesia without invoking damage to other pathways as mentioned above.

If it is true that damage both to amygdala and hippocampal systems in the diencephalon is necessary to cause a dense amnesia, it implies a certain parallel redundancy of the memory system which allows at least partial compensation when only one of the anatomical systems is damaged. This has been proposed by Mishkin (1982) and the findings in this paper are in keeping with this argument. There is, however, some contradictory evidence. Patient R.B. of Zola-Morgan *et al.* (1986) who had anoxic damage only in the hippocampal formation, had a clinically disabling amnesia. His memory did show mild improvement with time. In contrast, H.M., who probably has damage both to the hippocampus and amygdala bilaterally, had worse amnesia than R.B. (Zola-Morgan *et al.*, 1986) and has not improved with time. With regard to the diencephalon, the evidence to date is that damage to the diencephalic-related hippocampal structures alone (fornix: Woolsey and Nelson, 1975; Moss *et al.*, 1981; Zola-Morgan and Squire, 1985; Bachevalier *et al.*, 1985a; mamillary bodies: Victor *et al.*, 1971; and anterior nuclei: Mark *et al.*, 1970) does not necessarily cause a disabling amnesia. However, as pointed out earlier, the studies in man lack good neuropsychological measures of the amnesia and thus further studies in this area will be of great importance to clarify what at this time seem to be contradictory data.

The pattern of amnesia in our patients shows, as has that in others, that damage to the diencephalon may cause a marked anterograde verbal and visual amnesia. This is one of the first demonstrations of preserved motor learning in amnesic patients with thalamic infarctions (Nichelli *et al.*, 1988).

Case 1 had a temporal gradient (worse in the 1980s, better in the 1950s) on the Squire test of Recognition of Famous Events. This pattern differs from that described by Sanders and Warrington (1971) in a group of amnestics of mixed aetiology but is similar to several studies on patients with Korsakoff's syndrome (Squire *et al.*, 1975; Albert *et al.*, 1979). Winocur *et al.* (1984) studied retrograde memory in a patient with bilateral thalamic infarction and did not find the temporal gradient as seen in our Case 1. Thus because this pattern is seen in only 1 patient in our study and on only 1 test, and because of the contradictory available data, we do not believe any strong conclusion can yet be drawn from this finding.

There is some evidence from our observations in Case 1 and in the literature that the diencephalon may play a role in temporal orientation and the temporal sequencing of events. The first patient's memory was greatly improved when the examiner told her where in time she was; for example, as mentioned above, during an interview in 1982 she claimed Lyndon Johnson was President and when the examiner said it was later than that, she correctly named Ronald Reagan as President.

In 1956, Spiegel *et al.* reported that patients undergoing dorsomedial thalamotomy

often suffered from 'chronotaxis', i.e., disorientation for time. This occurred in 19 of 30 cases, 4 additional patients were disorientated for time and place, and 7 were not disorientated. In most instances the disorientation was short-lived. The transient nature of most of these cases makes it likely that other structures are also important in temporal orientation. In fact, we have observed that damage in the basal forebrain may result in disorientation-sensitive amnesia. For example, one of our patients (Damasio *et al.*, 1985), after sustaining damage in the basal forebrain from a ruptured anterior communicating aneurysm, during an interview several weeks after this haemorrhage denied being married. When orientated to this he correctly recalled a flood of information including his wife and children's names and their ages.

Experiments in Korsakoff's syndrome also support the notion that the diencephalon may be important in using time as a clue to remembering. Huppert and Piercy (1976) showed that patients with Korsakoff's syndrome are 'markedly impaired when required to make explicit judgements of temporal context'. These patients had greater difficulty identifying if they had seen pictures 10 min or 1 day before, than if they had seen the pictures at all. In another experiment, Squire (1982) came to a similar conclusion regarding Korsakoff's patients which he wrote 'were disproportionately impaired in the ability to make judgements about the temporal order of recent events'. He felt the deficit might be specific to the Korsakoff's patients because the same problem was not detected in a diencephalic amnesic (Case N.A.) and ECT patients who may have temporal lobe dysfunction after ECT. An alternative possibility is that Case N.A., who has an asymmetric diencephalic lesion may be better able to sequence events than Korsakoff's patients, who usually have bilateral lesions. Thus this finding of impaired judgement of temporal order may apply to diencephalic amnesics with bilateral lesions including Korsakoff's syndrome. This remains to be confirmed in future studies. Squire argued that this deficit was possibly related to frontal damage in Korsakoff's patients. All our patients had lesions which could compromise dorsomedial nucleus connections with the frontal lobe, which is in keeping with Squire's notion. Parkin and Leng (1988) also argued that Korsakoff's patients are particularly poor at making temporal discriminations. This was based on the performance of a group of Korsakoff's patients' performances on a learning task requiring recency judgements.

In conclusion, we have found that patients with bilateral medial thalamic infarcts in the interpeduncular profundus territory develop chronic amnesia when the lesions are anteriorly situated. This is in keeping with several other studies. These lesions can be small and strategically located to interfere both with the hippocampal-related neural systems such as the mamillothalamic tract and amygdala-related neural systems such as the ventroamygdalofugal pathway. A specific component of the latter that connects the amygdala to the dorsomedial thalamic nucleus is situated lateral but immediately adjacent to the mamillothalamic tract in the monkey. On review of the animal and human data of anatomically well described lesions affecting the diencephalon and its connections, together with the data from this study, we believe that, as in the temporal lobe, damage to diencephalic nuclei and/or their connections related both to the amygdala and hippocampus is more likely to cause a dense amnesia. We raise the possibility that the

diencephalon may be particularly important in temporal aspects of memory. Other characteristics of the amnesia are deficits in anterograde verbal and visual learning, retrograde amnesia, and preserved motor learning.

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