

Diencephalic temporal order amnesia

J E Shuren, D H Jacobs, K M Heilman

Abstract

Objective—Amnesia for temporal relations may occur without amnesia for content memories. The aim was to determine whether a patient with mild memory loss due to a thalamic lesion had amnesia for temporal relations, and whether the amnesia was specific for particular material.

Methods—A male patient had an isolated right dorsomedial thalamic infarct and resolving amnesia. He was tested on tasks relating to content (what) and temporal (when) memories for both verbal and non-verbal material, three and seven months after his infarct.

Results—Three months after his infarct, the man had amnesia for temporal, but not content memories using non-verbal stimuli, and normal performance using verbal stimuli. Seven months after his infarct, he had a normal performance using verbal and non-verbal stimuli.

Conclusions—Patients with thalamic lesions may have a material specific amnesia for temporal relations in the absence of amnesia for content.

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Keywords: amnesia; thalamus; stroke; dementia

The dorsomedial nucleus of the thalamus has been implicated as a structure important for subserving memory.^{1–3} Prominent amnesia may result from a single thalamic lesion if the lesion is located anteriorly thereby interrupting the mammillothalamic tract (connections with hippocampal related structures) and the ventral part of the internal medullary lamina that contains fibres from the anterior and inferior thalamic peduncles, due to disconnection of the dorsomedial nucleus from the neocortex.^{4,5} Unilateral thalamic damage may result in material specific amnesias, wherein right sided lesions produce a non-verbal amnesia, and left sided lesions produce a verbal amnesia or a global verbal and non-verbal amnesia.^{6,7}

Graff-Radford *et al*⁸ have proposed that the thalamus may be especially important in processing the contextual aspects of memory, including memory for temporal order, due to the extensive connections between the thalamus and the frontal cortex. Previous studies have suggested that damage to the frontal lobes results in deficits in the memory of temporal order (memory of when one stimulus or event

occurred in temporal relation to another—for example, which of two items was seen most recently). Material specific temporal order amnesias have also been reported with unilateral frontal lobe lesions.^{9,10} The dorsomedial nucleus has extensive connections with the frontal lobes. In particular, the lateral parvocellular region of the dorsomedial nucleus has connections with the dorsolateral frontal cortex¹¹ making the dorsomedial nucleus a possible participant in the neuronal system that mediates temporal order memory processing.

We report a man with a mild, transient amnesia from a single right thalamic infarct, affecting predominantly the lateral parvocellular region of the dorsomedial nucleus. We wanted to determine whether this patient would be impaired on tasks measuring the temporal ordering of information and whether the material specificity of the amnesia for temporal ordering of information would be present in this patient with a thalamic lesion.

Methods

CASE HISTORY

A 25 year old right handed man was admitted to hospital after an episode of lightheadedness, nausea, fatigue, and headache that had developed near the pits at a motor race. He was on no medication and had had 12 years of education. On admission to the hospital he was disoriented and had slurred speech. During the succeeding days he returned to a normal level of arousal without evidence of visual loss, focal weakness, or sensory loss. A limited neuropsychological evaluation performed during the first week after the event was remarkable for impaired copying of the Rey-Osterreith complex figure¹² (score 28.5, < 10th percentile) as well as poor immediate recall (score of 13; < 10th percentile) and delayed recall (13.5; < 10th percentile) of the figure that could not be explained by his impaired copying ability alone (normative data from Lezak¹³). By contrast with deficits in non-verbal memory, verbal memory as assessed by the California verbal learning test¹⁴ was normal. Finger tapping was normal bilaterally.¹⁵ Brain CT taken five days after admission showed a hypodense area in the right thalamus consistent with an infarct. Laboratory studies including serum electrolytes, complete blood count, clotting factors, sedimentation rate, antinuclear antibodies, fluorescent treponemal antibody, antiphospholipid antibodies, lupus anticoagulant, protein C, and lipid profile were normal. Chest radiography, ECG, Holter monitor, and

Department of
Neurology, University
of Cincinnati, Ohio,
USA

J E Shuren

Tufts University
School of Medicine,
Boston,
Massachusetts, USA
D H Jacobs

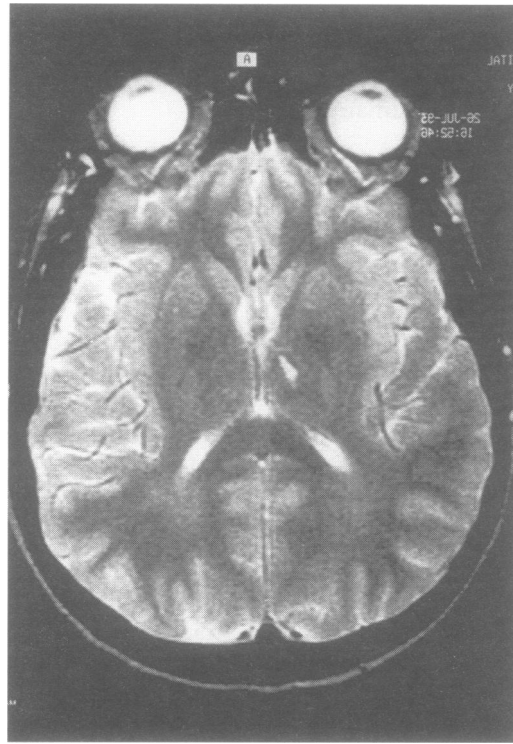
Center for
Neuropsychological
Studies, the
Department of
Neurology, University
of Florida and
Veterans
Administration
Medical Center,
Gainesville, Florida,
USA

J E Shuren
D H Jacobs
K M Heilman

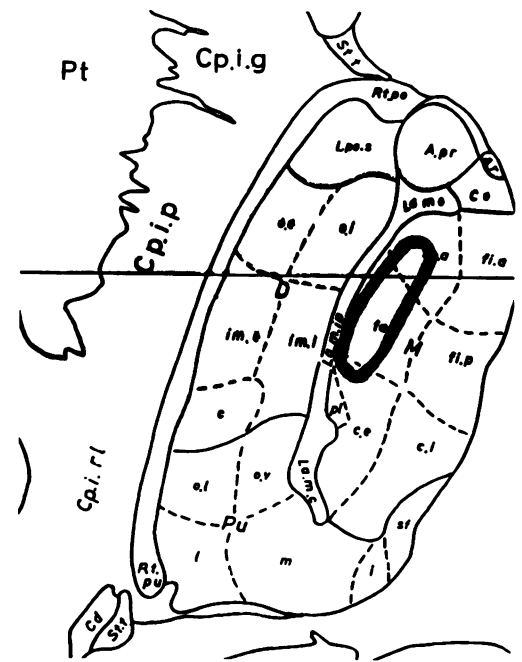
Correspondence to:
Dr D H Jacobs, Department
of Neurology, New England
Medical Center Box 314,
750 Washington St, Boston,
MA, USA.

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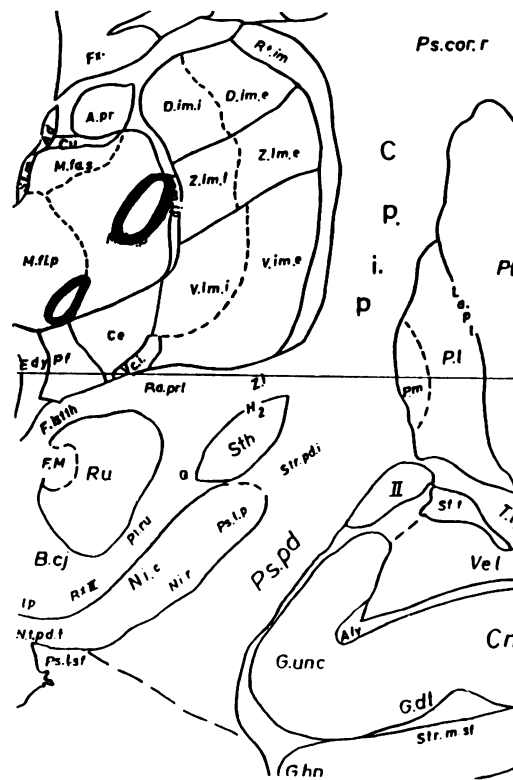
(A) T2 weighted MRI image in the axial plane of the patient's right thalamic infarct; (B) mapping of the infarct in the axial (Hd +8.0), and (C) in the coronal planes (left Fp + 5.0, right Fp + 10.0) using the atlas of Schaltenbrand and Bailey.¹⁶ A.pr = anteroventral nucleus; Ce.mc, Ce.pc = centromedian nucleus (one of the intralaminar nuclei); D.c = lateral posterior nucleus; D.im.e, D.im.i = ventrolateral nucleus; D.o.e, D.o.i = ventral anterior nucleus; La.m.c, La.m.ip = internal medullary lamina; L.po.s = ventral anterior nucleus; M.fa.a, M.fa.p, M.c.e = lateral parvocellular region of the dorsomedial nucleus; M.fi.a, M.fi.p, M.c.i = medial magnocellular region of the dorsomedial nucleus; Pu.l, Pu.m, Pu.o.l, Pu.o.m = lateral posterior nucleus and dorsal parts of the pulvinar nucleus; Rt.c, Rt.po, Rt.pu = reticular nucleus; V.c.e, V.c.i = ventral posterolateral nucleus; V.im.e, V.im.i = ventrolateral nucleus; Z.c.e, Z.c.i = ventral posterolateral nucleus; Z.im.e, Z.im.i = parts of the ventrolateral and ventral posterolateral nuclei.



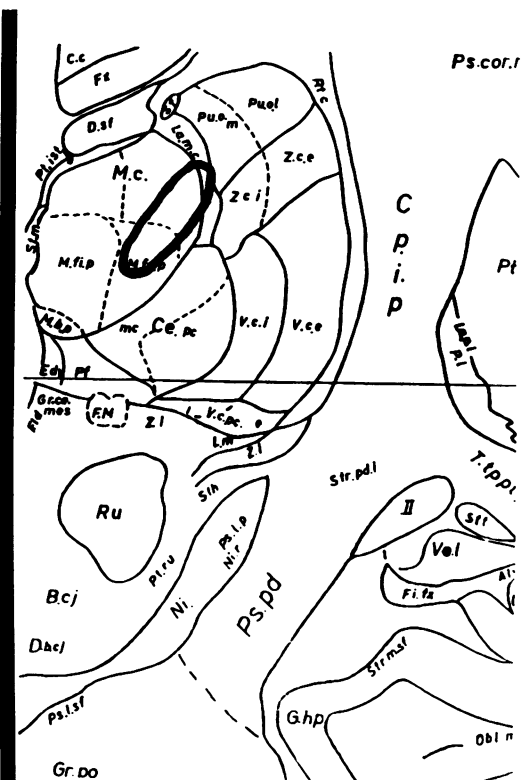
A



B



C



two dimensional transthoracic and transoesophageal echocardiograms were also normal.

When we first examined the patient, three months after his stroke, he was alert and fully oriented and attentive and had a digit span of eight digits forwards and six digits backwards. He recalled three of three words after a five minute delay. Spontaneous speech, comprehension, repetition, and naming were normal.

He could copy simple figures. There was no evidence of right-left disorientation, finger agnosia, apraxia, or hemispatial neglect. He could perform simple calculations accurately. The remainder of his neurological examination was normal.

MRI ANALYSIS

Brain MRI was performed on a 1.5-Tesla scanner about three months after his stroke.

Neuropsychology test scores at three months after stroke

Test	Raw score	Test	Raw score
Wechsler adult intelligence scale-revised:			
Digit span	9 (scaled score)	Wechsler memory scale revised:	
Object assembly	12 (scaled score)	Visual reproductions	
Block design	9 (scaled score)	Immediate	37
Digit symbol	7 (scaled score)	Delay	37
Digit span:		Logical memory	
Forward	8	Immediate	29
Backward	6	Delay	27
Visual span		California verbal learning test:	
Forward	9	Total (1-5)	59
Backward	8	Trial 5	14
Complex figure test		Trial 1	8
Copy	33 (60th percentile)	Delay 1	13
Immediate	30 (98th percentile)	Delay 2	13
Delayed	31 (100th percentile)	Semantic	
Continuous visual memory test:		Short	13
d-Prime	2-12	Long	13
Total score	82	Levels of processing test:	
Trailmaking test:		Verbal	35
Part A	35 s	Nonverbal	29
Part B	68 s	Design fluency:	
Facial recognition test	49	Free	24
Judgment of line orientation	22	Fixed	22
"A" Cancellation	50	Wisconsin card sorting test:	
Line cancellation	60	Categories	7
Multilingual aphasia examination:		Correct	19
Repetition	12	Errors	
Naming	52	Non-perseverative	11
Stroop:		Perseverative	19
Read words	49 s	Florida affect battery - tasks:	
Name colours	62 s	Facial identity	
Interference	128 s	discrimination	95%
		Facial affect	
		discrimination	85%
		Non-emotional prosody	
		discrimination	60%
		Emotional prosody	
		discrimination	100%
		Imagery tasks:	
		Facial emotional imagery	84%
		Object imagery task	85%

All test scores are normal for age and education. All tests are referenced within the text.¹

Axial, coronal, and sagittal 4 mm sections through the lesion were obtained (figure). The lesion was mapped on to plates from the atlas of Schaltenbrand and Bailey.¹⁶ The mapping was highly consistent among planes.

The lesion was mapped to a discrete area within the right dorsomedial nucleus affecting the lateral parvocellular region and a small area of the medial magnocellular region. The lateral border of the lesion extended into the internal medullary lamina in the coronal and sagittal planes and barely abutted on the internal medullary lamina in the axial plane. The mammillary bodies, mammillothalamic tract, intralaminar nuclei, and anterior thalamic nuclei were spared.

NEUROPSYCHOLOGICAL ASSESSMENT THREE MONTHS AFTER INJURY

More extensive neuropsychological testing was performed three months after his stroke. The table gives all the scores. The tests showed resolution of previously seen abnormalities on visuo-perceptual and visuo-spatial tasks as evidenced by normal performances on the facial recognition test,¹⁷ judgment of line orientation,¹⁸ letter cancellation test,¹⁹ line cancellation test,²⁰ copy of the Rey-Osterreith complex figure, and the object assembly and block design subtests from the Wechsler adult intelligence scale revised.²¹ Executive function as assessed by the Wisconsin card sorting test,²² Stroop test,²³ and design fluency²⁴ was also normal. His performance on the trail making test²⁵ was normal. There was no evidence of

aphasia and he performed in the low normal range on the naming and repetition subtests of the multilingual aphasia examination.²⁶

MEMORY TESTS (TABLE)

Verbal memory, evaluated using the California verbal learning test and logical stories from the Wechsler memory scale revised,²⁷ was normal. A task using the levels of processing paradigm of Craik and Tulving²⁸ was administered to the patient utilising semantic, orthographic, and phonemic cues to aid encoding of 36 words. Recall was subsequently assessed with a recognition task. His performance was normal.

Non-verbal memory, evaluated using the immediate and delayed recall of the Rey-Osterreith complex figure, visual reproductions from the Wechsler memory scale revised, and the continuous visual memory test,²⁹ was normal. The patient was given a levels of processing paradigm in which he viewed 30 faces one at a time making a judgment on either the occupation (for example, "Would this person make a good teacher?"), affective expression (for example, "Is this a happy person?"), or gender (for example, "Is this person female?") of each face. Recognition on this task was normal.

TEMPORAL ORDER MEMORY TESTS

Experimental methods

Temporal order memory was evaluated using temporal order and recency judgment tasks from Bowers *et al.*³⁰ These experimental tasks were originally designed for Bowers *et al.*'s 1988 study. The television test³¹ was also given to assess remote memory. All tests were administered to five male normal controls matched for age²⁴⁻²⁷ and education (11-12 years) after informed consent had been obtained. The temporal order and recency judgment tasks had previously been administered to 33 people (mean age = 39.2 years; mean educational level = 15.7 years) by Bowers *et al.*³⁰ Scores for the controls are presented as mean values.

TEMPORAL ORDER JUDGMENT TASK

The patient and controls viewed each of eight different stimuli (list 1) for two seconds. Thirty minutes later they viewed another eight stimuli (list 2). Two minutes after the presentation of list 2, a 32 item list composed of the 16 stimuli from list 1 or 2 randomly intermixed with 16 distractors was presented and the patient was asked to determine whether or not he had been presented with the stimulus before (recognition) and, if he had, whether or not the stimulus had been on list 1 or list 2 (temporal order). Both verbal and non-verbal forms of the test were given. Thirty two simple declarative sentences (for example, "The cooks burned the bread") were used in the verbal task and 32 unfamiliar male faces from a medical school yearbook were used for the non-verbal task. Recognition accuracy and accuracy of temporal order judgments were calculated. Temporal order judgments were assessed only on items on which an accurate recognition was previously made.

REGENCY JUDGMENT TASK

Each word from a list of concrete words was printed on a card and presented one at a time to the patient and controls, who were asked to read each word aloud. Immediately afterwards they were shown a card with two words (both nouns) printed on it of which one word came from the list and one did not (test of recognition) or both words were from the list (test of recency). The patient and controls were asked which word had been read more recently. A word was not used more than once during the test.

In the recency judgment trials the two stimuli were always separated on the list by five words but the number of words from the second stimulus to the end of the list varied. The first stimulus was always presented as the first, second, third, or fourth item on the list. In condition I the second stimulus word was the last item on the list. In conditions II–IV the number of intervening words from the second stimulus to the end of the list were four, eight, and 16 respectively. Total list length therefore varied from eight to 26 items. Conditions I–IV were also repeated for recognition judgment trials. Six lists were used for each recency condition and four lists for each recognition condition (40 lists total).

A non-verbal analogue of the verbal recency judgment task was also designed using unfamiliar faces from a medical school yearbook. Lists contained only all male or all female faces. Each face was shown for three seconds. However, this task differed from the original task of Bowers *et al.*³⁰ in that we used unfamiliar faces whereas Bowers *et al.* used pictures of objects. We chose not to use object pictures because real objects can be verbally encoded. In all other respects the tasks were identical.

TELEVISION TEST

The patient and controls were given the 1991 version of the television test of Squire and Slater³¹ to assess remote memory. They were given a 72 question four item multiple choice test in which they were to choose which of the four items had been a show on television. The correct response was always a show that had been on television for only one year. There were 15 shows from 1988 to 1990 (I), 14 from 1985 to 1987 (II), 13 from 1982 to 1984 (III), 14 from 1979 to 1981 (IV), and 15 from 1976 to 1978 (V). The percentage correct for each time period was calculated. Our normative data were combined with those of eight subjects (mean age 23.5, mean education 14.1 years) tested in Dr Squire's laboratory.

Results

TEMPORAL ORDER JUDGMENT TASK

On the verbal task the patient had a recognition accuracy of 91% (mean (SD) for controls (MC) 90 (1.6)%; mean for controls of Bowers *et al.*³⁰ (MCB) 85 (12.9)%), and an accuracy of temporal order judgments of 93.7% (MC 78 (5.8)%; MCB 78 (10.7)%). On the non-verbal task the patient had a recognition accuracy of 78.1% (MC 69 (4.7)%; MCB 75.3 (9.1)%)

but his accuracy of temporal order judgments was below chance (26.6%; MC 59.5 (2.0)%, MCB 63 (11.2)%). The patient's performance was consistent with a deficit in making non-verbal temporal order judgments. Although his accuracy in making such judgments was below chance, there was no systematic bias in the errors he made (for example, consistently choosing the second list *v* consistently choosing the first list as the source of the stimulus).

REGENCY JUDGMENT TASK

Both the patient and controls recognised all target words in all conditions (100%). On recency judgments both the patient and controls showed a progressive decline in performance (patient condition I 100%, condition II 83.3%, condition III 83.3%, condition IV 66.7%; mean for controls condition I 92%, condition II 88%, condition III 72%, condition IV 60%; controls of Bowers *et al.*³⁰ condition I 96%, condition II 74%, condition III 63%, condition IV 62%).

The non-verbal (face) recognition accuracy for the patient was 100% in conditions I–II and 83.3% in conditions III–IV. For the controls, face recognition accuracy was 100% in condition I, 92% in condition II, and 80% in condition III–condition IV. However, the patient's accuracy of recency judgments differed from that of the controls by more than 2SD. The mean (SD) accuracy for controls was condition I 100%, condition II 88 (SD 8.1)%, condition III 72 (SD 8.5)%, and condition IV 65 (SD 1.7)%. The patient's accuracy was condition I 100%, condition II 66.7%, condition III 33.3%, and condition IV 50%. His performance was consistent with an impaired ability to make nonverbal recency judgments.

TELEVISION TEST

The patient's scores were 53.3% (I), 35.7% (II), 30.8% (III), 50% (IV), and 40% (V) compared with the controls' mean (SD) scores of 48 (10.7)% (I), 59.3 (13.5)% (II), 53.1 (15.1)% (III), 47.5 (10.4)% (IV), and 41.3 (10.7)% (V). The patient's scores were within 2 SD of the scores of the controls. Therefore, the patient's remote memory was in the low range of normal to mildly impaired.

In summary, the patient showed a non-verbal anterograde temporal order amnesia with relatively preserved remote memory three months after his stroke.

TESTING AT SEVEN MONTHS AFTER STROKE

The temporal order judgment task was readministered to the patient seven months after his stroke. On the verbal task his recognition accuracy was 91% and his temporal order judgment accuracy was 100%. On the non-verbal task his recognition accuracy was 81% and his temporal order judgment accuracy was 81% which are superior to the performance of both our controls and those of Bowers *et al.*³⁰

Discussion

Our patient initially developed a selective

amnesia for non-verbal content due to a right thalamic infarct. Three months later the amnesia for content had resolved.

However, a material specific amnesia for temporal ordering of non-verbal material was evident. Both short term (impaired recency judgment) and long term (impaired temporal order judgment) anterograde temporal order memory were impaired without abnormal performance on the recognition (content) portion of those two tasks. This performance suggests a reproducible anterograde material specific amnesia for temporal ordering of non-verbal stimuli. The patient performed normally on a third task, the television test, that differs from the two other tasks as it measures whether a retrograde component existed for the amnesia in this patient. The results suggest that such a component did not exist. In agreement with Milner *et al.*,³² we have found that temporal order amnesia can be material specific, with the new additional finding that the material specificity of the amnesia for temporal ordering exists in patients with thalamic lesions.

The role of the thalamus in processing contextual aspects of memory has also been considered by Shinamura and Squire, who found that a group of patients with Korsakoff's syndrome performed poorly on a source memory task in which patients were asked to identify the source of a memory.³³ Moreover, their performances did not correlate with their ability to recall facts, suggesting that contextual memories and fact memories measure slightly different abilities. Kopelman³⁴ showed that patients with Korsakoff's syndrome as well as patients with Alzheimer's disease did poorly on a task of providing temporal context about a memory as well as being amnesic for the content of the memory. Hunkin *et al.*³⁵ reported that amnesics with diencephalic lesions did worse than those with temporal lobe lesions on a temporal discrimination task.

Content (what) memories and temporal (when) memories may be processed differently.^{9, 36, 37} Milner *et al.*³² found that patients with unilateral left temporal excisions had impaired verbal recognition memory but preserved verbal recency judgments, whereas patients with left frontal excisions had impaired verbal recency judgments but preserved verbal recognition memory. Patients with right temporal or frontal excisions showed the same patterns of deficits as their left sided counterparts except that the processing deficits were only for non-verbal rather than verbal material. Poor recency judgment followed removal of the mid-lateral frontal cortex. One amnesic patient, who had bilateral temporal excisions, had relative sparing of temporal order memory in the presence of profound deficits for recognition (content) memory.³⁶

The double dissociations described above make much less likely the possibility that patients perform worse on a temporal ordering task because it is more difficult; it would then be impossible to explain the performance of those patients with temporal excisions who did worse on the recognition memory tasks than on the recency judgment tasks. Moreover, our

patient showed normal to superior performance on other comparably difficult tasks that involved either memory (for example, verbal recency judgment tasks and temporal order judgment tasks, immediate and delayed recall of the Rey-Osterreich complex figure) or non-memory processing (for example, the Wisconsin card sorting test). Therefore his performance cannot be attributed to a generalised memory or cognitive abnormality.

Whereas the thalamus seems to be important for processing the temporal aspects of memory, Bowers *et al.*³⁰ showed temporal order amnesia in a patient with a lesion in the retrosplenial cortex, an area that has extensive connections to the thalamus. Sagar *et al.* reported that patients with Parkinson's disease had abnormalities on tasks of temporal ordering.³⁸ Therefore, a variety of extralimbic structures in addition to the frontal lobes may be important for processing the context of memories, including the temporal ordering of information.

The thalamus may be important for both the content and the context of memory. Kritchevsky *et al.* noted that patients with medial thalamic damage affecting only the dorsomedial nucleus may have mild and transient amnesias.³⁹ Similarly, Von Cramon *et al.*⁴ suggested that thalamic lesions of the anterior nucleus of the thalamus are more likely than those of the dorsomedial nucleus to produce severe target amnesias (amnesia for content of memories). Whereas others have noted that large dorsomedial lesions, particularly those that also impinge on the mammillothalamic tract, may also produce a lasting amnesia,⁸ our patient and others with circumscribed lesions within the dorsomedial nucleus of the thalamus have recovered relatively well from their amnesias. Therefore, our patient's performance on memory tasks is like that of other reported patients.

Mennemeier *et al.*⁴⁰ proposed that an attentional-amnesic disturbance may be associated with a thalamic intralaminar nucleus lesion. Our patient did not, at three months after injury, show evidence of either impaired content memory or abnormal attention on digit span or the trailmaking test (table). Therefore, the available evidence does not support the alternative explanation that our patient had an attentional disturbance.

Arguably, our results could have been an artifact of our test design.

Temporal order and recency judgments may require recall whereas the recognition paradigm does not. However, on both the recall paradigms of the Rey-Osterreich complex figure and the Wechsler memory scale revised, our patient scored in the high normal range. Secondly, his performance on the verbal temporal order and recency judgment paradigms was normal. Therefore, other tasks that were given do not strongly support this interpretation, as he performed normally on other recall tasks.

MECHANISM OF TEMPORAL ORDER AMNESIA

The mechanism of temporal ordering is unknown. Several suggestions have been made

regarding the possible mechanism. Recalling when an event took place may occur through an indirect means whereby a mechanism either discriminates or compares two events and determines which event occurred before or after the other⁴¹⁻⁴³ or reconstructs the order of events using general knowledge (deductive reasoning) about other events that may have occurred at that time (for example, "I must have taken the test in December because it was given a few days before Christmas").⁴⁴ Alternatively, a direct means may be used whereby specific temporal information is recalled (for example, "The gun was fired on Monday at 10 o'clock in the morning").^{45,46} Based on our data, it is not possible to determine which mechanism might be impaired in our patient.

Sagar *et al*³⁶ propose that temporal order memory processing by indirect means is subserved by the frontal lobes whereas temporal order memory processing by direct means is subserved by limbic-diencephalic structures. Both the frontal lobes and the limbic system have connections with the dorsomedial thalamic nucleus. The dorsomedial nucleus can be divided into medial and lateral regions. The lateral, parvocellular region of the dorsomedial nucleus, the portion that was damaged the most in our patient, has connections with the lateral prefrontal cortex, whereas the medial magnocellular region has connections with medial prefrontal and orbitofrontal cortices, amygdala (ventroamygdalofugal pathway), entorhinal, perirhinal, and temporal polar cortices.⁴⁷ Damage to the lateral region of the dorsomedial nucleus may result in the loss of temporal order memories in isolation, perhaps due to disrupted dorsolateral prefrontal connections.

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