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TEMPORAL GRADIENT IN THE REMOTE MEMORY IMPAIRMENT OF AMNESIC PATIENTS WITH LESIONS IN THE BASAL FOREBRAIN*

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Abstract—Recall and recognition of premorbid public events were studied in four groups of subjects. Dementia patients showed equal losses from all time periods compared to normal controls. In contrast, two groups of amnesic patients showed extensive remote memory losses, which were most marked for the last few years prior to onset. The difference between recall and recognition was similar in the groups. The results indicate that the retrograde amnesia associated with aneurysms of the anterior communicating artery cannot be distinguished from that of amnesia with other etiologies. Implications of the finding of a temporal gradient in the retrograde amnesia of non-alcoholic amnesics are discussed.

INTRODUCTION

RETROGRADE amnesia, the phenomenon of loss of memory for events that occurred before trauma, has greatly influenced views of both normal memory function and of what constitutes the central deficit in amnesia [16, 65, 66, 74]. Three basic patterns of remote memory loss have been identified in humans [1].

Retrograde amnesia may be relatively short, affecting only a few years before trauma. This has been quite consistently shown as a reversible deficit after bilateral electro-convulsive therapy [22, 63, 64, 69], and a similar irreversible mild deficit has been described in the amnesic cases H.M. [23, 43], N.A. [22, 68], and R.B. [80]. SQUIRE and co-workers [64, 69] inferred from these results that resistance of memory to disruptions grows stronger over several years. In further development of this notion, medial temporal regions are seen as specifically involved in prolonged memory consolidation processes, and the pattern of short retrograde amnesia may be characteristic of and possibly limited to patients with medial temporal amnesia [65, 66].

Extensive retrograde amnesias affecting even the most remote time periods covered by the remote memory tests have been shown to exist in two varieties. "Flat" curves with equal losses from all time periods have been found in each of three types of progressive dementing illness: Huntington's disease [3, 4], presenile and senile dementia of Alzheimer type [25, 47, 78], and Parkinson's disease patients with dementia [28, 34]. Similar results have been

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obtained in studies of chronic progressive multiple sclerosis [11] and a heterogeneous brain injured group [39], and to our knowledge only two exceptions to this pattern in dementia exist [36, 58]. In contrast, amnesic patients with alcoholic Korsakoff's syndrome have in seven independent studies demonstrated a clear time gradient with later events more poorly recalled than more remote events [4, 5, 22, 36, 43, 45, 64]. One study failed to demonstrate a time gradient [61]. In the other studies the time gradient was a robust phenomenon that appeared to be independent of test measure employed, item difficulty [5], and presence or type of cueing [4]. However, this extensive time-graded remote memory loss has not found any ready explanation. Most observers seem to agree that no single factor could cause this pattern, and the most commonly advanced two-factor model assumes that the Korsakoff patients' time gradient may be related to their history of alcohol abuse. According to this view, a slowly progressive anterograde amnesia during the years before the Wernicke encephalopathy and the onset of manifest amnesia may lead to gradually fewer events being registered and retained [1, 12, 16, 22, 27, 45, 64, 66]. This assumed consequence of the "continuity hypothesis" received some limited support by the finding of a mild time graded deficit in chronic alcoholics compared to non-alcoholic controls [2, 22]. Alternative explanations of time graded retrograde amnesia in Korsakoff patients have involved their premorbid life style and preoccupation with alcohol, leading to less attention to current events [2], and state dependent learning [35]. Recently serious reservations about the adequacy of the continuity hypothesis as an explanation of temporal gradients have been expressed by CERMAK and BUTTERS [15, 18, 20], apparently mainly prompted by their observations of patient P.Z. This alcoholic Korsakoff patient had a severe temporally graded retrograde amnesia for material mentioned in his autobiography published shortly before he became amnesic. Obviously, P.Z.'s retrograde amnesia could not be secondary to deficient original learning.

We believe that further evidence may necessitate a revision of theories of temporal gradients in retrograde amnesia. It has been noted previously [16] that one implication of the two-factor model relating the Korsakoff patients' time gradient in retrograde amnesia to previous anterograde amnesia, is that some patient populations other than Korsakoff's should demonstrate ungraded remote memory loss. As discussed above, this was the case for certain progressive dementing illnesses. However, a further implication is that non-alcoholic amnesic syndromes of sudden onset should demonstrate patterns of remote memory loss different from that of the long graded retrograde amnesia of the Korsakoff's syndrome. Extensive, graded remote memory loss has been noted in single case studies of non-alcoholic amnesia patients [60]. Other patterns have been described as well, however, and no identifiable predominant pattern has emerged from compilations of single clinical cases [42, 55]. Until recently, the only group of non-alcoholic amnesics tested on a quantitative test of remote memory was three postencephalitic cases [17]. These cases demonstrated an equally extensive and more severe retrograde amnesia than did Korsakoff patients on the Famous Faces test. The authors interpreted the temporal gradient as being different from that of Korsakoff's, but the difference is not clear. For the easy items, the curves of postencephalitic and Korsakoff amnesics appear to be parallel with a temporal gradient, and for the difficult items a floor effect may have concealed a similar gradient (see [17], Fig. 8.2). Recently Squire *et al.* provided clear-cut evidence of temporally graded impairments in both remote recall and recognition in two non-Korsakoff amnesic groups. Five patients with amnesia following an anoxic or ischemic episode were impaired for the past approximately 15 years [67], and in six patients tested during an attack of transient global amnesia the

remote memory impairment covered up to 30 years [37]. Thus, group studies of non-alcoholic amnesia patients with sudden onset do seem to indicate a pattern of remote memory loss similar to, rather than different from, that of Korsakoff patients. Also here, however, an exception can be found [25].

The present study was designed to further elucidate the patterns of remote memory loss in amnesic syndromes of non-alcoholic origin, particularly amnesia following surgery of aneurysms of the anterior communicating artery (ACoA). A remote memory task was developed and administered to three patient groups and a control group of normal subjects. The three patient groups were: a homogeneous group of patients with amnesia after surgery of aneurysms of the ACoA; a heterogeneous group of amnesic patients of mixed etiologies, and a group of patients with progressive dementing illnesses.

Our main finding is a basic similarity in the pattern of retrograde amnesia in the two amnesic groups. Both show an extensive time graded remote memory loss similar to that previously demonstrated in Korsakoff's syndrome.

METHOD

Subjects

The normal control subjects were examined during a usually rather brief hospitalization. Among the subjects in each of the three patient groups, approximately half were examined during hospitalization, half at out-patient visits to hospital.

All subjects except seven demented patients were administered four WAIS subtests (Information, Similarities, Digit Span, and Vocabulary) and the DART reading test of vocabulary [49]. A prorated Verbal IQ was calculated based on Danish standardization data [33, 38, 48].

Patients with amnesic syndrome after surgery for aneurysms of the anterior communicating artery (ACoA)

In this group of 20 patients, 18 had been identified in a prospective study [30] and were tested 2 years after onset, between June 1980 and May 1984. Two patients added later were tested 3 weeks and 8 months after onset. Twelve were men, and eight were women. Inclusion in the group was determined upon criteria of amnesia at a neuropsychological assessment 3 months after onset [30], and at the time of remote memory examination, 2 years after onset, five cases had recovered to normal or near normal levels. These, and possibly a few more relatively mild cases, would probably not have been included in similar studies using severe and clinically obvious amnesia as selection criteria. The average age of the group was 50.1 years, and their mean prorated verbal IQ was 105.8. Vital data of the group are presented in Table 1.

Amnesic patients with mixed etiologies (Mix)

This group of 19 patients represents an etiologically inhomogeneous group. Vital data are presented in Table 2. They all presented with clinically significant amnesia, which was occupationally disabling in all but one case. Their mean age was 44.1 years, and their mean prorated verbal IQ was 109.7. Their higher than average intelligence level is consistent with educational backgrounds above average.

Dementia patients (Dem)

Nineteen patients with mild to severe global cognitive impairment (on neuropsychological testing) with onset within the last 5 years were selected. All received a full neurological evaluation including CT. They were judged to have progressive presenile dementia based on neurological and neuropsychological criteria, the majority with presumed Alzheimer or vascular origin. Their mean age was 54.6 years. Verbal IQ was available in only 12, who obtained a mean of 99.8. The seven patients without known verbal IQ presented the most severe dementia.

Normal controls (NC)

Twenty-seven subjects, mean age 55.5 years, were recruited from the departments of orthopaedic surgery and neurosurgery. The majority of these subjects had limb fractures or peripheral nerve injuries, and all were without evidence of CNS disease. All were occupationally active. Details of the selection criteria have been reported elsewhere [32]. Mean prorated verbal IQ was 116.1.

Table 1. Characteristics of the ACoA amnesic group

Case	Age	Education/occupation	Onset	Exam	DART score	Verbal IQ
1	52	Office/manager	June 79	June 80	40	115
2	40	Correspondent	Dec 80	Dec 82	42	128
3	38	Driver	May 82	June 84	24	100
4	43	None/housewife	Apr 78	May 84	19	98
5	61	None/cleaner	July 78	Nov 80	20	103
7	60	None/worker	Oct 78	Oct 80	18	100
8	63	None/worker	May 79	Apr 81	20	91
9	44	Carpenter	June 79	June 81	30	110
10	43	None/worker	Dec 80	Jan 83	18	92
11*	56	Teacher/housewife	Mar 81	Apr 83	49	134
14	53	None/housewife	Nov 78	Apr 81	—	72
15	50	Nurses' aide	Mar 79	Feb 81	19	97
16	45	None/worker	June 79	June 81	25	98
17	45	Baker	Aug 79	Aug 81	19	109
18	40	Mechanic	Apr 80	May 82	22	101
19	35	Teacher	Oct 80	Nov 82	32	118
20	59	Engineer	Oct 78	Nov 80	28	112
21	60	None/housewife	Apr 79	June 81	19	101
23	56	Engineer	Jan 84	Jan 84	34	119
25*	58	Physician	Nov 85	June 86	45	118

*Unoperated.

Table 2. Characteristics of the mixed etiology amnesic group

Case	Age	Education/occupation	Etiology	Onset	Exam	DART score	Verbal IQ
3	39	Unskilled	Tumor III v	Nov 79	Jan 81	27	97
4	49	Watchmaker	Tumor III v	Apr 79	Feb 81	21	89
7	49	Office/housewife	Tumor III v	Jan 81	Apr 81	31	89
9	22	Student	Pineal tumor	June 80	Oct 81	27	108
10	62	Office	Korsakoff	May 81	Feb 82	43	136
11	40	Bricklayer	Korsakoff	Nov 80	Feb 81	14	84
12	37	Physician	Tumor III v	Dec 81	Mar 82	34	124
14	56	Professor	TGA	May 82	May 82	46	139
16	68	Architect	Tumor hypophys	May 82	Oct 82	44	107
17	34	Shipmate	Korsakoff	Oct 82	Nov 82	28	110
18	33	Bankemployee	Meningitis	Dec 81	May 83	32	110
19	41	Bookkeeper	Unknown	Mar 83	June 83	25	110
22	41	Office	Korsakoff	Nov 76	May 84	39	128
23	33	Carpenter	Meningitis	Mar 84	June 84	9	93
24	54	Nurses' aide	SAH. ACP	Feb 84	July 84	22	101
28	43	Shopkeeper	SAH. Left IC	July 82	Oct 84	33	104
30	53	Lawyer	Anoxia	Sep 79	July 86	46	133
32	42	Salesman	Korsakoff	July 86	Sep 86	36	110
33	41	Shippingman	Encephalitis	Sep 85	Sep 86	30	112

Abbreviations: III v: Third ventricle.
TGA: Transitory global amnesia.
SAH: Subarachnoid haemorrhage.
ACP: Posterior communicating artery aneurysm.
IC: Internal carotid artery aneurysm.

Procedure

Remote Memory test. The questionnaire was constructed in 1980 and consists of questions about events occurring between 1935 and 1979. All events were considered to have occupied a prominent position in the news media at the time of their occurrence, and typically involved politics, sports events, disasters, and persons famous for a relatively short period. The questions were grouped in 11 time periods, each covering 5 years from 1935–1969, 3 years from 1970–1975, and 2 years from 1976–1979. Originally each time period was covered by 12–16 questions. This version was administered to ten normal subjects, and for each time period 10 questions were retained to give an average of about 70% correct answers in the normal subjects. The shortened version was administered to the subjects in this study, which took place from 1980 to 1986. Ten of the normal controls were tested in 1981, and 17 in 1983. Testing began with the time period, during which the subject was 20 years old, and all questions were given in approximate chronological order. Only subjects who had resided in Denmark during the whole period covered by the test were included in the study.

Free recall of each event was first tested. No cues were provided, and a recall trial was terminated by an answer (correct or false), when the patient indicated he did not know the answer, of when approx 15 secs had elapsed. If failed, three alternative choices were given for recognition, and the subjects were required to guess if necessary. Recognition foils were plausible, and selected to minimize recognition based on familiarity. Recall and recognition were scored separately for each time period.

Measures of anterograde amnesia. All subjects were administered various tests of learning and retention. Results of a verbal associate learning test (15 words pairs [6]) and a list learning test with selective reminding (10 words; 5 trials [14]) are reported to provide an independent index of the patient's memory ability.

Dementia rating and amnesia rating. All subjects except seven normal controls were also administered an extended quantitative mental status examination consisting of 18 subtests [70]. The scores of seven of these tests were added to yield a dementia rating with a maximum score of 72. Lower scores indicated greater impairment. Maximum scores in each subtest are indicated in parentheses in the following list: Random letter test (20), mental arithmetic (8), serial sevens (10), auditory digit span, auditory sentence span (10), verbal similarities (8), and proverb interpretations (8).

The scores of five other subtests were added to yield an amnesia rating: Orientation (14), recall at delays of 10 and 30 min of three words (6), and of three hidden objects and their location (12), story recall (12), and category-cued recall of 30 named pictures (30). The maximum score was 74.

RESULTS

Background variables and intelligence measures

Differences between groups were first examined in analysis of variance, and when significant differences were indicated, the six possible group comparisons were tested by *t*-tests. The data are shown in Table 3. The groups differed in age ($F(3, 81) = 6.48$, $P < 0.001$), the mixed amnesia group being younger than each of the other three groups ($P < 0.001$ in comparison to normal controls and dementia patients; $P < 0.05$ in comparison to ACoA amnesics). The other three groups did not differ significantly from each other in age.

The groups also differed in education score ($F(3, 81) = 3.17$, $P < 0.05$). The mixed amnesia group had a significantly higher score than the ACoA amnesics ($P < 0.01$). The other group differences were not significant. Group differences in verbal IQ ($F(3, 74) = 4.11$, $P < 0.01$) were due to significantly higher verbal IQ in the normal control subjects than in ACoA amnesics ($P < 0.05$) and in dementia patients ($P < 0.01$), the other differences being non-significant. The groups did not differ significantly in DART reading score ($F(3, 73) = 1.71$, $P = 0.18$).

Verbal learning ability

Figure 1 illustrates the group means in "long term retrieval" (LTR) and consistent retrieval ("list learning") over five trials of Buschke's selective reminding list learning task [14]. The groups differed in both measures over all trials ($F(3, 79)$ range: 12.3–19.1, $P < 0.0001$). In all trials the normal subjects performed better than each of the three patient groups ($P < 0.0001$), which did not differ significantly in any instance.

Group means of number correct in one trial of the associate learning task [6] were: NC

Table 3. Background variables and intelligence measures of the four groups

		ACoA	Mix	Dem	NC
N		20	19	19	27
Age	$\bar{X}$	50.1	43.6	54.6	55.5
	SD	8.8	11.2	8.0	10.0
	range	35–63	22–68	37–67	31–73
Education score	$\bar{X}$	10.5	13.2	11.5	11.9
	SD	3.2	2.8	2.7	2.5
	range	8–17	9–17	8–17	8–17
Verbal IQ	$\bar{X}$	105.8	109.7	99.8*	116.1
	SD	13.8	15.8	13.1	13.7
	range	72–134	84–139	81–122	89–149
DART reading score	$\bar{X}$	27.5	30.9	26.1†	32.7
	SD	10.1	10.3	10.3	9.3
	range	18–49	9–46	13–44	13–46
Sex	M/F	12/8	11/8	13/6	17/10

*N: 12.
†N: 13.

7.8, Mix 1.4, ACoA 1.8, and Dem (N:11) 2.6 ($F(3, 72)=20.1$, $P<0.0001$). Normal controls performed significantly better ($P<0.0001$) than each of the patient groups, which among themselves did not differ significantly.

Amnesia rating and dementia rating

Group means of the two ratings based on mental status examination subtests are presented in Table 4 with both raw total scores and standardized total scores based on the distribution of scores in the normal control group. Differences in raw scores were examined in analysis of variance followed by *t*-tests. The groups differed in the amnesia rating ($F(3, 74)=17.9$, $P<0.0001$), with highly significant differences between normal controls and each of the patient groups ($P<0.0001$). The mixed amnesia group was inferior to ACoA amnesics ($P<0.01$), and marginally so to dementia patients ($P=0.06$).

In dementia rating group differences were also highly significant ($F(3, 74)=16.7$, $P<0.0001$), but this was due only to the inferior performance of the dementia patients. Differences between normal controls and the two amnesia groups did not reach statistical significance ($P>0.05$). In both amnesia groups, however, the standard deviations are greater than among normal controls, indicating inclusion in these groups of some patients with impairment in cognition.

Remote memory: group comparisons of discrete time periods

Questions from before 1945 were administered to only a few subjects, and are not considered. During all subsequent periods analysis of variance disclosed significant group differences. The data are shown in Table 5 together with *P*-values from *t*-tests of group comparisons. The dementia patients remembered significantly less than the normal controls from all periods in both recall and recognition. The same was the case for the ACoA amnesics except for recall 1960–1964 and recognition 1955–1959 and 1970–1972. Mixed amnesics were not significantly different from normal controls before 1965 except in free recall 1955–1959—from 1965 on they were consistently below. The three patient groups did not differ

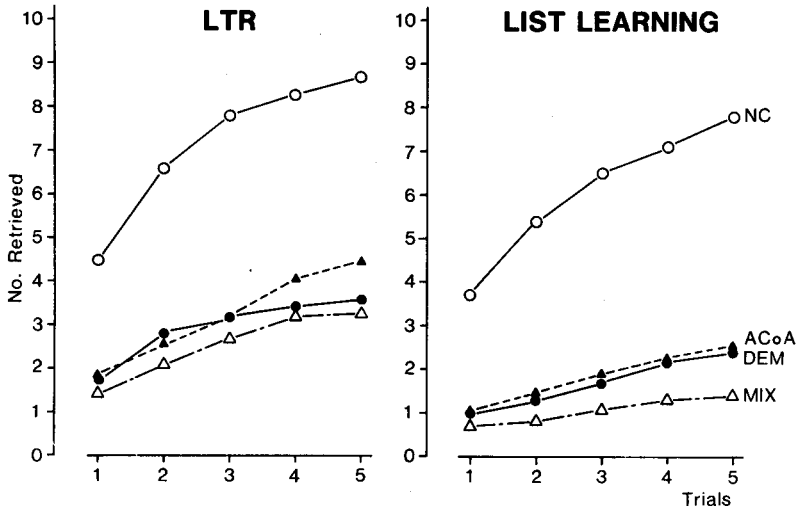

Fig. 1. Mean number of words retrieved from long term storage (LTR) and consistently retrieved (list learning) in the four groups in Buschke's [14] list learning with selective reminding. The list comprised 10 words. Dementia patients were tested over five trials, the other three groups over 10 trials or to criterion.

Table 4. Group means of amnesia rating and dementia rating

		ACoA	Mix	Dem	NC
N		20	19	19	20
Amnesia rating, raw scores	$\bar{X}$	39.1	29.7	36.6	54.8
	SD	12.7	10.2	14.1	5.4
Amnesia rating, T-scores	$\bar{X}$	20.9	3.5	16.3	50.0
	SD	23.6	18.8	26.1	10.0
Dementia rating, raw scores	$\bar{X}$	58.1	58.2	41.8	63.8
	SD	10.4	10.2	13.7	4.6
Dementia rating, T-scores	$\bar{X}$	37.7	38.0	2.7	50.0
	SD	22.4	22.1	29.6	10.0

significantly from each other in free recall in any time period. In recognition, ACoA amnesics scored at a significantly higher level than the dementia patients in 1955—59 ($P<0.05$), 1965–1969 ($P<0.05$) and 1970–1975 ($P<0.01$). All comparisons between mixed amnesics and dementia patients, and between the two amnesic groups, were non-significant.

In the ACoA group, five patients had onset of amnesia in 1978, and seven in 1979. In the mixed amnesia group four patients had onset before 1980. Their data from 1978–1979 can thus be expected to reflect both anterograde and retrograde amnesia, and the means of the remaining subjects have therefore been added to Table 5.

Temporal gradients

From both the data in Table 5 and from the results of a number of the individual amnesics we had the impression that their remote memory might be worse for the years closer to the

Table 5. Group means in recall and recognition from discrete time periods

Period		ACoA	Mix	Dem	NC	*P*-values. NC vs. ACoA	Mix	Dem
45–49	*N*	10	3	13	18			
	recall	5.8	6.3	5.0	7.8	0.03	NS	0.00
	recog.	7.7	9.0	7.7	9.3	0.01	NS	0.01
50–54	*N*	11	7	14	20			
	recall	4.9	5.3	3.8	6.8	0.03	NS	0.00
	recog.	7.3	7.7	7.3	8.9	0.01	NS	0.00
55–59	*N*	16	7	18	25			
	recall	4.6	4.3	3.2	6.7	0.01	0.03	0.00
	recog.	7.9	7.4	6.7	8.5	NS	NS	0.00
60–64	*N*	18	13	19	26			
	recall	5.8	5.2	4.5	6.9	NS	NS	0.00
	recog.	8.1	8.5	7.6	9.3	0.03	NS	0.00
65–69	*N*	20	16	19	27			
	recall	4.2	4.3	3.4	6.3	0.00	0.01	0.00
	recog.	7.9	7.4	6.8	9.0	0.02	0.00	0.00
70–72	*N*	20	18	19	27			
	recall	4.4	4.1	3.1	6.4	0.00	0.00	0.00
	recog.	8.1	7.4	6.5	8.9	NS	0.00	0.00
73–75	*N*	20	19	19	27			
	recall	4.5	4.4	3.7	6.2	0.01	0.01	0.00
	recog.	7.8	7.2	6.3	8.7	0.05	0.00	0.00
76–77	*N*	20	19	19	27			
	recall	3.4	2.2	2.1	5.9	0.00	0.00	0.00
	recog.	6.3	6.3	5.7	8.2	0.00	0.00	0.00
78–79	*N*	20	19	19	27			
	recall	3.6	2.7	3.8	6.6	0.00	0.00	0.00
	recog.	7.0	6.2	6.7	8.6	0.00	0.00	0.00
(78–79)*	*N*	8	15					
	recall	3.9	2.5					
	recog.	7.1	5.9					

*Patients with onset before 1980 excluded.

onset of amnesia than for the more remote periods. However, due to the variable number of subjects in the groups over time, the data in Table 5 could not be subjected to a direct statistical test of difference in curve slopes. We therefore combined the data in two ways for this analysis.

We first calculated each subject's means of the first and second halves of recalled events. Thus, for a subject tested on all questions from 1940 to 1979, the first half would comprise questions from 1940 to 1959, the second half questions from 1965 to 1979. For a subject tested from 1960 on, the first half covers 1960–1972, the second 1973–1979. (Thus, the number of questions rather than the time periods were grouped about the median.) Table 6 shows these data. A 4×2 analysis of variance showed a significant interaction of group and time ($F(3, 81) = 3.23$, $P < 0.05$). This was mainly due to differences between the mixed amnesia group and normal controls ($P < 0.01$), and between mixed amnesics and dementia patients ($P < 0.05$). The difference between the ACoA amnesia group and normal controls approached significance ($P = 0.053$).

Table 6. Group means of the data regrouped in individual first and second halves of recalled events (percentage correct) from age 20 to 1980

	ACoA	Mix	Dem	NC
1st half	51.9	47.2	41.2	69.8
2nd half	37.5	29.6	32.8	63.0
Difference	14.4	17.6	8.4	6.8

To further evaluate group differences in the changes in response between time periods data from 82 subjects were grouped for three time periods: 1960–1969, 1970–1975, and 1976–1979 (the three youngest patients in the mixed amnesia group had insufficient data). These data are illustrated in Fig. 2.

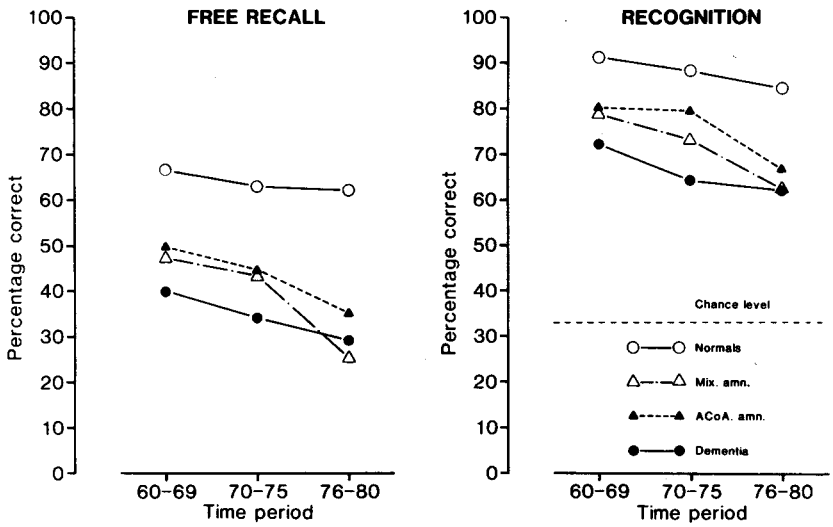

Fig. 2. Mean percentage of correct responses in the four groups of subjects over three collapsed time periods.

The important question is whether there is an interaction between the group and the memory period factors. Statistically, this can be tested by either univariate or multivariate analysis of variance. If there is no interaction the differences between memory periods should be the same in all groups, and a multivariate test can be made by analysing difference scores obtained by subtracting the mean score of each period from that of the previous period, e.g. (1960–1969) – (1970–1975) and (1970–1975) – (1976–1979). Significant group differences in these scores reflect an interaction, and for both recall and recognition we first tested the two difference scores simultaneously with a multivariate test (using the F approximation of the Pillai-Bartlett trace statistic [cf. 53]). For each difference score this was followed by a univariate test of group differences, and if significant by pairwise comparisons.

For recall the multivariate test indicated a significant interaction ($F(6, 156) = 2.58$, $P < 0.03$). Univariate tests indicated no significant group differences in the difference between periods (1960–1969) and (1970–1975), but the difference between periods (1970–1975) and

(1976–1979) showed significant group differences ($F(3, 78)=5.15$, $P<0.01$). Further analysis of the latter variable showed significant differences in recall between ACoA amnesics and normal controls ($P<0.05$) and between mixed amnesics and both normal controls ($P<0.001$) and dementia patients ($P<0.05$). Thus the amnesic groups recalled relatively less from the most recent time period (1976–1979).

The results for recognition were similar: Multivariate analysis of the difference scores indicated a significant interaction between the group and time period ($F(6, 156)=2.60$, $P<0.02$). In univariate tests only the difference between period (1970–1975) and (1976–1979) showed significant group differences ($F(3, 78)=4.59$, $P<0.01$). The ACoA amnesic group was significantly different from both normal controls ($P<0.01$) and dementia patients ($P<0.002$). Mixed amnesics differed from dementia patients ($P<0.05$), and although the difference between mixed amnesics and normal controls only approached significance ($P=0.074$), the analysis indicated that the amnesic groups recognized relatively less from the most recent time period.

Recognition improvement

To determine if the groups differed in their ability to improve performance given the three alternative choices when free recall failed, weighted means of recall and recognition and differences between them were calculated. Since the number of questions probed by forced choice differed between the groups, we corrected for the expected mean number of chance hits. We have not applied statistics to these data, since it is obvious from the data provided in Table 7 that the groups improved to the same degree.

Table 7. Recognition improvement in four groups corrected for the effect of guessing

	ACoA	Mix	Dem	NC
Recognition, weighted mean	7.5	7.2	6.8	8.8
Recall, weighted mean	4.4	4.0	3.7	6.6
Recognition–recall	3.1	3.2	3.1	2.2
Chance correction $\frac{(10\text{-recall})}{3}$	−1.9	−2.0	−2.1	−1.1
Recognition improvement	1.2	1.2	1.0	1.1

DISCUSSION

The results indicated that both groups of amnesic subjects displayed the pattern of extensive time graded remote memory loss previously found in alchoholic Korsakoff patients [4, 5, 22, 36, 43, 45, 62, 67]. This result cannot be due to differences in item difficulty, as the dementia patients, even though performing at a level far below the normal controls, showed a "flat" remote memory curve in parallel with that of the normal controls. The contribution of anterograde memory difficulties to the results should also be considered. In the mixed amnesia group, one patient had amnesia onset in 1976 and three in 1979, and in the ACoA amnesic group five patients had onset in 1978 and seven in 1979. Removal of these patients from their respective groups did not change the group means of recall or recognition from the 1978–1979 period appreciably (Table 5). We have also calculated the critical recall difference

scores (which differed between the amnesics and the two control groups and thus indicated the temporal gradient) in amnesics with onset before and after 1980 (listed in Table 8). It is apparent from these data, particularly in the ACoA group, that anterograde amnesia has not been a significant contributory factor to our finding of a temporal gradient.

Table 8. Comparison of mean recall difference scores of amnesics with onset before and after 1980

	MIX		ACoA	
	Before 80	After 80	Before 80	After 80
N	4	15	12	8
(70–75) – (76–79)	21.1	18.3	2.5	19.2
1st half–2nd half	17.0	17.8	11.1	19.6

In the mixed amnesia group five patients had Korsakoff's disease. Their mean percentage correct in recall during the three periods depicted in Fig. 2 was 58, 46, and 37, respectively. They averaged 56% correct in recall from the first half of the questions, 40% correct in the second half. Thus these five patients tend to be slightly better in their recall of remote events but the slope of their curve (the temporal gradient) is virtually identical with that of the remaining non-alcoholic amnesia patients in the group.

Continuity hypothesis

The majority of out amnesic subjects were not alcoholic, yet displayed the pattern of a long retrograde time gradient. Onset of the disease was sudden, and no possibility exists for a slowly progressive anterograde amnesia. Thus our results, as well as the results reported by SQUIRE *et al.* [37, 60, 67], seem to be contradictory to most previous attempts to explain retrograde amnesia with long time gradients, and the "continuity hypothesis" is probably not a correct explanation of the time gradient in Korsakoff patients. Inspection of data from individual amnesic patients in our groups reveals large differences in the temporal gradients, and it is by no means a universal finding. No readily discernible differences between those with steep temporal gradients and those with flat curves can be found in our data.

Error sources

Assessment of retrograde amnesia by remote memory questionnaires may entail many sources of error and imprecision [77]. In our construction of the test we attempted to select items which we thought would probe episodic memory rather than semantic memory [72], but common questionnaire items must also be part of "common knowledge", even if they concern events which are specific in time and place. The distinction between episodic and semantic memory is probably somewhat artificial when applied to information of this type [79]. Individual differences are large in normal subjects in their capacity to answer this type of questions, and the lack of correction for premorbid differences in amnesics is certainly a major contributor of noise in the data. Differences in onset time, and often a span of several years between the chronologically most recent question and onset, would tend to diminish the temporal gradient effect. In our study we also—perhaps unwisely—included several patients in the ACoA group, who appeared to be recovered, or nearly recovered, on measures of anterograde amnesia. Our finding of statistically significant, but in absolute terms

somewhat modest evidence of temporal gradients in amnesia, should be interpreted in the light of the many error sources. We believe the temporal gradients may actually be greater than we have demonstrated.

Episodic–semantic shift

If the "continuity hypothesis" is not tenable, how should we explain the time gradient of retrograde amnesia in Korsakoff's disease and in non-alcoholic amnesic syndromes? The answer may lie in some generalization of the notion of prolonged memory consolidation process put forward by SQUIRE *et al.* [64, 65]. CERMAK [20] (see also [41]) has noted that although normal subjects' memories from childhood and youth tend to appear vivid and detailed, they may actually to a great extent be familial folklore rather than truly remembered episodes. Through rehearsal and retelling they gradually become independent of their temporal and spatial contexts, thereby taking on the character of semantic rather than episodic memory. Consequently, tests based on normal remote recall may probe primarily semantic memory for the more distant decades, and primarily episodic memory for more recent decades, with a great deal of overlap between. To the extent that the amnesic memory loss involves episodic more than semantic memory [75], this proposed shift of information from episodic to semantic memory alone seems capable of explaining the relative preservation of older memories in amnesia. Since dementia may involve loss of episodic and semantic memory to a more nearly equal degree [19, 51, 57, 76], the flat remote memory curves found in Huntington's disease and Alzheimer's disease are compatible with the hypothesized explanation. Whether the proposed shift from episodic to semantic memory is best understood in purely psychological terms, or is to be understood also in terms of a shift in underlying neural mechanisms, is not clear. The differential effect on remote memory of amnesia and dementia syndromes suggests the possibility of a neural shift.

The heuristic value of the episodic-semantic distinction for understanding amnesia has been challenged, mainly because it is confounded by differences in the time periods from which episodic (recent) and semantic (very remote) memories are drawn [8, 79]. This criticism points to the danger of circular reasoning in any attempt to explain the observed phenomena of remote memory. It may be that learning of any kind, including such agreed-upon semantic material as word meaning and geographical knowledge, initially involves a stage of episodic memory, where the acquisition of the knowledge may still be characterized in time and place and be part of its memory structure. This possibility is consistent with descriptions of amnesic patients' failure to acquire postmorbid semantic knowledge [21, 29], and it would help explain the rarity of descriptions of childhood amnesia. Before maturity all memories may still be stored in an episodic context, and consequently vulnerable to amnesic treatment. The recent description of striking deficits on a wide variety of semantic memory tasks in a patient developing an amnesic syndrome at the age of 10 years [54] seems compatible with this view. The possibility that semantic memory represents the accumulated residue of many episodes has also been expressed by BADDELEY [9]. As a result of repetition of similar episodes, the individual episodic characteristics are lost while the core content of the instances remains.

Unrehearsed memories of discreet events tend to become lost eventually. Rehearsal may serve to strengthen the core content, but cannot prevent the gradual weakening of temporal and spatial contextual bonds. This is the proposed mechanism in the episodic–semantic shift.

In the monkey retrograde amnesia has been demonstrated without evidence of a temporal gradient [59]. Partly because the preoperatively learned discriminations were unrehearsed,

the particular paradigm used may not be relevant for human retrograde amnesia of real life events, where rehearsal seems to be the rule.

Recall, recognition, and the temporal gradient

In this study we found the same pattern of results in the recall and recognition portions of the test. Previously, an extensive temporal gradient in retrograde deficits has been found in six groups of Korsakoff patients [4, 5, 22, 36, 45, 67], and in patients during transient global amnesia [37] and following anoxia [67]. In each of these studies the temporal gradient was found in both recall and recognition. Thus, our two amnesic groups and other groups of non-alcoholic amnesic patients [37, 67] resemble Korsakoff patients both with respect to the time gradients and with respect to the similarity between recall and recognition deficits.

The data concerning dementia patients is, however, conflicting. We found an extensive "flat" remote memory deficit in both recall and recognition, as did some others [3, 4, 34]. SAGAR *et al.* [58], however, in a study of remote memory in Alzheimer and Parkinson patients found a temporal gradient of deficit in recall, but not in recognition. KOPELMAN [36] found in Alzheimer patients a temporal gradient which, although less pronounced than in Korsakoff patients, was present in both recall and recognition. These apparent discrepancies may be related to differences in tasks. SAGAR *et al.* [58] and KOPELMAN [36] used the Famous Scenes test, in which patients were given 1 min to relate as much as possible about the content and action of each picture, and about the event it represented, were then asked questions to probe for more specific information, and were finally given a recognition test concerning the picture. This format of the test may have created a more fine-grained and sensitive test than the traditional pass or fail oral public events questionnaire.

KOPELMAN [36] found that recognition improved performance compared to recall in both Korsakoff and Alzheimer patients to a greater extent than in normal controls, while we found no differences between groups in this respect. In our study we corrected for chance hits in guessing (Table 7). If Kopelman's results could survive a similar correction—as seems likely, partly because he used four recognition foils against our two—the greater improvement in recognition in his patient groups may possibly be related to a greater salience of cues in connection with pictorial stimuli.

Basal forebrain amnesia

A major result of the present study was the similarity of performance between ACoA amnesics and amnesics with other etiologies, particulary the identical temporal gradient and recognition improvement. Similarities have previously been demonstrated in several aspects of anterograde amnesia [24, 31], and the present results strengthen the evidence that the amnesia caused by aneurysms of the anterior communicating artery may be essentially similar to amnesia following diencephalic or medial temporal lesions. This is an important question, as the lesion in these cases seems to be different from that seen in other etiologies. Amnesia as a complication to surgery of ACoA aneurysms has been known for some time [10, 13, 40, 50, 52, 71], but the mechanism of action is unknown. Based on the anatomical description of small perforating arteries arising from the ACoA, it has been hypothesized that lack of blood supply through these arteries to their area of termination in midline portions of the basal forebrain including the septal nuclei and subcallosal area might be responsible [30]. This idea was supported by an analysis of the operative procedure used in a series of patients, which included the 12 ACoA amnesics in this study operated on in 1978 and 1979. In this series, the operative procedure of trapping the aneurysm—and thus blocking the blood

supply through the perforating vessels arising between the two trapping clips—was clearly related to the postoperative amnesia [30]. Evidence from CT scans of similar cases has also supported the basal forebrain localization of the lesion [26] and it was confirmed in a recent autopsy case [56]. The lesion in this amnesic patient was limited to the area of the septal grey, nucleus of the diagonal band of Broca, nucleus accumbens, and small segments of the rostroventral globus pallidus and anterior limb of the internal capsule. Which of these structures is the critical one for the memory disturbance is not yet clear. A PET study of two patients indicated that a secondary remote effect on the hippocampus may be involved [73], which would suggest a possible role of the magnocellular nuclei of the septum and the vertical nucleus of the diagonal band [44].

If depression of hippocampal activity is critically involved in the amnesia following ACoA aneurysms, no difference from medial temporal amnesia should perhaps be anticipated. However, an alternative to the hippocampal depression hypothesis has been suggested by results obtained in the monkey amnesia model when bilateral ablation of ventromedial frontal cortex resulted in amnesia [7]. The lesion comprised the prefrontal projection areas of both the anterior nuclei and the anterior part of the magnocellular portion of the mediodorsal nucleus of the thalamus, each of which is a stage in the two limbo-thalamic pathways suggested to subserve recognition memory in the monkey [46]. The possibility of an independent contribution of mesial prefrontal cortex to memory must thus be considered.

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