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Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions

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Abstract

Patients with focal diencephalic, temporal lobe, or frontal lobe lesions were examined on various measures of remote memory. Korsakoff patients showed a severe impairment with a characteristic 'temporal gradient', whereas two patients with focal diencephalic damage (and anterograde amnesia) were virtually unimpaired on remote memory measures. Patients with frontal lobe pathology were severely impaired in the recall of autobiographical incidents and famous news events. Patients with temporal lobe pathology showed severe impairment but a relatively 'flat' temporal gradient, largely attributable to herpes encephalitis patients. From recognition and cued recall tasks, it is argued that there is an important retrieval component to the remote memory deficit across all the lesion groups. In general, the pattern of performance by the frontal lobe and temporal lobe groups was closely similar, and there was no evidence of any major access/storage difference between them. However, laterality comparisons across these groups indicated that the right temporal and frontal lobe regions may make a greater contribution to the retrieval of past episodic (incident and event) memories, whereas the left temporal region is more closely involved in the lexical-semantic labelling of remote memories. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Recent neuropsychological research into retrograde amnesia has tended to focus upon patients with either diencephalic, temporal lobe, or frontal lobe lesions, and to seek dissociations across different aspects of remote memory performance (for review, see [26]). However, there has been a relative lack of studies involving direct comparisons of patients with lesions in the different sites, examining their performance both quantitatively and qualitatively.

In *diencephalic amnesia* resulting from Wernicke–Korsakoff pathology, an extensive remote memory loss with a 'temporal gradient' (relative sparing of early memories) has been established for the recall of autobiographical incidents and of public information in both group and single-case studies [1, 2, 4, 23, 45, 67]. However, it has been suggested that this retrograde amnesia results, in fact, from concomitant frontal pathology [24, 25]. Consistent with this, patients with traumatic or vascular lesions in the diencephalon have been described, in whom remote memory appears to have been either spared or disrupted in the presence of either intact or impaired 'frontal' test function, respectively [10, 15, 20, 44, 46, 66]. In cases of *temporal lobe amnesia* in whom the lesion is confined to the medial temporal structures, a relatively brief (three years or less) retrograde amnesia has often been reported [13, 32, 33, 34, 68]. However, a few patients have recently been described in whom a more extensive retrograde amnesia apparently resulted from more widespread pathology within the hippocampi bilaterally [22, 37, 48]. More typically, patients with temporal lobe pathology extending beyond the medial structures manifest a much more extensive retrograde deficit [6, 8, 23, 41, 50, 54, 60]. In *frontal amnesia*, patients can manifest either impoverished fluency in retrieving autobiographical memories or inappropriate and inaccurate retrieval of memories ('spontaneous' confabulation) [3]. Della Sala et al. [9] found that 37% of patients with focal lesions confined to the frontal lobes manifested a severe deficit in autobiographical memory retrieval, including all the patients in their sample who had bilateral pathology.

There are other studies which have postulated either

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single- or double-dissociations within remote memory [26]. First, Warrington and McCarthy [64] provided evidence of preserved factual knowledge in a single-case, elicited on word-completion cueing tasks or on making familiarity judgements, despite severe retrograde amnesia on conventional recall tasks. This single dissociation was partially corroborated by Eslinger et al. [11] in one of two herpes encephalitis patients, but it has not yet been examined in larger group studies or patients with other pathologies. Secondly, De Renzi et al. [8] have described a patient with a large left temporal lobe lesion, in whom factual information about public events or famous people had been lost, but in whom autobiographical memories were relatively intact. The other half of a double-dissociation was postulated by O'Connor et al. [41], who described a patient with extensive damage in the right temporal lobe, resulting in a disproportionately severe impairment in the recall of autobiographical incidents, relative to remote semantic (factual) information. The patient also exhibited severe visuo-perceptual deficits, and the authors argued that she might have a particular difficulty in conjuring up visual images necessary for the retrieval of past autobiographical experiences. Ogden [42] described a related deficit, and postulated a closely similar explanation, in a patient in whom right hemisphere occipito-temporal projections had been damaged.

A number of issues remain unclear. *First*, there have not previously been any direct comparisons of patients with diencephalic, temporal, or frontal lobe pathology, examining for differences in the severity, temporal gradient, or pattern (autobiographical vs semantic) of retrograde amnesia. Any such comparison needs to take account of whether any observed differences result from features specific to particular underlying diagnoses (e.g., herpes encephalitis vs hypoxia) or concomitant pathology elsewhere (e.g., frontal lobe involvement in the Korsakoff syndrome). *Secondly*, we lack evidence concerning whether temporal lobe lesions produce a qualitatively different retrograde amnesia from frontal lesions, possibly a storage rather than an access/retrieval deficit, and whether patients in these two groups would benefit differentially from contextual, recognition, or other cues [26], the frontal patients being more likely to respond to cues if theirs was predominantly a problem of access. *Thirdly*, it needs to be established whether the apparent dissociations between autobiographical and semantic (factual) remote memory, identified in single-case studies, can also be detected in larger groups of patients with focal lesions, and whether this dissociation does indeed reflect differential hemispheric function.

In the present study, these issues have been investigated. Patients with memory impairment from diencephalic, temporal lobe, or frontal lobe lesions were compared across various measures of remote memory, using tasks which require recall and/or recognition of publicly available knowledge, personal 'semantic' facts, and autobiographical incidents. The findings were analysed in three separate ways, which relate to the above issues: (a) an overall analysis across lesion groups, taking account of any differences between underlying aetiologies; (b) an analysis considering the effects of cueing (recognition and word-completion); and (c) an analysis considering the laterality (or bilaterality) of the lesion. It was predicted that: (i) All these lesion groups would be vulnerable to extensive remote memory loss, except for any patients in whom the lesion was confined to diencephalic or to medial temporal structures. (ii) To the extent that the Korsakoff group's retrograde amnesia results from concomitant frontal involvement, their performance would resemble the frontal group across the various tasks. (iii) We predicted that if the problem was primarily of access in the frontal patients and of storage in the temporal lobe patients, the former would show differential benefits from cueing and (possibly) flatter remote memory curves. (iv) We predicted that right-sided lesions would particularly disrupt autobiographical memory and left-sided lesions would affect more 'semantic' tasks, but that the severity of the impairment might also relate to the extent of bilateral involvement, particularly in the frontal group.

2. Subject groups

2.1. Clinical and CT description

The patients were selected in all cases on the basis of their having significant anterograde memory impairment in association with clinical and CT scan evidence of predominantly focal lesions in either the temporal or frontal lobes or the diencephalon. As part of the research protocol, they received an MRI (magnetic resonance) scan and a PET (positron emission tomography) scan as well as cognitive assessment. On the basis of our clinical and CT criteria, we included for study 15 patients with diencephalic lesions, 14 patients with temporal lobe lesions, 15 with frontal lobe lesions, and 20 healthy control subjects.

The 15 patients with *diencephalic lesions* included 13 patients who had an alcoholic Korsakoff syndrome. Twelve of these 13 patients had either a documented history or residual signs of a Wernicke episode which preceded their amnesic syndrome and, in all 13 patients, memory was affected out of all proportion to any other cognitive deficit [27, 62]. Mean length of drinking history was 27.5 years (range = 18–48) and mean duration of amnesia was 42.2 months (range 1 = 204). In addition, we included two patients who manifested an amnesic syndrome following surgical excision *and* irradiation of a Pituitary adenoma in both cases. One of these patients has been described elsewhere [17]: she had an IQ minus General MQ (memory quotient) discrepancy of 49 points, whilst the other patient had an IQ minus General MQ discrepancy of 27 points. Plotting the radiotherapy planning fields against these patients' MRI scans indicated that structures affected by >90% of the irradiation included the anterior thalamus, the mammillary bodies, the mammillo-thalamic tract, and the fornix, and it is plausible that these structures may also have been affected by ischaemia during the operation [17]. Hence, these two patients were treated as cases of 'diencephalic' amnesia.

The *temporal lobe lesion* group included nine patients with probable or definite (antibody confirmed) herpes encephalitis, all of whom had CT evidence of temporal lobe damage. They also included four patients with hypoxic brain damage. One of these patients became hypoxic following a heroin overdose and a period of prolonged unconsciousness: his CT scan showed enlargement of the temporal horns of the ventricles bilaterally, indicating temporal lobe atrophy. A second patient had attempted to hang himself, and his initial CT scan showed a large area of infarction in the left temporal lobe. A third patient showed left temporo-parietal infarction following a respiratory arrest. The fourth patient developed amnesia after a prolonged period of unconsciousness of uncertain cause: although his CT scan showed nothing abnormal, visual inspection of his PET was thought to show focal hypometabolism in the temporal lobes. The final patient in the temporal lobe group had a prolonged history of complex partial seizures with bilateral temporal lobe foci evident on EEG. This patient's CT scan showed some temporal lobe atrophy. He was complaining of impaired memory, but there was no evidence either at initial assessment or at (3-year) follow-up of generalised dementia.

The *frontal lobe lesion* group included nine patients who were assessed two weeks following a bilateral frontal tractotomy. In this operation, yttrium rods are implanted in the frontal lobes for treatment of chronic affective disorders. On MRI scan, the yttrium rods could be seen in the medial and mid-frontal white matter, surrounded by a small area of radiation necrosis and a much larger area of oedema, and there was extensive frontal hypometabolism on FDG (fluoro-deoxy-glucose) PET. These patients were tested after any confusion had subsided, usually in the second post-operative week, occasionally the third, because Kartsounis et al. [21] have found that these patients behave most like patients with large frontal lesions at this time. Kartsounis et al. [21] demonstrated statistically significant impairments on executive/frontal lobe and recognition memory tests two weeks post-operatively, although these deficits were not present either pre-operatively (despite severe depression) or six months later. In addition, we examined six patients with focal frontal lesions. One patient had old leucotomy scars from a bilateral operation in 1974 (i.e., 18 years before testing), and the others had lesions resulting from a glioma, haematoma, infarcts, or craniotomy. Three of these six patients had right frontal lesions, one had a left frontal lesion, and two had bilateral lesions.

2.2. Background neuropsychological findings

2.2.1. Mean age, IQ, memory quotients

These are shown in Table 1, including estimated premorbid IQ (NART-R [39]) and current IQ (WAIS-R [65]). The groups did not differ significantly in terms of either mean age, NART-R IQ or current IQ, although the frontal lobe group showed a mean NART-R minus IQ discrepancy of approximately 9.5 points, against 8.0 points in the temporal lobe group, 7.0 points in the diencephalic group, and 2.2 points in the healthy controls. Table 1 also shows mean immediate (general) and delayed memory quotients (GMQ, DMQ) in the subject groups on the WMS-R [5], as well as mean IQ minus DMQ difference scores. The diencephalic and temporal lobe patient groups were severely and similarly impaired. The present sample of frontal lobe lesion patients showed a lesser but quite severe degree of memory impairment relative to healthy controls.

2.2.2. Executive/frontal lobe tests

As indicated in Table 2 the four groups differed significantly across all the tasks. The two amnesic groups (diencephalic and temporal lobe) performed worse than healthy controls across the four measures: planned *t*-tests showed that the diencephalic group performed significantly worse than controls on cognitive estimates [51], card-sorting categories and percentage perseverations [38], and the temporal lobe group differed significantly from controls on cognitive estimates ($P < 0.05$). The frontal lobe group showed highly significant differences from controls on all four measures ($P < 0.01$ to $P < 0.0001$), and also differed significantly from the temporal lobe group on cognitive estimates ($P < 0.05$).

2.2.3. Individual diagnostic groups

Findings are summarised in Table 3 in terms of the key background measures. In addition, the patients had been screened on a modified version of the Snodgrass test. On this, the herpes encephalitis group showed impairment relative to the other patient groups, ($F(5,38) = 3.18$, $P < 0.02$). This impairment was mainly attributable to two patients with unilateral left temporal lesions who scored a mean of 7.75% correct on this task: no other subject scored below 47%. When these two subjects were excluded, there was no significant difference across the patient groups ($F(5,36) = 1.75$, ns).

2.3. Synopsis of Neuro-imaging findings

The MRI's have been segmented and analysed according to pre-determined structural definitions using a hierarchical segmentation programme which allows fine-

Table 1
Mean age, IQ and memory quotients (WMS-R), and IQ-DMQ difference scores

	Healthy controls		Frontal lobe patients		Diencephalic patients		Temporal lobe patients		ANOVA
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
N	20		15		15		14		
Mean age	45.9	±17.3	45.7	±10.2	54.4	±8.2	45.1	±16.3	ns
NART IQ ('Premorbid')	104.3	±14.4	105.1	±12.9	108.7	±11.8	104.0	±9.4	ns
Current IQ (WAIS-R)	102.1	±15.4	95.5	+16.3	101.7	±17.7	95.9	+11.7	ns
General MQ (WMS-R) (GMQ)	103.1	±16.4	83.1	±17.2	70.0	±20.5	68.4	±14.6	<0.0001
Delayed MQ (WMS-R) (DMQ)	105.2	±19.0	73.5	+15.4	65.0	+21.0	65.9	±14.0	<0.0001
IQ-DMQ	−3.1	±14.0	21.9	±11.8	36.7	+13.1	29.9	±18.2	<0.0001
Lesion laterality*			9 bilaterals 3 right unilateral 1 left unilateral		All bilateral		6 bilateral 3 predom. right unilat. 3 predom. left unilat. 2 left unilateral		

* For definitions, see text.

Table 2
Frontal/executive tasks

	Healthy controls		Frontal lobe patients		Diencephalic patients		Temporal lobe patients		ANOVA
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
FAS verbal fluency	40.3	±13.7	23.7	±13.7	32.2	±15.5	32.8	±13.6	<0.01
Card sorting categories	5.0	±1.6	3.3	±1.9	3.7	±1.9	4.4	±1.7	<0.05
% perseverations*	13.1	±14.7	41.3	±30.0	32.9	±31.4	23.9	±25.4	<0.01
Cognitive estimates	3.9	±2.7	8.9	±3.9	6.9	±4.4	6.1	±3.2	<0.002

* (Perseverative errors ÷ Total errors)%.

grained measures of volume [16, 28]. Quantitative fluorodeoxy glucose (FDG) PET was carried out and analysed in terms of regions-of-interest (R-o-I) and the statistical parametric mapping (SPM) program [12]. A detailed account of these analyses will be published elsewhere, and we will give here only a brief synopsis of the findings pertinent to identifying focal lesions or atrophy. Statistical analysis is reported in terms of one-way ANOVAs across 7 diagnostic groups (controls, Korsakoff, pituitary irradiation, herpes encephalitis, hypoxia, frontal tractotomy, and frontal focal) with Newman–Keuls post-hoc tests (at $P \leqslant 0.05$) to compare each patient group with the healthy control group, unless otherwise specified. All 13 *Korsakoff* patients showed evidence of thalamic atrophy on MRI and, as a group, they differed significantly from the controls in this regard. Nine out of 13 Korsakoff patients also showed evidence of mammillary body atrophy. One patient who had a definite history of a Wernicke episode, followed by a Korsakoff syndrome, was found on scanning also to have a left thalamic infarct. Otherwise, abnormalities in the Korsakoff group were symmetrical in all cases. The Korsakoff group also showed evidence of frontal atrophy on MRI, consistent with earlier CT and neuropathological studies [18, 19, 53, 58]; and on SPM PET analysis, they showed hypometabolism in the frontal poles bilaterally ($P < 0.05$), mainly attributable to four patients, although they did not show any evidence of hypometabolism elsewhere in the brain. The two *pituitary adenoma* patients did not show any evidence of atrophy or hypometabolism but, as mentioned above, superimposing the irradiation fields on the MRI clearly indicated that the anterior thalamus, mammillo-thalamic tract, mammillary bodies, and fornix were implicated at a microscopic level [17]. The *herpes encephalitis* group showed significant reductions in medial temporal ($P < 0.01$) parahippocampal ($P < 0.05$), and hippocampal volumes ($P < 0.05$), as well as significant hypometabolism throughout the temporal lobe but not elsewhere in the brain on PET R-o-I and SPM analysis. The *hypoxic* group showed a significant reduction in total hippocampal volume ($P = 0.05$). The *focal frontal* group had lesions confined to the frontal lobes according to both MRI and PET criteria, and they showed a significant reduction in frontal volume after lesion volume was subtracted, but no significant differences elsewhere. In the *frontal tractotomy* group, the region of frontal necrosis was compensated for by brain swelling from oedema so that total brain volume did not differ significantly from

Table 3
Background data for diagnostic subgroups

	Korsakoff patients		Pituitary irradiation		Herpes encephalitis		Anoxia/epilepsy		Frontal tractotomy		Frontal focal		ANOVA
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P
N	13		2		9		5		9		6		
Mean age	55.4	±8.1	48.0	±7.1	46.1	±14.6	43.4	±20.8	40.9	±9.9	53.0	±5.2	ns
NART-R IQ	107.8	±12.5	114.5	±3.5	100.2	±13.8	105.0	±6.1	103.6	±12.8	107.5	±14.0	ns
IQ-DMQ	38.1	±11.2	28.0	±26.8	31.9	±18.1	26.4	±19.9	19.3	±13.1	25.8	±9.3	ns
Card sorting categories	3.5	±1.9	5.0	±1.4	4.7	±1.7	4.0	±2.0	2.9	±2.0	4.0	±1.7	ns
% perserverations	37.2	±31.8	7.0	±9.9	26.6	±29.2	18.7	±18.0	53.3	±32.3	23.3	±14.3	ns
Cognitive estimates	7.1	±4.4	5.5	±6.4	5.4	±3.4	7.4	±2.4	8.7	±3.6	9.2	±4.7	ns
Lesion laterality*	All bilateral		Bilateral		1 bilateral 3 predom. right unilat. 3 predom. left unilat. 2 left unilateral		All bilateral		All bilateral		2 bilateral 3 right unilateral 1 left unilateral		

* For definition, see text.

controls. They showed statistically significant hypometabolism (R-o-I and SPM) throughout the frontal cortex and in the anterior cingulate, but not elsewhere in the brain. Figure 1A illustrates their extensive frontal abnormality on MRI. Figure 1B shows a lower axial slice at the level of the septal nuclei, showing sparing of these nuclei although tissue anterior to this was implicated. This is consistent with Newcombe's [40] observation in 25 cases that: "None of the lesions extend(ed) back sufficiently far to directly involve the substantia innominata" (nucleus basalis), (compare [7]).

3. Experiment 1: remote memory performance and temporal gradients

The first experiment compared the lesion groups in terms of their overall level of performance and temporal gradients across a number of measures of remote memory.

3.1. Methods

3.1.1. Personal semantic memory

This schedule involves a semi-structured interview, part of the Autobiographical Memory Interview (AMI) [29]). Patients were asked to answer specific questions which probe their knowledge of facts about their past from different time-periods: 'childhood', 'young adult', and 'recent' life. The veracity of the patients' responses was checked in four different ways: (i) Inaccuracies were sometimes indicated by inconsistencies in the patients' replies to items within the questionnaire. (ii) Fairly extensive medical records and clinical histories were available in all cases, and these were examined carefully. (iii) Current care staff were interviewed, thereby providing information about recent facts. (iv) The next-of-kin was traced and interviewed in approximately half the patients to obtain further information, particularly about earlier time-periods. Consistent with previous studies [29], only very minor amendments had to be made as a result of interviewing the next-of-kin, and this did not affect the overall pattern of results or the temporal gradients obtained.

3.1.2. Autobiographical incidents

Administered concurrently with the personal semantic memory schedule as part of the AMI, participants were required to produce memories of incidents or events to specific cues from 'childhood', 'young adult', and 'recent life'. They were encouraged to produce a specific incident, rather than to give a general description of things they used to do, and to describe when and where it happened. When a participant failed to produce a memory, he or she was prompted with predetermined cues. A handwritten record of each memory produced was taken down as close to verbatim as possible. Scoring was in terms of the

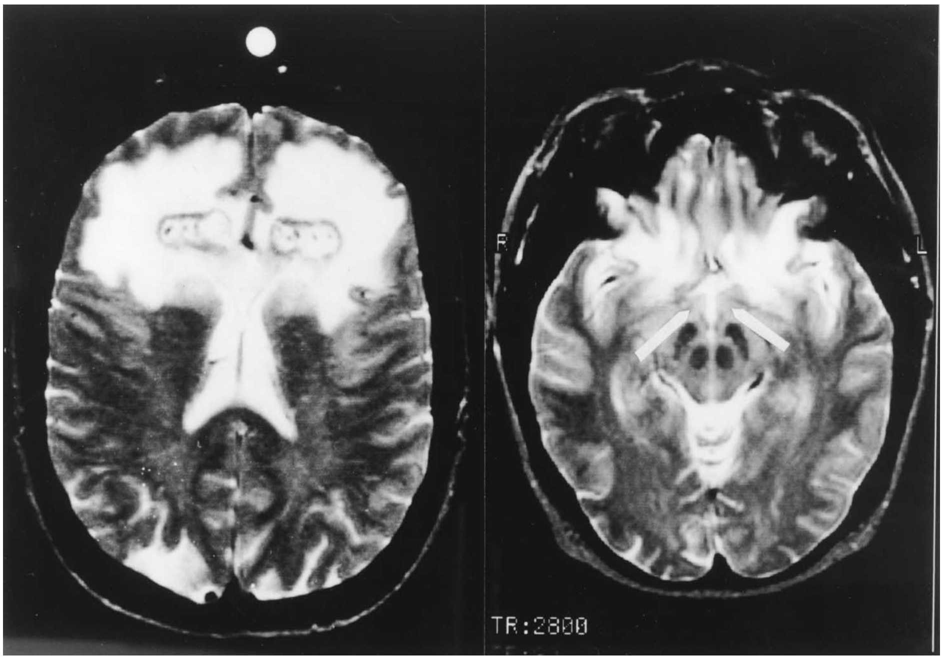

Fig. 1. A: an axial MRI view in a frontal tractotomy patient. The yttrium deposits bilaterally are surrounded by a small area of radio-necrosis, and there is a much larger area of oedema which always spared the cortical margin. B: shows a lower axial cut at the level of the septal nuclei (indicated), which were spared, as were the other basal forebrain structures (compare Newcombe (1975)).

descriptive richness of an incident and its specificity in time and place. A global (0–3 point) rating scale was employed (half-points were permitted). In earlier studies, each schedule was rated by two assessors, from whom a mean inter-rater reliability coefficient of $r = 0.85$ was obtained [29]. As in previous studies, rating in the present investigation was by two assessors and, where disagreement existed, the mean score was taken. The authenticity of subjects' responses was checked at the same time and in the same way as for the personal semantic memory schedule. Confabulated statements were indicated on the schedules and did not contribute towards scoring.

3.1.3. News events test

This test was modified from that employed by Kopelman [23]. The subjects were shown 30 pictures of 'famous' news events, familiar to British subjects. There were 10 pictures from each decade, 1960–1990, randomly distributed within the test. For each picture, participants were asked a 'recall' question, requiring them to identify the event depicted to score a full point. A half-point was awarded for an incomplete identification, but no points were given for a simple description of the picture without any evidence of having identified the event. The test was designed to give a slight recency effect in the performance of healthy subjects, consistent with studies of remote memory in healthy populations [14, 49, 67].

3.2. Results

3.2.1. Personal semantic memory

Findings are shown in Fig. 2. Within the diencephalic

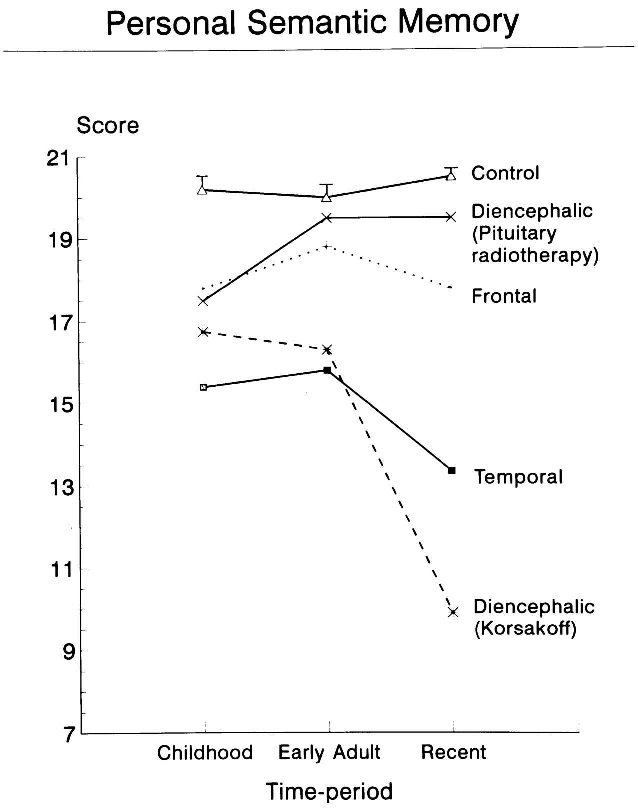

Fig. 2. Mean scores of the healthy controls (C), Pituitary patients (P), Frontal (F), Temporal lobe (T), and Korsakoff (K) patients in the recall of personal semantic facts. Error bars = ± SE in controls. Standard deviations (SD's) = C's: 1.5, 1.4, 0.9, P's: 1.4, 2.1, 2.1, F's: 5.1, 2.7, 4.5, K's: 3.9, 3.6, 5.6, T's: 3.9, 2.0, 5.2.

group, the pituitary radiotherapy patients are shown separately from the Korsakoff patients, because of their very different patterns of performance. The pituitary radiotherapy group scored within one standard deviation of the healthy controls for 'early adult' and 'recent' facts, although their 'childhood' score was between one and two standard deviations below the healthy control group. It can also be readily seen that the frontal lobe group showed only a mild impairment on this task, whereas the temporal lobe and Korsakoff groups showed more severe impairments with relative sparing of early memories (a 'temporal gradient'). Analysis of variance across the five groups showed a highly significant main effect of group (F (4,59) = 17.45, $P < 0.0001$), and a significant group by time-period interaction effect (F(8,118) = 4.01, $P < 0.001$). A planned contrast between the frontal lobe group and the healthy controls showed a significant main effect of group (F(1,33) = 6.63, $P < 0.02$), indicating impairment in the frontal lobe group, but there was no significant group by time-period interaction effect (F(2,66) = 0.48), i.e., no temporal gradient. The temporal lobe group was also significantly impaired, relative to the healthy controls (main effect (F(1,32) = 46.11, $P < 0.0001$)): Figure 2 indicates that there was evidence of a gentle temporal gradient in this group, although the group by time-period interaction effect was not statistically significant (F(2,64) = 1.36). The Korsakoff group showed an overall severity of impairment similar to that of the temporal lobe group (F(1,25) = 0.03), but there was a significant group by time-period interaction effect (F(2,50) = 5.55, $P < 0.005$), indicating a steeper gradient in the Korsakoff than the temporal lobe group; and the Korsakoff group also showed a highly significant group by time-period interaction effect when compared with the healthy controls, (F(2,62) = 13.60, $P < 0.0001$).

3.2.2. *Autobiographical memory*

Recall scores are shown in Fig. 3. Again, the pituitary irradiation group showed only a weak trend towards impairment, and their findings are represented separately from the Korsakoff group. The pituitary irradiation group matched the healthy controls for 'childhood' memories and were approximately one standard deviation below the controls for 'early adult' and 'recent' memories. It can be seen from Fig. 3 that the other three patient groups (frontal, temporal lobe, and Korsakoff) closely matched one another in terms of their severity of impairment in autobiographical recollection, although there were differences in temporal gradient. An overall analysis of variance gave a highly significant main effect of group (F(4,59) = 10.95, $P < 0.0001$], and also a statistically significant group by time-period interaction (F(8,118) = 2.50, $P < 0.02$). Contrast analysis between the frontal lobe group and healthy controls gave a highly significant main effect (F(1,33) = 19.84, $P < 0.0001$), indicating a severe impairment in the frontal patients,

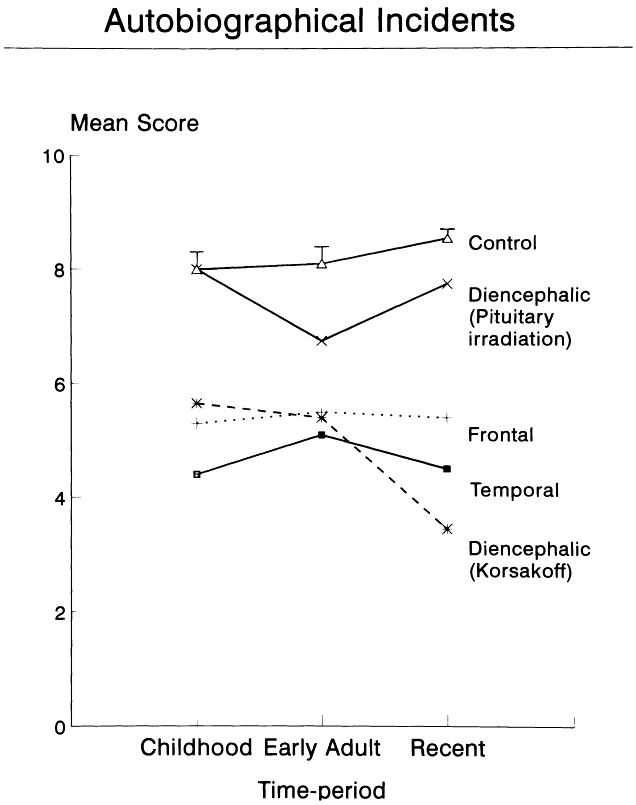

Fig. 3. Mean scores of the subject groups for recall of autobiographical incidents. Error bars = ±1 SE in controls. SD's = C's: 1.3, 1.3, 0.7, P's: 0.7, 1.1, 0.4, F's: 2.8, 2.7, 2.6, K's: 2.8, 2.7, 2.6, T's: 3.0, 2.2, 2.5.

but no significant group by time-period interaction (F(2,66) = 0.25). Comparing the temporal lobe group with the frontal lobe group, there was no significant main effect of group (F(1,27) = 1.20), or interaction effect (F(2,54) = 0.12), indicating that the two groups did not differ in either the overall severity of their impairment or in temporal gradient. Comparing the Korsakoff group with the temporal lobe group also failed to give a statistically significant main effect of group (F(1,25) = 0.09), but this comparison did give a statistically significant group by time-period interaction (F(2,50) = 4.47, $P < 0.02$), indicating a significantly steeper temporal gradient in the Korsakoff group. Comparing the Korsakoff group with healthy controls also gave a highly significant group by time-period interaction (F(2,62) = 8.38, $P < 0.001$), confirming the temporal gradient in the Korsakoff group.

3.2.3. *News event recall*

Results are shown in Fig. 4. Data are shown only for subjects aged 30 or over, as temporal gradients in younger subjects would not have been valid. Included in this analysis are 16 healthy controls, 14 frontal lesion patients, 13 Korsakoff and two pituitary irradiation patients, and 10 temporal lesion patients. The latter consisted of eight patients with herpes encephalitis, one with anoxic brain

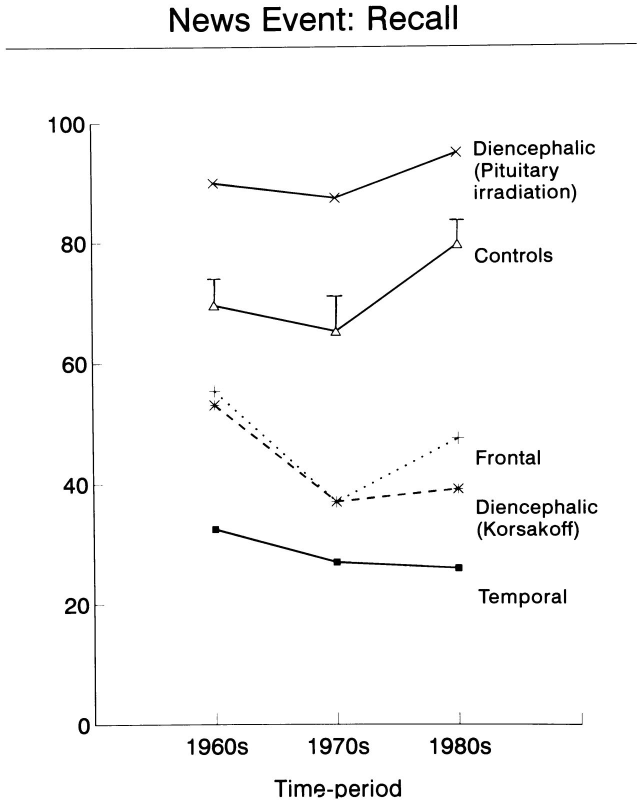

Fig. 4. Mean scores of the subject groups (subjects aged over 30 years only) on the recall of news events. Error bars = ±1 SE in controls. SD's = C's: 17.3, 23.3, 16.2, P's: 7.1, 10.6, 7.1, F's: 28.2, 29.2, 25.2, K's: 25.7, 31.8, 30.1, T's: 23.5, 17.4, 18.8.

damage, and one patient with seizures arising from the temporal lobes: hence, this group's performance is largely attributable to the herpes encephalitis patients. Figure 4 shows that, on this test, the pituitary irradiation group was actually performing better than the controls, whereas the frontal lobe group showed a pattern of performance closely similar to that of the Korsakoff patients, and the temporal lobe group manifested the greatest impairment. Analysis of variance across the five groups gave a significant main effect of groups (F (4,50) = 7.68, $P < 0.0001$), and a significant group by decade interaction (F(8,100) = 3.80, $P < 0.001$), consistent with temporal gradients in three of the amnesic groups. A planned contrast analysis between the Korsakoff group and the healthy controls gave a significant main effect of group (F(1,27) = 10.68, $P < 0.002$), and a significant group by decade interaction (F(2,54) = 10.51, $P < 0.0001$), indicating a temporal gradient in the Korsakoff patients. Similarly, comparing the frontal lobe group with the controls, there was a significant main effect of group (F(1,28) = 8.98, $P < 0.005$), and a statistically significant interaction (F(2,56) = 6.37, $P < 0.0025$), indicating a temporal gradient in the frontal lobe group. Comparing the temporal lobe patients with the controls, there was a significant main effect of group (F(1,24) = 22.06, $P < 0.0001$), and a significant group by decade interaction (F(2,48) = 5.60, $P < 0.005$), indicating a temporal gradient in this group as well. However, comparing the Korsakoff and temporal lobe group, there were no significant differences in terms of either main effect (F(1,21) = 2.56), or group by decade interaction (F(2,42) = 1.15).

3.2.4. Duration of amnesia

Although there was no significant difference in mean duration across our patient groups (F(3,40) = 0.41, ns), there was wide variability within each group. We investigated the importance of this on test performance in two ways: (i) a correlational analysis and (ii) by examining a subgroup of patients with a narrower range of durations (2 months to 6 years). The latter analysis included nine Korsakoff, two pituitary, 11 temporal, and five frontal patients as well as 20 controls. Within the total patient group, the correlations of duration of amnesia with total scores on the personal semantic, autobiographical, and news events' tests were −0.20, −0.11, and −0.11, respectively, all non-significant. Figure 5 shows the findings for the selected subgroups across the different tasks. As in the overall analyses, there were highly significant main effects of group across each analysis, $P < 0.0004$ to $P < 0.0001$. The group by time-period interactions were statistically significant, $P < 0.05$, for personal semantic memory and news event recall, but this interaction showed only a non-significant trend for autobiographical incidents.

3.2.5. Drinking history

Within the Korsakoff group, the estimated duration of heavy drinking was usually lengthy (compare [19, 62]). Consequently, we examined the correlations between total drinking history (in years), duration of amnesia (months), the sum of these two measures, and performance on our remote memory tasks in the total Korsakoff group. None of these correlations were statistically significant. Likewise, when we compared those with a drinking history ⩾ or <25 years or those with a duration of amnesia > or <1 year, there were negligible differences between them.

3.2.6. Diagnostic subgroups

Finally, we compared the performance of the diagnostic subgroups within the temporal lobe and frontal lesion groups. Within the temporal lobe group, the herpes patients showed a flatter gradient on personal semantic memory (childhood − recent mean difference = 0.94 (SD = 6.39)) than the anoxic/epilepsy group (mean difference = 3.50 (±2.78)). The same was true for autobiographical incidents (young adult − recent = 0.11 (±2.39) vs 1.30 (±2.02)), but neither of these differences was statistically significant in these small groups. On news events (Fig. 4), eight out of 10 of the subjects over 30

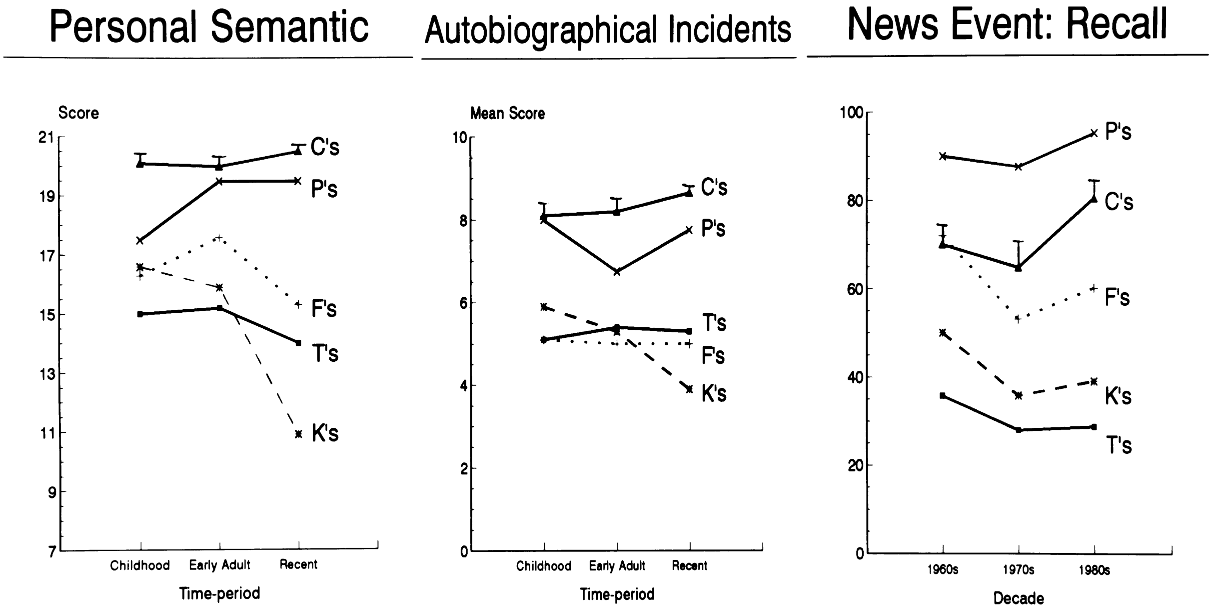

Fig. 5. Mean scores of subgroups of patients with a duration of amnesia between 2 months and 6 years, compared with healthy control's performance: (a) Personal Semantic memory, (b) Autobiographical Incident recall, (c) News Events. C's = Controls, P's = Pituitary, F's = Frontal lesions, T's = Temporal lobe, K's = Korsakoff patients. Error bars = ± 1 SE in controls. SD's (controls and pituitary group as Figures 2 and 4): (a) F's: 7.9, 2.9, 6.0, K's: 4.1, 3.6, 5.8, T's: 4.2, 1.9, 4.2; (b) F's: 3.5, 2.8, 3.1, K's: 2.7, 2.7, 2.3, T's: 3.0, 2.2, 2.2; (c) F's: 27.7, 36.7, 29.2, K's: 17.7, 29.4, 30.0, T's: 27.6, 21.0, 22.3.

were herpes patients, and again they showed a fairly flat temporal gradient. Within the frontal group, the only significant difference between the subgroups was that the focal lesion group performed worse than the tractotomy group on personal semantic facts ($F(1,13) = 4.96$, $P < 0.05$). Otherwise, there were no significant differences between the diagnostic subgroups.

3.3. Discussion

Summarising our findings, the Korsakoff, frontal, and temporal lobe groups all showed significant remote memory impairments, and only the pituitary group did not. Our findings were not attributable either to the duration of amnesia or (in Korsakoff patients) to the length of drinking history, and it is striking that even the tractotomy patients (with a duration of only two weeks) showed an extensive retrograde loss, particularly on autobiographical incidents and news events. We will consider these individual groups in turn.

The Korsakoff patients showed a severe deficit across all three tasks, involving memories from their childhood as well as early adult and more recent life. In addition, they showed a steep temporal gradient such that there was relative sparing of their earlier memories, compared with the recall of more recent facts, incidents, and events, indicated by highly significant group by time-period interaction effects. These findings are consistent with the clinical accounts by Korsakoff [30] and Moll [35], indicating an extensive retrograde amnesia, as well as with the observations of more recent neuropsychological studies [1, 4, 32, 67]. In particular, Kopelman [23] previously showed memory impairments extending back into childhood plus a steep temporal gradient in these patients, using earlier versions of these same memory tasks. The determinants of the temporal gradient in Korsakoff patients have been discussed elsewhere, but the consensus is that a progressive anterograde loss during the period of heavy drinking makes only a minor contribution to the temporal gradient [4, 23, 26, 45]. The absence of significant correlations between length of drinking history and remote memory performance in the present study is consistent with this viewpoint.

By contrast, the patients who had received irradiation to their diencephalic structures, as treatment for pituitary adenomas [17], showed no significant differences from the healthy controls, with only minimal impairment in recalling facts and incidents from their lives and actually performing better than the controls in the recall of famous news events. They performed significantly better than the Korsakoff patients across all three measures, and this difference requires further consideration. Although more than 90% of the irradiation dose in the pituitary patients affected diencephalic structures, small portions of the antero-medial temporal lobe region and the infero-medial frontal lobes may also have been caught by a lesser degree (30% to 40%) of irradiation [17] but, otherwise, their cerebral cortex should have been largely spared. By contrast, Korsakoff patients show pathological changes particularly affecting the frontal lobes [18, 58], and, in the present study, there were MRI and PET findings indicative of a moderate degree of frontal atrophy [28] and hypometabolism in the group as a whole. In a previous investigation, performance on 'frontal' tests was a close correlate of remote memory scores in Korsakoff patients, accounting for 68% of the variance, compared with 21% of the variance predicted by anterograde memory measures [24, 25]. Hence, whilst the minor involvement of the medial frontal and anterior temporal regions may have influenced the mild impairment of the pituitary irradiation group on autobiographical memory measures, the more widespread frontal involvement in the Korsakoff group may have contributed to their severely impaired level of performance on all three remote memory tasks.

In this connection, the performance of the frontal lobe group is of great interest. On the news events task, the overall frontal lobe group closely matched the Korsakoff group in terms of the severity and pattern of their impairment. On the autobiographical incidents task, the frontal group were nearly as severely impaired as the Korsakoff group, but they did not show a temporal gradient. However, in the recall of personal semantic facts, the tractotomy patients performed much better than the Korsakoff group, and the focal lesion group showed a moderate impairment (Fig. 5). The frontal group's deficits on autobiographical incidents and news events are consistent with those of previous studies, which have demonstrated a correlation of remote memory performance with 'frontal' measures in Korsakoff and Alzheimer patients [24] or have revealed deficits in autobiographical or remote memory recall in other patients with focal frontal lesions [9, 31]. A possible way of interpreting the present findings would be to suggest that frontal lobe pathology does indeed produce an impairment in the strategic retrieval [36] of remote memories (hence the 'flat' curve for autobiographical incidents). Because personal 'facts' tend to be highly rehearsed and familiar, this retrieval deficit has a lesser effect (although perceptible) upon recall from personal semantic memory. We do not think that the frontal group's impairment on these tasks can be attributed to involvement of basal forebrain/hippocampal circuits because (i) the septal nuclei, the diagonal band of Broca, and the nucleus basalis appeared to be spared in all cases including the tractotomy patients (Fig. 1), and (ii) patients with basal forebrain lesions characteristically show sparing of remote memory [47, 63].

The temporal lobe lesion group showed a similar severity of deficit to the Korsakoff group across all three tasks. Compared with the healthy controls, the temporal lobe group also showed a statistically significant temporal gradient for news events and a trend in the same direction for personal semantic facts. However, on all three tasks, their temporal gradient was not so steep as that of the Korsakoff group, and this latter difference was statistically significant for the two autobiographical measures. At first sight, this might seem surprising as others have argued that temporal lobe patients have either a steeper gradient [43] or the same gradient [55] as Korsakoff patients. However, the relatively flat temporal gradient in our group was largely attributable to the herpes encephalitis patients, who had flatter gradients than the other temporal lobe patients for the recall of personal semantic facts and autobiographical incidents. These relatively flat temporal gradients, compared with the Korsakoff group, resembled those found on these same tasks in Alzheimer patients [23, 50, 54] who also have extensive temporal lobe pathology. The flatter gradient of Alzheimer patients compared with Korsakoff patients has previously been attributed to (i) semantic memory involvement in the Alzheimer group, affecting well-rehearsed or 'semanticised' early memories, and, perhaps less importantly, (ii) the heavy drinking in Korsakoff patients, particularly affecting recent memories [26, 50]. Similarly, in the herpes encephalitis group, semantic memory impairment (evident on the picture naming test) may have contributed to the relatively flat remote memory curve for early memories in this group [54, 61].

4. Experiment 2: recognition and cued recall

As described in the Introduction, our second analysis concerned the effects of cueing in recognition and word-completion versions of the News Events test. Previous studies [23, 45] have found that Korsakoff patients show a proportionately greater improvement than healthy controls in response to recognition or contextual cues on remote memory tasks, and this can be interpreted in terms of a retrieval deficit. Likewise, Warrington and McCarthy [64] found that a herpes encephalitis patient showed a substantial response to word-stem completion cues in a famous faces' task, relative to this patient's identification of past famous faces by free recall. In the present study, we hypothesised that our patients would show a disproportionate benefit from recognition memory or name completion cues, relative to healthy controls, on versions of the famous news events' test, and that frontal lesion patients would show greater benefit than patients with temporal lobe pathology.

4.1. Method

This study involved the same subjects over 30 years of age, used in the News Events' task in Experiment 1, and it was administered immediately following the free recall version of that test. The subjects completed a forced-choice recognition memory task, in which they were required to identify the correct event depicted from five plausible choices (cf. [23]). They were required to do this, whether or not they had just responded correctly to the free recall question. (No feedback had been given concerning their performance at the free recall task.) Half the subjects in each group (selected randomly) performed recognition testing on all the items in the News Events test, whilst the remaining subjects performed recognition testing on half the items and these subjects carried out a word-completion cued recall task on the remaining items. (This procedure enabled us to check that the items/subjects selected for the word-completion procedure did not differ in terms of difficulty/severity of impairment from the remaining items/subjects).

The word-completion task was performed on those items which involved a famous face, and it was modelled on a task employed by Warrington and McCarthy [64]. Subjects were asked to identify the name of each face depicted, and then they were cued visually with the forename and first letter of the surname for each person (e.g., Richard N____ for Nixon, Harold M____ for MacMillan) and were asked to 'complete' the name. Subjects were administered the name-completion cues, whether or not they had just given the correct name on free recall. Again, no feedback was given during the course of this experiment.

4.2. Results

4.2.1. Recognition memory

There was no significant difference across the total sample (or within the individual patient groups) in terms of percent recognition scores across the decades for those subjects who had performed the full recognition test and those subjects who had performed recognition testing on half the items only (main effect ($F(1,53) = 0.25$); interaction effect ($F(2,106) = 0.13$), both non-significant). Consequently, the percent recognition scores for each decade were pooled from all subjects for further analyses. Figure 6 compares recognition and recall memory scores across the four main groups (controls, Korsakoffs, frontal, and temporal lobe), the shaded areas representing recognition minus recall difference scores. The patient groups showed a disproportionate impairment in recall performance relative to recognition: comparing recall-/recognition proportion scores, there was a significant main effect of subject group ($F(3,49) = 6.62$, $P < 0.001$). Planned comparisons showed that the Korsakoff ($F(1,27) = 7.27$, $P < 0.01$), temporal lobe ($F(1,24) = 18.50$, $P < 0.0001$), and frontal ($F(1,28) = 6.95$, $P < 0.02$) groups each obtained significantly lower recall/recognition scores than healthy controls, but there were no significant differences between the patient groups. Similarly, in terms of absolute (mean) recognition minus recall difference scores, the total patient group showed a significantly greater benefit from recognition cues than did the controls ($t = 2.44$, df $= 51$, $P < 0.01$, 1-tailed). This was particularly the case in the temporal lobe group ($t = 3.04$, df $= 24$, $P < 0.01$, 1-tailed), but it was also true of the Korsakoff and frontal patients combined ($t = 1.87$, df $= 41$, $P < 0.05$, 1-tailed), and again there were no significant differences between the individual patient groups.

Uncued recall and cued recall for faces are shown in Fig. 7, where the cues were name-stems for completion. For uncued memory, there were highly significant differences across the groups, the three patient groups being severely impaired on this task compared with controls (main effect ($F(3,21) = 8.63$, $P < 0.001$)), consistent with the overall News Event findings. For cued recall this significant difference disappeared, the patient groups performing virtually as well as the healthy controls ($F(3,21) = 2.70$, ns). Consistent with these findings, there was a disproportionate impairment in uncued/cued scores in the patient groups ($F(3,21) = 9.61$, $P < 0.001$), contrast analysis showing that this was true of both the temporal lobe group ($F(1,11) = 28.0$, $P < 0.0001$) and a combined Korsakoff and frontal group ($F(1,17) = 4.55$, $P < 0.05$). In terms of absolute cued minus uncued difference scores, the total patient group showed significantly greater benefit from cueing than the controls ($t = 1.96$, df $= 23$, $P < 0.05$, 1-tailed): this was true of both the temporal lobe group ($t = 1.97$, df $= 11$, $P < 0.05$, 1-tailed) and a combined Korsakoff and frontal group ($t = 1.71$, df 17, $P = 0.05$, 1-tailed), and there were no significant differences between the patient groups.

Close inspection of the data in Fig. 7 indicates that the only patient group to show impairment on the cued recall task was the temporal lobe group. This was mainly accounted for by two herpes encephalitis patients who had unilateral left temporal lobe lesions and were severely anomic (see Background neuropsychological findings, above). Omitting these two anomic patients from the analysis, Fig. 7 indicates that the temporal lobe group performed as well on cued recall for famous faces as the other three subject groups. The mean scores for the two anomic patients on cued recall are also shown on Fig. 7, and were several standard deviations below the means of the other temporal lobe patients, although they had not differed significantly from the rest of the temporal lobe group in terms of their news events scores and actually performed better on autobiographical incidents (see next section).

4.2.2. Discussion

Analysis of the recall/recognition and the uncued/cued findings, both in terms of proportions and absolute differences, indicated differential benefits from cueing in the patient groups. These benefits from recognition testing and cueing were evident across all three patient groups. They are unlikely to be attributable to a ceiling effect on recognition in the control group, because they were also obtained in an earlier Korsakoff and Alzheimer study [23], in which the controls were not so close to ceiling. Although the Korsakoff finding was not so strong as in the earlier study, that mainly reflects the greater number of data-points collected in that study. As emphasised previously [23], any benefit from retrieval cues for

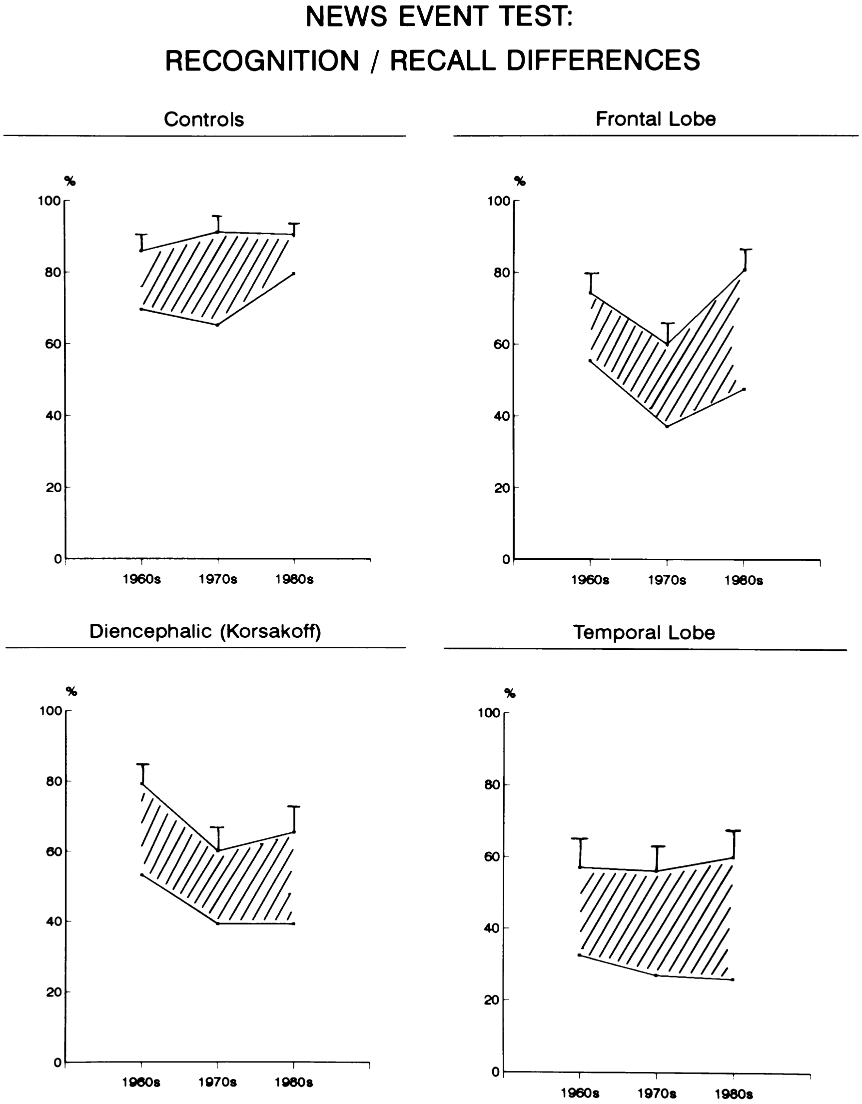

Fig. 6. Mean scores of the subject groups (aged over 30 years) on news event recognition, compared with recall scores. Shaded areas = recognition minus recall difference. Error bars = ± 1 SE for recognition scores.

memories long preceding the onset of an amnesic or dementing syndrome must indicate a retrieval or access component to the deficit in free recall.

The cued recall finding is consistent with Warrington and McCarthy's [64] original observation in a single patient. Similarly, Eslinger et al. [11] found that a patient with right-sided temporal lobe pathology from herpes encephalitis was able to respond to name-completion cues on a famous faces task. However, Eslinger et al. [11] also found that a herpes encephalitis patient with left inferior and antero-medial temporal lobe damage could not respond to the cues, similar to our two anomic patients. In the present investigation, the most striking feature was the marked benefit from cues, occurring across all the patient groups with the sole exception of the two anomic patients. All three patient groups showed a response to cueing, the main difference between the groups being that the temporal lobe group showed the poorest initial level of 'free recall' performance. Squire et al. [57] have presented findings from two patients to argue that making name-completion cues more difficult attenuates the beneficial effects, and it is plausible that more difficult cues presented to our subjects might have produced a lessened effect. Nevertheless, given the severe retrograde amnesia across all these patient groups, the response to cueing remains very striking, as also is the failure of the two anomic patients to show a response to lexical-semantic cues.

5. Experiment 3: are there left/right hemisphere dissociations?

As discussed in the introduction and elsewhere [26], disproportionate impairment of remote factual infor-

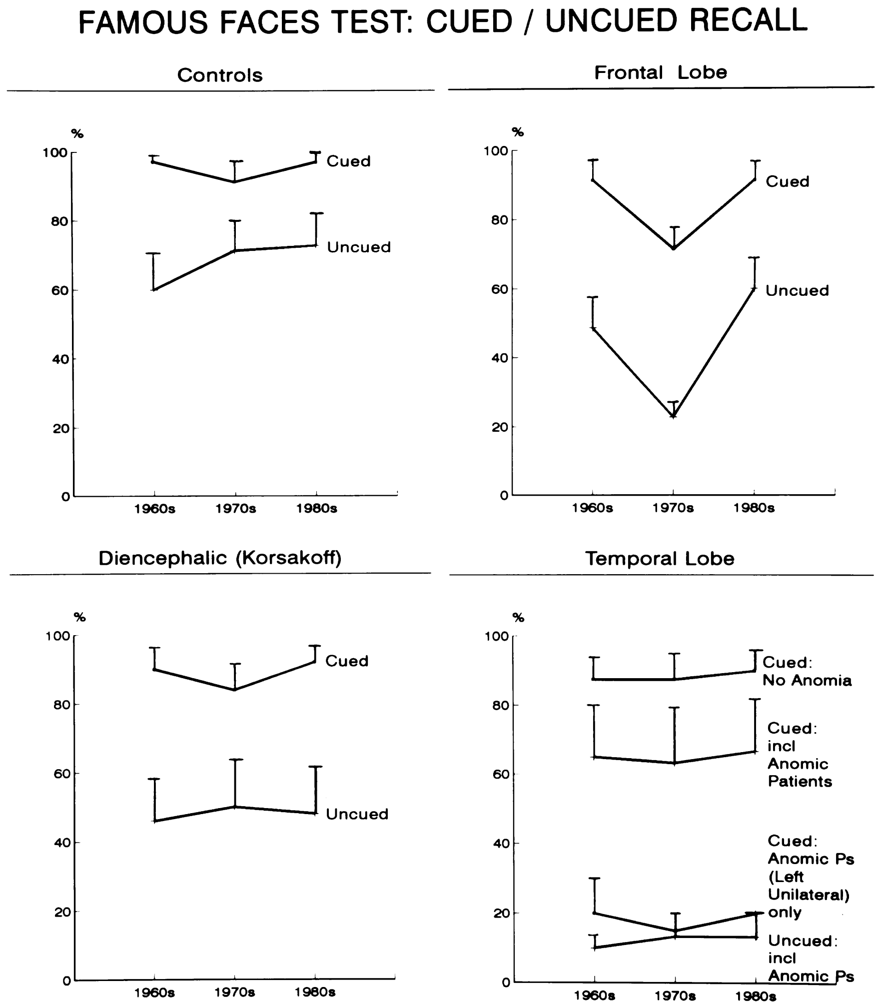

Fig 7. Mean scores of the subject groups on (a) uncued and (b) cued (word-completion) recall of famous faces. Error bars = ± 1 SE.

mation or of autobiographical memory has been related to left and right temporal lobe pathology, respectively [8, 41, 42]. Within the frontal lobes, Della Sala et al. [9] found that bilateral lesions were most likely to produce autobiographical memory deficits; and this finding is consistent with the postulated role of (bilateral) frontal pathology in producing impaired retrieval from remote memory in Korsakoff and Alzheimer patients [24, 25]. The hypothesis concerning left/right temporal lobe dissociations in retrograde amnesia arises from isolated case-reports [26], and even the Della Sala et al. [9] study of frontal lesions involved only four cases of bilateral damage. Consequently, the present study provided an excellent opportunity to examine these hypotheses, because our patients had been selected for having relatively focal lesions producing anterograde memory impairment, but they had not been selected for the presence or absence of any particular pattern of retrograde amnesia. It was hypothesised that the patients with relatively focal right temporal lesions would show disproportionate impairment on the autobiographical incidents schedule of the AMI, whereas patients with left temporal lesions might show a disproportionate impairment of factual knowledge on the Famous News Events task and the Personal Semantic schedule of the AMI. Secondly, it was hypothesised that patients with bilateral frontal damage might show a disproportionate impairment across remote memory tests, compared with patients who had unilateral frontal damage.

5.1. Method

T1 and T2 weighted MRI images from the patients in the frontal lobe and temporal lobe groups were examined by DK, a Consultant Neuroradiologist at the National Hospital, Queen Square, London, who was blind to any knowledge of the patients' cognitive test scores. They were also categorised independently as left/right/bilateral lesions by MDK. Moreover, detailed descriptions of the lesions were available from Dr B. Kendall, Consultant Neuroradiologist, National Hospital. In practice, it was very easy to group the MRI findings in terms of left/right lesions, and there was 100% agreement between DK and MDK in terms of the classification below.

The frontal tractotomy patients all showed bilateral damage, involving an extensive region of frontal oedema surrounding small areas of radio-necrosis around the yttrium rods. However, the cortical margins were always spared (Fig. 1A). The remaining six patients, who had focal frontal lesions, were sub-divided into two patients with bilateral focal frontal lesions (Fig. 8a), three patients with right unilateral frontal lesions (Fig. 8b) and one patient with a left unilateral frontal lesion. Because of the small sample sizes, we pooled the data from the tractotomy and bilateral focal frontal subgroups into a 'bilateral' group, and we merged the left and right lesion subjects into a 'unilateral' group for statistical analysis.

The T1 and T2 weighted MRI images from the patients with herpes encephalitis were also sub-divided according to the laterality of hemisphere involvement. Six of these patients showed widespread pathology in one temporal lobe, involving the anterior, lateral, medial, and inferior temporal cortex, with a much lesser degree of involvement (usually antero-medial) in the opposite temporal lobe. For the present purposes, these patients were categorised as three with 'predominantly right' (Fig. 9a) and three with 'predominantly left' (Fig. 9b) temporal lobe pathology. In addition, there were two patients in whom there was left unilateral temporal lobe involvement with negligible changes in the opposite hemisphere (Fig. 9c). There was one other patient with a clinical diagnosis of herpes encephalitis who showed only bilateral atrophy on MRI scan, and she was grouped with the five patients who had CT or EEG evidence of bilateral temporal lobe changes following anoxia or epilepsy to produce a group of six 'bilateral' patients, although it should be emphasised that the degree of pathology visible on MRI scan in these patients was considerably less than in the herpes encephalitis patients.

Cognitive findings from Experiment 1 were re-analysed in terms of these classifications. As we were interested in hemisphere differences in this part of the study, rather than temporal gradients, data from subjects under 30 years of age were included for all analyses. Because of the small size of the samples, non-parametrical statistical analyses (Kruskal–Wallis H; Mann–Whitney U) were carried out in addition to parametric. For non-parametric analyses, 'main effects' were calculated in terms of total scores on each task, and interactions in terms of difference scores between the earliest ('childhood', 1960s) and most recent ('recent', 1980's) time-periods on each task. Findings for non-parametric analyses were entirely consistent with parametric except where specified below.

5.2. Results

5.2.1. Frontal lobe groups

Findings on the *autobiographical incidents* schedule in the bilateral and unilateral groups are shown in Fig. 10a. In this analysis, the bilateral group comprised the combined tractotomy and bilateral focal lesion groups, who were the two poorest performing subgroups across each data-point. Comparing the healthy controls, bilateral frontal, and unilateral frontal groups, there was a significant main effect of groups ($F(2,32) = 14,73$, $P < 0.0001$). Contrast analysis revealed that both the

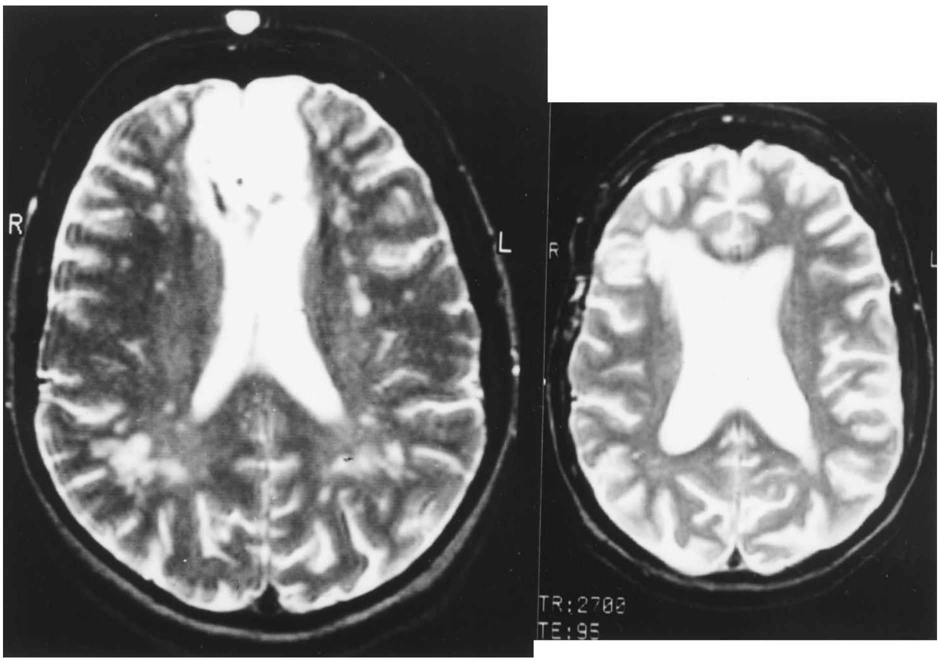

Fig. 8. Axial MRI views of patients with (a) bilateral and (b) right unilateral focal frontal lesions (both vascular).

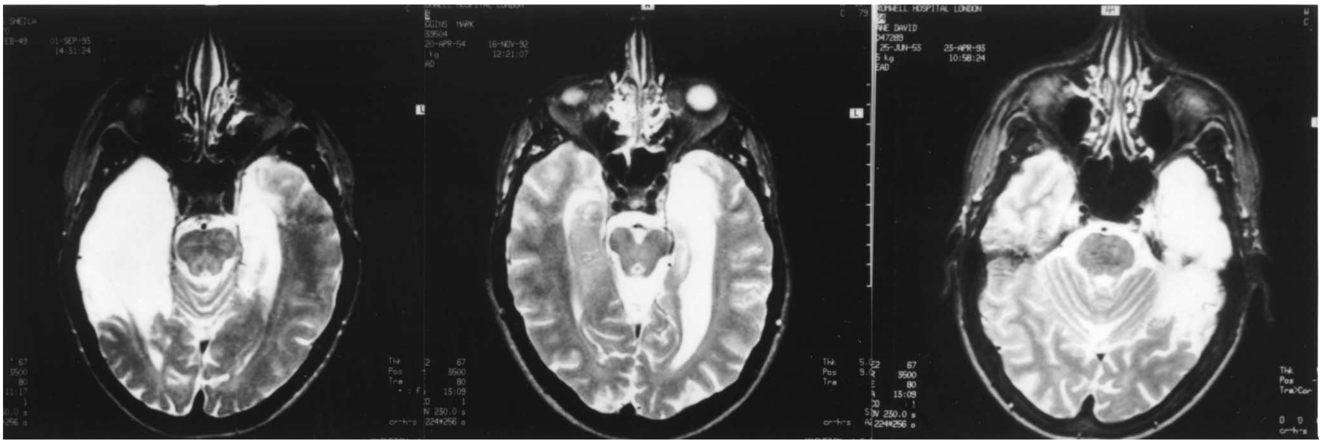

Fig. 9. Axial MRI views of patients with (a) predominantly right-sided, (b) predominantly left-sided, (c) unilateral left-sided pathology (all herpes encephalitis).

bilateral ($F(1,29) = 28.00$, $P < 0.0001$), and the unilateral groups ($F(1,22) = 6.03$, $P < 0.025$), performed significantly worse than controls, but did not differ significantly from each other ($F(1,13) = 1.21$). Figure 10b shows that, for the recall of *famous news events*, the bilateral group again performed poorest at each data-point, and the groups differed significantly ($F(2,31) = 10.27$, $P < 0.0005$). There was also a significant group X delay interaction effect ($F(4,62) = 4.80$, $P < 0.002$). In this case, the bilateral group differed significantly from the control group in terms of both main effect ($F(1,28) = 18.50$, $P < 0.00025$), and interaction effect ($F(2,56) = 6.50$, $P < 0.005$), and differed significantly from the unilateral group in terms of main effect ($F(1,13) = 10.01$, $P < 0.005$), whereas the unilateral group did not differ significantly from controls in terms of the main effect ($F(1,22) = 0.14$). For *personal semantic facts* (not shown), there was a main effect of group ($F(2,32) = 6.22$, $P = 0.005$), the patients with the bilateral focal lesions performing poorest. The bilateral group ($F(1,29) = 5.41$, $P < 0.05$) and the unilateral group ($F(1,22) = 9.85$, $P < 0.01$), both differed significantly from the controls in terms of the main effect but, in this case, they did not differ significantly from each other ($F(1,13) = 0.93$].

5.2.2. Temporal lobe groups

Figure 11a shows that all temporal lobe patients in whom there was some degree of bilateral pathology performed poorly on *autobiographical incidents* (more than two standard deviations below healthy subjects at all

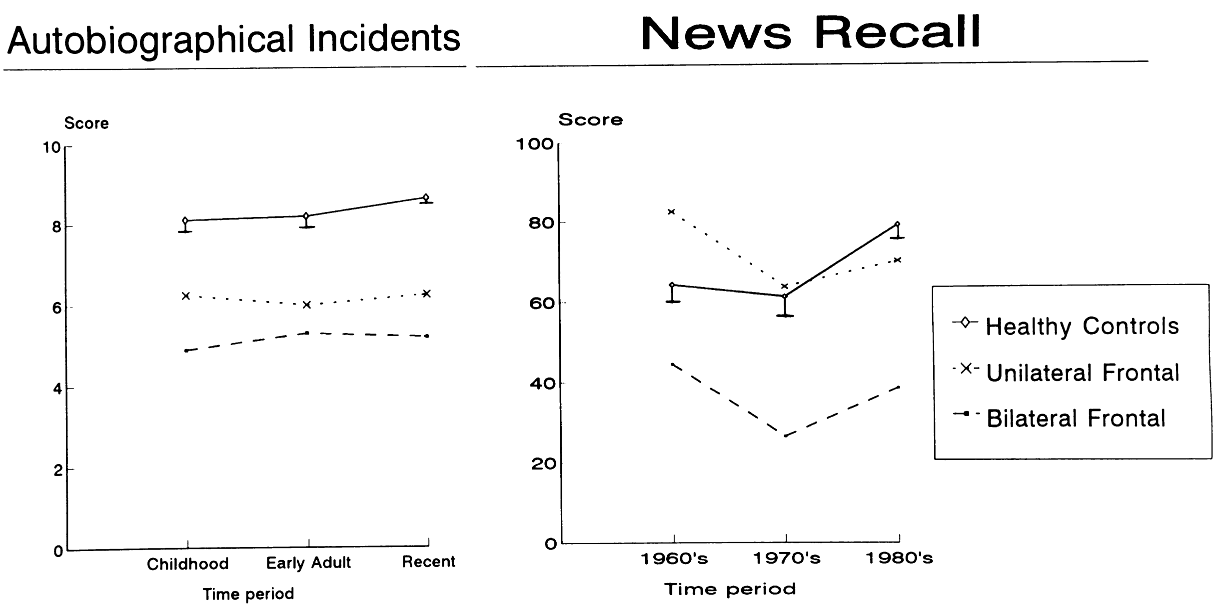

Fig. 10. Mean scores of the healthy controls, bilateral (BL) frontal, and unilateral (UL) frontal groups on (a) autobiographical incidents, and (b) news events. Error bars = ±1 SE. for controls. SD's (controls as Figs 3 and 4): (a) BL: 2.8, 2.9, 2.9, UL: 2.8, 2.0, 1.4; (b) BL: 24.3, 21.2, 21.1, UL: 17.1, 32.0, 21.6.

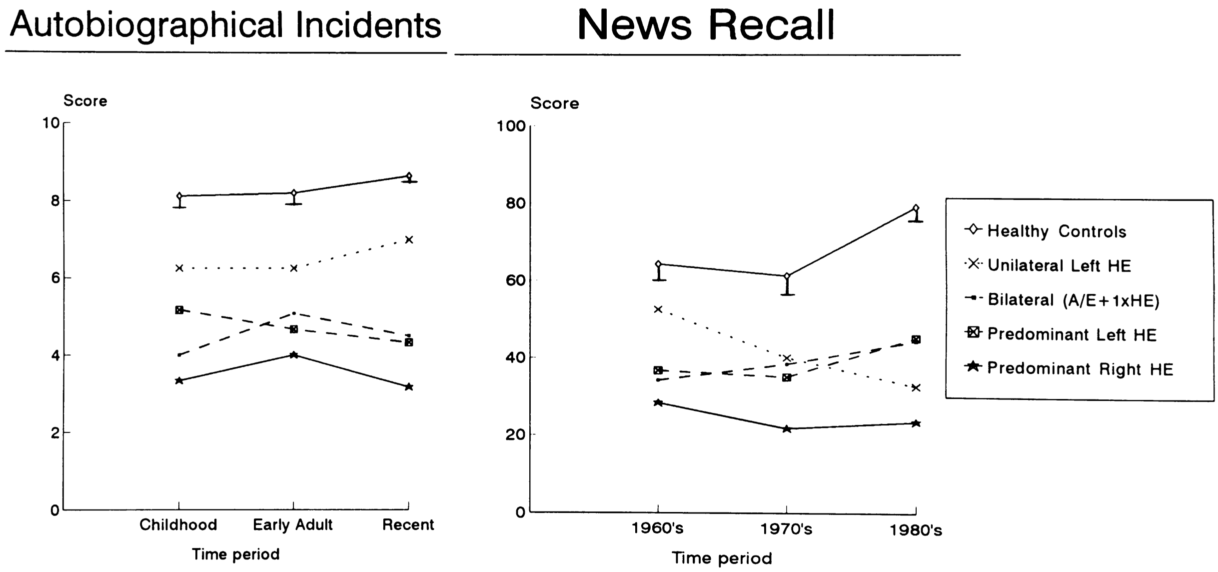

Fig. 11. Mean scores of the healthy controls, unilateral left (ULL), predominantly right (PR), predominantly left (PL) and bilateral (BL) groups on (a) autobiographical incidents, and (b) news events. HE = herpes encephalitis. A/E = anoxia/epilepsy. Error bars = ±1 SE for controls. SD's (controls as Figs 3 and 4): (a) ULL: 0.4, 1.8, 0.7, PR: 2.3, 0.9, 3.5, PL: 3.2, 3.1, 0.8, BL: 3.8, 2.5, 2.7; (b) ULL: 45.9, 35.3, 38.9, PR: 14.4, 2.9, 10.4, PL: 7.6, 5.0, 20.0, BL: 23.1, 27.0, 32.5.

data-points), with the 'predominantly right' herpes encephalitis performing worst. There was a highly significant main effect of groups ($F(4,29) = 14.01$, $P < 0.0001$), and a planned contrast between the 'predominantly right' group and healthy controls gave a highly significant main effect ($F(1,21) = 27.61$, $P < 0.001$). On the other hand, the unilateral left herpes encephalitis group did not differ from the controls in terms of either the main ($F(1,20) = 2.75$), or interaction effect ($F(2,40) = 0.02$), but this group did differ significantly from the predominantly right herpes encephalitis group in terms of the main effect on the parametric analysis ($F(1,3) = 4.91$, $P < 0.05$) with a trend in the same direction on non-parametric analysis ($U = 0.0$, $P = 0.10$). On the recall of *famous news events*, Fig. 11b shows that the 'predominantly right' herpes encephalitis group again performed worst, approximately two standard deviations below healthy subjects for memories from the 1960's and 1970's and well below two standard deviations for memories from 1980's. There was a highly significant main effect of groups ($F(4,29) = 5.76$, $P < 0.002$), and contrast analysis showed that the predominantly right group differed significantly from controls in terms of the main effect ($F(1,21) = 12.82$, $P < 0.002$). The unilateral left herpes encephalitis group again showed relative sparing of early memories, scoring within one standard deviation of healthy subjects for memories from the 1960's and 1970's, but performed poorly for memories from the 1980's: contrast analysis revealed that they did not differ significantly from the controls in terms of main effect ($F(1,20) = 3.28$, ns), but they did so in terms of the subgroup by decade interaction effect ($F(2,40) = 5.31$, $P < 0.01$). In terms of *personal semantic facts*, the four patient subgroups performed much more closely to one another. There was a significant overall main effect ($F(4,29) = 20.84$, $P < 0.0001$) but, when the controls were excluded from the analysis, there was no significant difference between the patient groups ($F(3,10) = 0.23$).

5.2.3. *Memory for faces*

We also examined whether the differences between the left and right unilateral temporal lobe groups on news event recall were partially accountable in terms of differing performance between those news event items in which a famous face was prominent and those items not containing a famous face (items subdivided as for Experiment 2). The combined unilateral and 'predominantly left' temporal lobe groups identified 43.3% of news events correctly where a famous face was involved, against 38.0% of 'non-face' news events; whereas the 'predominantly right' group correctly identified 17.8% of 'face' news event items against 31.1% of 'non-face' news event items. This difference just failed to reach statistical significance (group by face interaction ($F(1,6) = 5.25$, $P = 0.06$]. On the basis that previous studies [24, 31], as well as this one, have shown that frontal pathology can impair recall of famous faces or news events, we included the left and right unilateral frontal cases in the analysis: when this was done, the difference became statistically significant (left lesions: 51.1% face items correct vs 41.1% non-face items; right-sided lesions: 44.5% vs 51.7%; ($F(1,10) = 9.01$, $P < 0.02$)).

5.2.4. *Incident recall vs cued naming*

Finally, we contrasted the performance of the unilateral left and predominantly right temporal lobe groups in terms of autobiographical incident recall (Experiment 3) and cued recall of the names of famous faces (Experiment 2). As mentioned above, on the autobiographical incidents task, the right lesion group performed significantly worse than the unilateral left group ($F(1,3) = 4.91$, $P < 0.05$). By contrast, on cued name-completion, the left unilateral group performed significantly worse than the right lesion group ($F = 146.42$, $P < 0.001$). (Consistent with this, on non-parametric analysis, the right lesion group performed significantly worse than the controls on autobiographical incidents, $U = 0.0$, $P < 0.002$, but not on cued faces, $U = 4.5$, ns; whereas the left unilateral group performed significantly worse than controls on cued faces, $U = 0.0$, $P < 0.05$, but not on autobiographical incidents, $U = 4.0$, ns). In order to examine this further, we converted these subjects' scores on each task into Z-scores, based on the means and standard deviations for each measure in the control group. We then carried out a three-way group by task by time-period ANOVA. The main effect of group was not statistically significant, but there was a significant group by task interaction effect ($F(1,2) = 98.05$, $P < 0.01$), indicating the differing patterns of performance by the left and right lesion patients on the two tasks. There was also a significant group by task by time-period interaction ($F(2,4) = 12.45$, $P < 0.05$), resulting from the right lesion group showing a steeper temporal gradient on autobiographical memory than the left unilateral group did on cued name-completion.

5.3. Discussion

In summary, performance on the recall of famous news events in both patients groups tended to resemble that on the autobiographical incidents' schedule, whereas the sub-groups were more closely clustered in the recall of personal semantic facts. This suggests that the recall of news events does indeed entail an 'episodic' component and is not simply dependent upon retrieval from a well-rehearsed semantic knowledge system.

In the frontal groups, patients with bilateral focal lesions performed worst across all three tasks, and, for the 'episodic' measures (autobiographical incidents and news event recall), the frontal tractotomy group, also with bilateral lesions, were the second most impaired group. The bilateral frontal patients performed significantly worse than the unilateral frontal group on news events, and there was a trend in the same direction for autobiographical incidents (cf. [9]). It was also the case (not shown above) that the right frontal patients tended to perform worse than the single patient with a left frontal lesion, consistent with the purported role of the right frontal lobe in memory retrieval processes [52, 59]. However, the left frontal lobe must interact with the right frontal region in important ways in the retrieval of remote or autobiographical memories, because patients with bilateral frontal lesions performed worst on these tasks.

Within the temporal lobe groups, right-sided lesions were more damaging than left-sided lesions on 'episodic' memory tests (autobiographical incidents and news events), and there was suggestive evidence that bilateral lesions have a more profound effect upon remote memory than do unilateral lesions. The 'predominantly right' herpes encephalitis group, who had pathology throughout the right temporal lobe and in the medial or antero-medial aspects of the left temporal lobe, performed worst on 'episodic' memory tests. The other two groups with bilateral pathology (labelled 'bilateral' and 'predominantly left') were also severely impaired on these tasks, whereas the two patients with left unilateral temporal lobe damage showed relative (although not absolute) sparing, particularly of early memories. On the other hand, all temporal lobe patients were severely impaired at personal semantic memory and their scores were clustered quite closely together. None of the laterality findings could be explained in terms of lesion size or IQ or MQ differences.

Pooling the results from the frontal and temporal lobe patients, we found that patients with right-sided lesions performed particularly poorly on news event items involving a famous face, consistent with the view that the right hemisphere is critical to certain aspects of visual processing or mental imagery [41, 42] or to knowledge of people [11], and that impairments in visual imagery may be particularly damaging to the retrieval of remote episodic or autobiographical memories [41, 42]. However, the findings also suggest a concomitant contribution from left hemisphere pathology in patients with bilateral lesions. Consistent with the latter observation, the two patients with unilateral left temporal lobe pathology showed a (non-significant) trend for impairment (compared with controls) in the recall of autobiographical incidents and a significant (group by time-period) interaction effect for the news event task.

Although we did not obtain the double dissociation we had originally hypothesised (in terms of a contrast between autobiographical incidents on the one hand, and news events or personal semantic memory on the other), there was a statistically significant double dissociation between tasks involving an episodic memory component (autobiographical incidents, recall of famous news events) and tasks involving a lexical-semantic component (cued recall for the names of famous faces). Whilst the 'predominantly right' temporal lobe group showed very severe impairment on 'episodic' remote memory tasks (autobiographic incidents and famous news events), they showed a good response to cueing in naming famous faces (Experiment 2). On the other hand, the unilateral left temporal lobe patients showed relative sparing on the episodic remote memory tasks and severe impairment on the cued recall (name-completion) version of the famous faces task (Experiment 2).

6. General discussion

Patients who had received irradiation to the diencephalon as well as surgical treatment of pituitary adenomas showed spared performance on remote memory tasks despite severe impairments on anterograde memory measures (a 49-point discrepancy between WAIS-R and WMS-R quotients in one of these two patients). This finding is consistent with those previous studies which have demonstrated brief or absent retrograde amnesia in patients with either focal diencephalic or basal forebrain pathology [15, 20, 55, 63, 66]. A review of these findings [26] suggested that isolated limbic-diencephalic lesions generally produce a relatively brief period of retrograde amnesia, three years or less. In contrast, Korsakoff patients, who have some degree of frontal atrophy and hypometabolism as well as diencephalic pathology, show an extensive remote memory loss. A previous study indicated that this extends back 25 years or more [23], and the present findings are consistent with this. As in previous studies [24, 25], we found that the Korsakoff group showed a retrieval component to the deficit as well as a striking 'temporal gradient' across all measures i.e., relative sparing of early memories.

The contribution of the frontal lobes to retrieval from remote memory has been corroborated in other studies of patients with focal frontal lesions [3, 9, 31], each of which employed a single measure of either autobiographical or remote memory in a small group of patients with frontal lobe lesions. The present investigation establishes that patients with focal frontal lesions, including patients whose lesions have arisen only very recently (the frontal tractotomy group), show impairment in the recall of both autobiographical incidents and famous news events, and that this was comparable in severity with that seen in patients with Korsakoff's syndrome or temporal lobe lesions. Bilateral frontal lesions were more damaging across all measures than unilateral lesions (a significant difference on news events and a trend on autobiographical incidents) and, within our small groups, the patients with right frontal pathology performed worse than a patient with left frontal pathology. In brief, these findings confirm that focal frontal lesions can indeed produce deficits across a number of remote memory tasks, and the findings are consistent with the view that bilateral frontal pathology may make a major contribution to the remote memory impairment of Korsakoff patients [24, 61]. However, it has also to be acknowledged that there were differences in the pattern of impairment across the frontal and Korsakoff groups: the frontal patients were less severely affected on personal semantic memory and their temporal gradients were generally flatter. As discussed above, this may have resulted from frontal lobe pathology primarily affecting the more strategic aspects of retrieval processes [36], and the combination of frontal and diencephalic pathology (in Korsakoff patients) may have a more detrimental effect than either in isolation.

Patients with temporal lobe pathology showed an extensive retrograde amnesia of comparable severity to that of Korsakoff patients, although they showed a 'flatter' temporal gradient. This flatter gradient resulted from a more severe impairment of early memories in the herpes encephalitis patients, which may in turn result from semantic memory being implicated in this group. There was a double dissociation, whereby patients with predominantly right temporal lobe pathology showed disproportionate impairment on 'episodic' remote memory tasks (the recall of autobiographical incidents and famous news events), whereas patients with unilateral left temporal lobe lesions showed disproportionate impairment in cued-recall of the names of famous faces. The right-sided group was particularly impaired in identifying news events in which a famous face was prominent, although this did not fully account for their deficit, and we suggest that this is consistent with the view that certain aspects of visual imagery or processing are particularly critical for the retrieval of remote 'episodic' memories.

The patient groups showed a disproportionate, and absolutely greater, impairment in recall scores, relative to recognition, on the famous news events test compared with healthy subjects, consistent with previous observations in Korsakoff and Alzheimer patients [23]. Even more striking was the 'intact' performance of all patients on a cued recall task for the names of famous faces, with the sole exception of the two anomic (left unilateral) patients in the temporal lobe group. Taken together, these findings indicate an important retrieval or access component to the remote memory deficit in these patient groups.

With regard to our opening predictions:

(i) When we examined diagnoses within the main lesion groups, the only important difference was between the pituitary irradiation group and the Korsakoff group, consistent with the view that focal diencephalic pathology gives rise to a brief (less than 3 years) or absent retrograde amnesia, whereas widespread frontal and/or temporal cortex pathology produces a temporally extensive impairment.

(ii) The severity of impairment was comparable for the Korsakoff and frontal groups on the autobiographical incidents and news events' task, consistent with there being a common, underlying retrieval deficit, but the frontal group was less severely affected at personal semantic memory and their temporal gradients were generally flatter. This was attributed to the frontal lobes particularly affecting the more strategic components of retrieval, as well as to combined frontal-diencephalic damage being worse than frontal alone.

(iii) Within the present study, only minimal differences in performance were found between the frontal lobe and the temporal lobe groups. The severity of their impairment was comparable for autobiographical incidents and news events, and they did not differ significantly in terms of temporal gradient on any of the tasks. Findings from the recognition and cued recall experiments were suggestive of a retrieval/access problem across all the patient groups and, in particular, the frontal and temporal groups did not differ overall on these tasks. Taken together, these findings suggest that both the frontal and temporal cortex both make important contributions to the networks involved in the storage and retrieval of remote memories, and that assumptions of functional separation between them on the basis of storage (temporal) versus retrieval (frontal) are unsupported.

(iv) Bilateral pathology was generally more damaging than unilateral (this difference being statistically significant for the frontal group's news event result), but we did not obtain our hypothesised right/left double dissociation between autobiographical incident recall and news events/personal semantic memory. It seems that the recall of famous news events involves an episodic memory component, and there was a statistically significant double dissociation between tasks involving episodic remote memory (autobiographical incidents, famous news events) and those with a lexical-semantic component (cued recall for the names of famous faces). Right temporal (and possibly right frontal) lobe lesions particularly damaged the retrieval of past episodic (incident and event) memories, whereas left temporal pathology caused impairment in the lexical-semantic labelling of remote memories.

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