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California Verbal Learning Test: performance by patients with focal frontal and non-frontal lesions

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Summary

Although frontal lobe lesions do not cause classic amnesia, they may disrupt learning and memory in a number of ways. To investigate in finer detail the regions of frontal injury that are associated with impaired learning and to define the cognitive processing deficits specific to each region that disrupt memory, we compared 33 patients with focal frontal injury with patients with non-frontal injury and with normal controls on a standard neuropsychological instrument, the California Verbal Learning Test (CVLT). Subgroups of patients with distinct lesion site profiles were compared in a number of learning measures. All of the subgroups of patients with frontal lesions (with one exception) had inefficient learning due to poor implementation of a strategy of subjective organization. Despite this organizational deficiency, the performance of patients with frontopolar lesions normalized across trials. Only the subgroups with lesions centred either on the left posterior dorsolateral frontal region or the posterior medial frontal region had overall impaired learning and recall. The left posterior dorsolateral frontal group was most significantly impaired on all measures. This recall impairment was secondary to a mild lexical–semantic deficit. A recognition memory deficit in the same group was due to an abnormal response bias. Several groups had a modest increase in perseverative recalls; the underlying mechanisms differed. Disruption of different cognitive processes associated with specific frontal regions underlies the varied patterns of memory impairment. This study has demonstrated even finer differentiations within the frontal region than previously known.

Keywords: list learning; memory; frontal lobe; recognition memory; strategic deficits

Abbreviations: AMF = anterior medial frontal; ant. LDF = anterior left dorsolateral frontal; ant. RDF = anterior right dorsolateral frontal; CART = Classification and Regression Tree; CVLT = California Verbal Learning Test; LNF = left non-frontal; NART-R = National Adult Reading Test—Revised; PMF = posterior medial frontal; post. LDF = posterior left dorsolateral frontal; post. RDF = posterior right dorsolateral frontal; RNF = right non-frontal

Introduction

Patients with purely frontal lesions do not have classic amnesia. Damage in the frontal lobes in humans may, however, result in a variety of memory impairments, such as loss of source memory (Janowsky *et al*., 1989*b*; Johnson *et al*., 1993), disturbed memory for temporal order (Butters *et al*., 1994) and other complex aspects of memory that are sometimes considered metamemory or the 'use' of memories (Moscovitch, 1992). These deficits are secondary to defects in one or more executive functions, such as attention, working memory, strategy formulation, inhibition of competing recollections, and monitoring ongoing mental activity.

There is controversy about the extent of impairments that patients with frontal lobe lesions show in straightforward learning tasks that call for an uncertain amount of executive function. Group studies are required to determine possible regional differences in the effects of frontal damage. Of the few group studies reported, most have amalgamated lesions in all frontal regions into a single frontal group to be compared with a non-frontal group. Others have been assembled from patients of convenience in a particular clinic and have poorly represented the range of frontal regional injury. Most investigations of this question have used

list-learning tasks, an appropriate approach, but with rare exceptions (Janowsky *et al*., 1989*a*; Eslinger and Grattan, 1994) the lists were idiosyncratically crafted to explore particular hypotheses about frontal lesions and memory. The traditional neuropsychological instrument that has been most studied is the Rey Auditory Verbal Learning Test, which consists of 15 unrelated words. Eslinger and Grattan (1994) and Janowsky *et al*. (1989*a*) found poor performance on the Rey test in heterogeneous groups of patients with frontal injuries. Both groups attributed poor performance primarily to poor subjective organization during encoding of the lists. In a previous report, we analysed the performance of patients with frontal lesions, grouped *a priori* by coarse regional differences, on an experimental list that was categorized and unblocked (Stuss *et al*., 1994), i.e. the items are from a small group of semantic categories but the words are presented pseudorandomly so that items from the same category are not presented sequentially. There were regional differences in recall, recognition and error types. Poor subjective organization accounted for only a portion of the impairment. Failure to take advantage of the potential for semantic categorization did not contribute to poor performance.

We report the results of a new group of patients with frontal lesions, who had well-defined and limited focal injury in a wide range of discrete regions. These patients were compared with patients with non-frontal lesions and with normal controls on a standard presentation of the California Verbal Learning Test (CVLT), another neuropsychological test of learning and memory that is widely used in clinical neurology. The CVLT differs from the Rey Auditory Verbal Learning Test in that it is a categorized, unblocked list.

There were two goals for this research: to confirm the distinctive profiles of memory impairment associated with different regions of frontal injury using a previously unexamined test (CVLT), and, if confirmed, to extend our previous analysis of the effects of regional frontal injury on verbal learning. If performance on the CVLT is comparable to performance on the other list-learning tasks, combining results reported on standard instruments (e.g. Eslinger and Grattan, 1994) and experimental ones (e.g. Stuss *et al*., 1999), four predictions can be made: (i) only lesions in a subset of frontal regions will impair recognition; (ii) patients with frontal lesions of all locations will have poor recall due to deficits in secondary memory and subjective organization; (iii) failure to demonstrate semantic clustering during recall will not account for these impairments; and (iv) patients with right dorsolateral lesions will have increased intra-list repetitions of recall.

Methods

Patients were selected according to the following inclusion criteria: (i) the aetiology was an acute event—infarction, haemorrhage, traumatic contusion or resection of a benign tumour; (ii) they were at least 2 months after onset (one exception was 1.8 months) and had completely recovered from any acute-phase complications; and (iii) CT or MRI scans were available showing lesions entirely in frontal structures or entirely in non-frontal structures. Patients were all fluent English speakers. By report, some of the patients had been mildly aphasic in the acute phase of injury, but none of the patients were overtly aphasic at the time of testing. All had fluent grammatical output without paraphasias, with normal word and sentence repetition and normal auditory comprehension. Some had mild deficits in confrontation naming. They were excluded for uncorrected hearing loss, recent seizures, untreated hydrocephalus, history of alcoholism, symptomatic depression or prior unrelated neurological illness. A total of 33 patients with frontal and 11 with non-frontal patients fitted our criteria for study inclusion (see below for lesion groupings).

A control group of 14 normal volunteers with no history of neurological disease, psychiatric disorder or alcoholism were recruited as controls. They were matched to the patient group for gender, age and education. The study was approved by The University of Toronto/Baycrest Centre research ethics committee. Each participant was fully informed of the project and signed consent was obtained.

Experimental measures

The CVLT was administered by the standard method (Delis *et al*., 1987). Performance was measured as prescribed in the standard clinical manner, and additional probes were implemented to measure various specific memory processes not routinely assessed by clinical scoring.

Immediate free recall

The CVLT consists of two different lists of words (A and B), each list composed of 16 words, four words from four different catagories presented in a pseudo random manner. List A is presented five times, List B once immediately after List A fifth presentation recall.

For list A, the following measures were obtained: number correct for each of the five trials and total correct for all five trials summed. For list B, the total correct was noted for the single presentation. The direct comparison of list A, first trial, with list B assesses proactive interference.

Primacy and recency for recall were scored according to the CVLT standards: primacy (first four items); middle (interior eight items); recency (last four items). Primary memory is the total recall of words for which the intra-trial retention interval was seven words or fewer. Secondary memory is the total recall of all words with intra-trial intervals greater than seven (Tulving and Colotla, 1970). The intra-trial retention interval is the total number of words interpolated between presentation of a word and recall, including words presented after the word or recalled before the word.

Recognition performance

Recognition was assessed by performance on the target/distractor items at 20 min delayed recall. The CVLT discriminability and response biases were calculated. Hits, false alarms, and hits minus false alarms were also measured.

Delayed recall

For both immediate and long delay, correct words were measured in both free and cued recall conditions.

Errors and efficiencies

(i) Intrusions are 'recalled' words that were not actually on the list. They were measured for free and cued recall, and divided into semantic intrusions (words that were semantically related to a target word) and non-semantic intrusions. (ii) Intra-list repetitions are repetitions of a word within the same recall trial. They can be immediate perseverations or double recalls, i.e. words separated by other items. This analysis was corrected for the total number of words recalled on a trial. (iii) Inconsistency is the failure to recall a word on a later trial when it had been recalled on an earlier trial. This analysis also controlled for the total number of words recalled. This measure is the converse of the standard CVLT consistency score.

Organization in free recall

(i) Serial order recall is the number of words recalled in the same order as presented. A proportional measure was obtained by dividing the number of serial order clusters by the theoretically maximal number of order clusters, which in turn depends on the total number of words recalled. (ii) Semantic organization is measured as the number of consecutively recalled words from the same semantic category. The control for the number of words presented was completed by calculating a ratio of repetition measures (Frender and Doubilet, 1974). In the CVLT, this measure is calculated using the total number of words recalled, including intrusions and perseverations. We also calculated the semantic organization score as proposed by Stricker *et al*. (2002) for comparison. (iii) Subjective organization was measured by Pair Frequency Analysis (Sternberg and Tulving, 1977). This measure, which adjusts for the number of words recalled, tabulates the number of word pairs recalled together from one trial to the next.

Imaging

All scans (CT or MRI) were converted to standard templates (Damasio and Damasio, 1989). For patients with frontal lesions, individual subregions were identified as involved or not according to templates and methods described and implemented previously (Stuss *et al*., 1995). All patients with non-frontal lesions were classified simply as 'left' or 'right'. Our goal was to isolate specific effects of lesions in different frontal regions on CVLT performance. Within the frontal lesion group, patients had various combinations of multiple regional damage. For each patient, imaging templates were examined for lesions in each area defined by Stuss *et al*. (1995), regardless of what other areas might also be involved.

Standard anatomical groupings can obscure more specific brain–behaviour relations. Our approach has been to use a modified case study group approach (Shallice, 1988; Stuss *et al*., 1994) in which patients are grouped by performance on a defined process, and the relation to lesion site is then sought. Using the architectonic divisions defined by Petrides and Pandya (1994) and superimposed on an adult human brain template, each architectonic region is identified for each patient as damaged or not. We then used a regression procedure, the Classification and Regression Tree (CART; Breiman *et al*., 1984), to identify the most precise and logical subgroups of lesions that had maximally separable performance on the primary measure. The total number of words recalled on all five trials of immediate free recall of list A of the CVLT was defined as the primary measure of memory. If a reasonable number of patients have pathology in regions of interest, then the relationship between a defined performance measure and each specific region can be calculated. This procedure splits a large heterogeneous lesion group into smaller discrete lesion groups that are homogeneous on the primary measure, avoiding *ad hoc* creation of regions of interest.

The CART analysis separated the frontal patients into five groups with distinct performances on the primary measure of list A total recall. There were 10 patients with left lateral lesions. The CART procedure separated them into two groups. The posterior left dorsolateral frontal (post. LDF) group ($n = 5$) was very homogeneous; one patient had only a large capsular–striatal lesion. In the group labelled 'anterior left dorsolateral frontal' (ant. LDF; $n = 5$) there was some involvement of medial polar areas, but all five patients had dorsolateral involvement generally centred a few centimetres anterior to the position in the post. LDF patients. The eight right dorsolateral frontal patients had lesions in dorsolateral structures, although four of the other eight had some involvement of medial structures. Each patient was assigned to a group based solely on the CART.

Although the original CART procedure did not distinguish two right frontal groups with distinctive performances on the criterion recall task, we divided the right dorsolateral frontal group into a posterior subgroup (post. RDF; $n = 5$) and an anterior subgroup (ant. RDF; $n = 3$) to create a parallel with the other frontal lesion groups. The anatomical parallels of the right and left dorsolateral groups are clear in Fig. 1. The majority of the 15 patients with medial lesions had bilateral lesions, which were symmetrical except as indicated in Table 1. One of the groups created by the CART analysis had lesions entirely restricted to the orbital and polar regions. None had septal lesions, any cingulate damage was very

anterior, and only two had modest dorsolateral damage. Thus, we consider this group to be anterior, medial and polar frontal, left, right or bilateral (anterior medial frontal, AMF; $n = 8$). The last group had a lesion distribution similar to that of the previous group, but the lesions were bigger, extending further in two directions. There was much more damage posteriorly along superior, medial structures. All seven had considerable cingulate damage. There was also septal damage in four of the seven. Thus, we consider this group to be anterior and posterior inferior medial and polar frontal, left, right or bilateral (posterior medial frontal, PMF; $n = 7$).

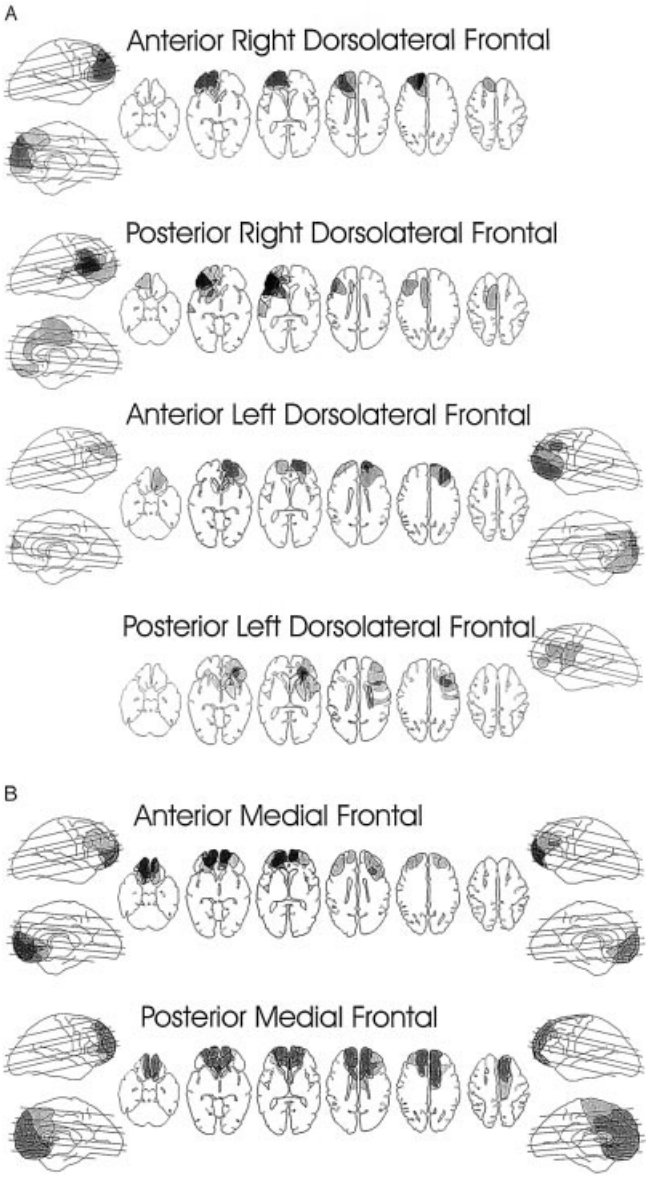

Fig. 1 Lesion overlaps of subjects within each of the six frontal patient groups. Selected axial slices and medial and lateral views are presented for each group. Anterior right dorsolateral frontal (right lateral involvement anterior to the posterior right dorsolateral group, with some involvement of medial polar areas) (ant. RDF); posterior right dorsolateral frontal (post. RDF); anterior left dorsolateral frontal (ant. LDF); posterior left dorsolateral frontal (post. LDF); anterior medial frontal (medial lesion entirely restricted to the orbital and polar regions) (AMF); posterior medial frontal (medial lesions with extension to more caudal medial areas, including septum) (PMF). Scans for the posterior patients (right non-frontal, RNF; left non-frontal, LNF) are not presented; scans for posterior lesioned subjects 2055, 1058, 2036, and 2054 were available for lesion documentation but not quantification. Descriptions of lesion locations for all patients are listed in Table 1.

The lesion overlaps in each patient group are displayed in Fig. 1 and the individual lesions are described in Table 1. We have labelled them by the dominant region involved. Not all patients had lesions in the cortex, so the cortical maps may under-represent the actual lesion extent. These groups have the maximally distinct profiles of performance on immediate free recall, but they are obviously less than perfectly distinct anatomically. The lesions of the groups do have different central foci, but there are individual patients within some of the groups with divergent lesions. Nevertheless, the groups constructed by performance on a cognitive test have reasonable anatomical coherence.

In summary, there were patients with right or left dorsolateral or with medial (unilateral or bilateral) frontal lesions, and each of these patient groups was further subdivided into those with more posterior or anterior lesions. That an independent statistical analysis of performance on a cognitive task generated five of these six groups and that the groups are generally coherent anatomically suggests that there are real differences in function within these groups. These six frontal subgroups were compared with two posterior lesioned control groups [right non-frontal (RNF; $n = 5$); left non-frontal (LNF; $n = 6$)] and one normal control group (note that the posteriors were not entered into the CART) in all subsequent analyses.

Lesion size was computed by superimposing the lesion from templates to a constant pixel diagram and counting the pixels. The lesion total was divided by the total pixel count for all axial slices, giving a measure of the percentage of the brain involved. The lesion location, lesion size and time after onset for each patient are presented in Table 1.

Results

For all analyses, only results exceeding $P < 0.01$ will be reported.

Neuropsychological measures

There were no significant group differences for the National Adult Reading Test—Revised (NART-R) or forward digit span. The effect on the Boston Naming Test approached significance [$F(7,49) = 2.5$, $P < 0.03$], the post. LDF group ($\bar{x} = 39.4$) being significantly worse than the control group ($\bar{x} = 55.5$). There was also a significant group effect on letter fluency (FAS) [$F(8,46) = 4.97$, $P < 0.001$]. The PMF ($\bar{x} = 28.5$), ant. LDF ($\bar{x} = 23.0$), post. LDF ($\bar{x} = 16.5$) and RDF

(ant., $\bar{x}$ = 30.7; post., $\bar{x}$ = 28.4) groups were all worse than the control group ($\bar{x}$ = 47.5).

CVLT measures

Immediate free recall

List A, total five trials (Fig. 2). Recall that this effect was used to define the study groups and is a creation of the CART procedure. There was a significant group effect [$F(8,48) = 5.62$, $P < 0.001$]. The post. LDF group performed the worst, all but the PMF, ant. LDF and post. RDF groups being significantly better. The CTL and RNF groups were also significantly better than the PMF and post. RDF groups.

List A, first trial. There was a significant group difference in the number of words recalled in the first trial [$F(8,48) = 5.62$, $P < 0.001$]. The post. LDF and PMF groups were impaired compared with the RNF and CTL groups; the ant. LDF and post. RDF groups were impaired compared with the RNF group only.

List A, trial by group (see Figure 3). There was a significant group effect [$F(9,48) = 7.85$, $P < 0.001$], a significant effect for trials [$F(3.3,192) = 57.31$, $P < 0.001$] and a significant group × trial interaction [$F(3.3, 29.7) = 2.1$, $P = 0.002$]. *Post hoc* analysis revealed that PMF and post. LDF were impaired compared with other groups. The RNF and CTL groups performed significantly better than the PMF and post. LDF groups on all five trials. AMF and ant. RDF had significantly higher scores than post. LDF on trials 2–5. The ant. RDF group was also significantly better the PMF group on trial 4. LNF was significantly better than post. LDF on trials 3–5. The LNF group primarily had problems on trial 1, having a significantly worse score than the RNF and CTL groups. Similarly, the ant. LDF group was significantly impaired compared with the RNF group on trial 1 only. AMF was better than PMF on trial 4. Post. RDF was impaired compared with RNF on trials 1, 2, and 4, the control group on trials 3 and 4, and the AMF group on trial 4. In addition to the deficits on individual trials, the post. LDF group had poor improvement over trials. There was a significant group difference in the learning slopes [$F(8, 48) = 2.9$, $P = 0.011$], the post. LDF group having the flattest curve ($\bar{x}$ = 0.42).

Primacy/recency and primary/secondary memory. There were no group differences in the standard CVLT measures for the serial position effect (primacy, middle or recency) when controlled for the number of words. There was also no group effect for primary memory (Sternberg and Tulving, 1977), but for secondary memory the group effect was significant [$F(8,48) = 7.73$, $P < 0.001$]. *Post hoc* analyses revealed essentially the same group differences as the overall free recall scores on list A.

List B. There was a trend to a significant group effect [$F(8,48) = 2.71$, $P = 0.015$], the control group ($\bar{x}$ = 8.2) performing better than the post. LDF group ($\bar{x}$ = 3.4). Performance on list B was compared with the first trial of list A. There was a non-significant group × list interaction, implying that a proactive interference effect was not present in any group.

Recognition memory

There was a significant hits minus false alarms group effect, indicating a recognition deficit in one or more groups [$F(8,48) = 4.81$, $P < 0.001$]. *Post hoc* analysis indicated that the post. LDF group had a significantly lower score than all other groups except the post. RDF group. Since there was no significant group difference on recognition hits, this recognition deficit appears primarily to be secondary to the number of false alarms [$F(8,48) = 3.39$, $P = 0.004$]. The post. LDF group had more than double the false positives of the second highest group (Fig. 4).

Both the CVLT discriminability and response bias scores were also analysed. There was a significant group discriminability difference [$F(8,48) = 4.81$, $P < 0.001$]. The post. LDF group ($\bar{x}$ = 70.0) performed significantly worse than all other groups except the post. RDF group ($\bar{x}$ = 85.9).

Delayed free recall

Short delay. A significant group difference on short-delay free recall [$F(8,48) = 5.39$, $P < 0.001$] was similar to the immediate free-recall findings. The post. LDF ($\bar{x}$ = 2.8) group was significantly worse than the control ($\bar{x}$ = 11.5), RNF ($\bar{x}$ = 11.4) and ant. RDF ($\bar{x}$ = 11.7) groups, and the PMF ($\bar{x}$ = 5.1) group was significantly different from the control group. The significant group difference in short-delay cued recall [$F(8,48) = 4.59$, $P = 0.001$] also showed the same pattern, the PMF group ($\bar{x}$ = 6.7) being significantly different from the RNF group ($\bar{x}$ = 13.4).

Long delay. A highly significant group effect was obtained for long-delay free recall [$F(8,48) = 6.16$, $P < 0.001$], and the *post hoc* analysis of group differences was similar to that obtained for the immediate total free-recall analysis. The post. LDF group ($\bar{x}$ = 2.8) was significantly inferior to all groups except the PMF ($\bar{x}$ = 5.0) and ant. LDF ($\bar{x}$ = 8.6) groups, and the PMF group was worse than the AMF ($\bar{x}$ = 11.0), RNF ($\bar{x}$ = 12.4), ant. RDF ($\bar{x}$ = 12.7) and control ($\bar{x}$ = 11.5) groups. The long-delay cued recall was also similar [$F(8,48) = 5.08$, $P < 0.001$], with the post. LDF ($\bar{x}$ = 3.8) and PMF ($\bar{x}$ = 6.3) groups worse than the control ($\bar{x}$ = 11.6) and RNF ($\bar{x}$ = 13.4) groups and the post. LDF group worse than the AMF ($\bar{x}$ = 11.8) and ant. RDF ($\bar{x}$ = 12.3) groups.

Errors and efficiencies

Intrusions. There were no significant group differences.

Double recalls. There was no significant group effect using the CVLT measure of total perseverations across all trials ($P = 0.11$).

Table 1 *Lesion location and aetiology within patient groups*

Patient group and subject number	Lesion location	Aetiology	Lesion size	Chronicity (months)
Anterior right dorsolateral frontal				
1054	Inferior medial, dorsolateral, ACG	Tumour	2.55	24.7
2005	Medial, dorsolateral, ACG	Tumour	3.42	3.6
2044	Dorsolateral, polar, superior medial, ACG	Tumour	1.76	3.6
Mean (SD)			2.6 (0.8)	10.6 (12.2)
Posterior right dorsolateral frontal				
1041	Dorsolateral, inferior medial	Lobectomy	2.92	4.2
1067	Dorsolateral	Stroke	0.84	21.0
1068	Dorsolateral, striatal	Stroke	2.41	7.4
2011	Superior medial, ACG	Stroke	1.6	3.6
2024	Dorsolateral, striatal	Stroke	1.74	2.5
Mean (SD)			1.9 (0.8)	7.7 (7.6)
Anterior left dorsolateral frontal				
2002	Medial, dorsolateral, ACG (L)	Infarct	1.19	4.6
2012	Dorsolateral, SM, polar, ACG	Tumour	1.46	3.8
2056	Dorsolateral	Tumour	0.57	10.4
2058	Medial, dorsolateral	Tumour	2.53	74.5
2102	Dorsolateral, SM, polar, ACG	Trauma	2.48	4.2
Mean (SD)			1.6 (0.8)	19.5 (30.8)
Posterior left dorsolateral frontal				
1043	Dorsolateral	Stroke	0.22	15.1
1053	Dorsolateral	Trauma	0.92	291.1
1071	Dorsolateral, parietal	Stroke	3.12	12.7
1079	Striatal	Stroke	0.99	10.7
1081	Dorsolateral	Haemorrhage	2.05	10.0
Mean (SD)			1.5 (1.1)	67.9 (124.8)
Anterior medial frontal				
1056	Inferior medial, ACG	Stroke	1.6	33.1
1059	Inferior medial, dorsolateral, ACG	Trauma	4.47	34.1
1065	Inferior medial	Trauma	1.3	15.6
1069	Inferior medial	Tumour	0.22	2.5
1077	Inferior medial, ACG	Trauma	2.16	10.2
2047	Inferior medial	Stroke	0.38	3.5
2049	Inferior medial, Polar	Haemorrhage	0.18	3.4
2053	Inferior medial (R), dorsolateral (L), ACG (R)	Trauma	2.44	3.4
Mean (SD)			1.6 (1.5)	13.2 (13.4)
Posterior medial frontal				
1060	Medial, ACG	Stroke	2.6	6.1
1070	Medial, ACG (R)	Stroke	0.14	2.6
1075	Medial, ACG, septal	Haemorrhage	6.77	22.1
2013	Inferior medial, septal, ACG	Stroke	0.07	8.9
2039	Medial, ACG, dorsolateral (L)	Haemorrhage	5.74	1.8
2045	Medial, septal, ACG	Stroke	7.43	59.8
2100	Medial, ACG, septal	Stroke	7.2	9.8
Mean (SD)			4.3 (3.3)	15.8 (20.5)
Right non-frontal				
2040	Temporal	Lobectomy	2.06	89.3
2043	Occipital	Stroke	0.48	36.3
2055	Temporal	Haemorrhage	NA	55.3
2057	Temporal	Lobectomy	2.66	134.6
2103	Parietal, occipital (small)	Stroke	0.74	34.6
Mean (SD)			1.5 (1.0)	70.0 (42.3)
Left non-frontal				
1058	Parietal	Stroke	NA	3.5
2028	Temporal, occipital	Stroke	0.95	28.5
2032	Temporal	Lobectomy	1.6	49.6
2036	Temporal	Lobectomy	NA	91.3
2038	Temporal	Lobectomy	1.17	144.7
2054	Temporal	Lobectomy	NA	142.6
Mean (SD)			1.2 (0.3)	76.7 (59.3)

L = left; R = right; ACG = anterior cingulate gyrus; SM = superior medial.

Inconsistency. When the inconsistency score was taken as a proportion of the total correct words recalled, there was a significant group difference [$F(8,48) = 6.26$, $P < 0.001$]. The post. LDF group ($\bar{x}$ = 46.3) had a significantly higher inconsistency score than all groups except the post. RDF ($\bar{x}$ = 36.0) and PMF ($\bar{x}$ = 31.7) groups, and the PMF group was significantly worse than the control group ($\bar{x}$ = 10.4).

Organization

Serial order recall. The CVLT serial cluster ratio for number of words recalled in the same order as presented showed no significant group effects ($P = 0.278$).

Semantic categorization. There was no significant semantic categorization effect when we controlled for the number of words presented ($P = 0.226$). Controlling for the total possible semantic clusters presented (Stricker *et al*., 2002), there was also no significant group effect ($P = 0.312$).

Subjective organization. For comparison with our earlier study (Stuss *et al*., 1994), we first evaluated all frontal patients relative to non-frontal and control groups. The frontal group was significantly impaired compared with controls (Fig. 5) [$F(2,53) = 7.98$ $P = 0.001$]. There was also a significant group effect in the nine-group analysis ($P = 0.007$), the post. RDF group having a significantly worse subjective organization score than the control group.

Test correlations

No correlational results met the level of significance established *a priori*. Several approximated significance, and are presented for future research and as a potential mechanism underlying memory problems in some of the patient groups. Total correct recall and recognition scores (hits minus false alarms) had very few correlations with any neuropsychological result. For the PMF ($r = 0.95$, $P = 0.011$) and ant. LDF groups (r = 0.93, P = 0.02) there was a correlation of recognition memory and digit span backwards. For the post. LDF group, total correct in recall correlated with letter fluency (FAS) (r = 0.97, P = 0.035), and recognition (hits only) correlated with the Boston Naming Test (r = 0.93, P = 0.02).

Discussion

Patients with frontal lesions may show difficulties with any aspect of an unstructured list-learning task, but there is no single frontal lobe syndrome of memory impairment. There are distinctions with lesions in different frontal subregions. This study has demonstrated important new frontal anatomical functional divisions. In addition to left–right differences, there are distinctions within the left lateral, right lateral and ventral medial regions.

Immediate free recall was impaired primarily in patients with post. LDF lesions, but also in those with PMF lesions, usually bilateral, involving the septal region, and to a lesser degree in those with post. RDF lesions. The demonstration that delayed free recall, both short and long, was also impaired after post. LDF and PMF lesions reinforces the conclusion that damage to these areas, uniquely among frontal lesions, impairs recall. Many patients with frontal lesions may show slow improvement in learning across trials, but performance is fairly normal by trial 5 and in delayed recall. This is not the case for those with post. LDF and PMF lesions.

For recognition memory, only the post. LDF group was impaired. The deficient performance was entirely due to false-positive endorsements of foils. The standard CVLT measure for recognition also isolated the post. LDF group. The post. LDF group demonstrated abnormal bias. If a criterion distinction is required, this group appeared to default to the posture that everything is a target. We documented a similar bias problem in left frontal patients using a reaction time task (Stuss *et al*., 2002). In the present study this bias may reflect defective semantic encoding, producing only a

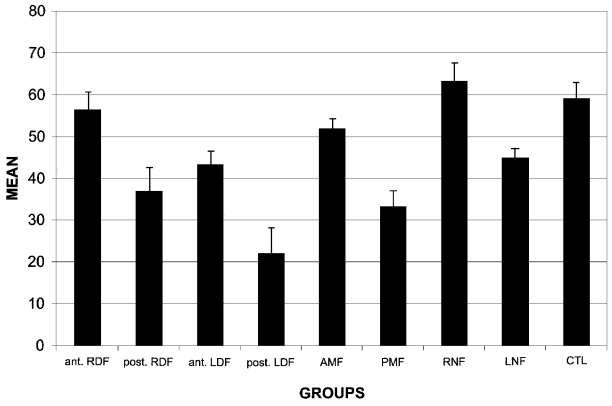

Fig. 2 Mean total correct free-recall memory score for each group over the five presentations of the word list. Patient groups are defined in the caption of Fig. 1. CTL = control group.

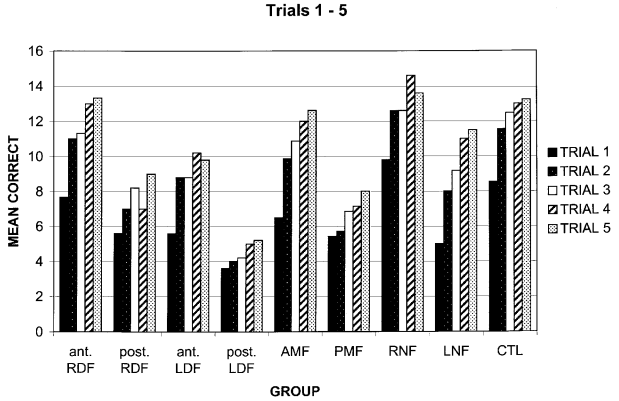

Fig. 3 Mean correct words recalled for each of the five trials for each group. Groups are defined in the caption of Figs. 1 and 2.

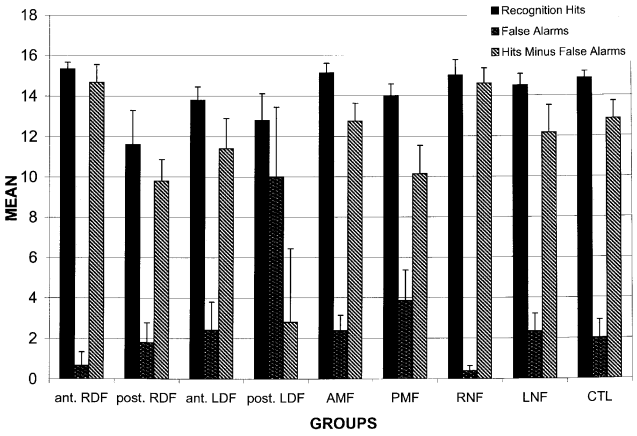

Fig. 4 Mean scores for recognition hits, false alarms, and hits minus false alarms for each group. Groups are defined in the caption of Fig. 2. The post. LDF group was significantly impaired on false alarms, and hits minus false alarms.

general semantic sense to guide the construction of a criterion.

Where do the inefficiencies in learning and the defective overall learning in some groups arise? There are several reports on the performance of patients with frontal lesions on list-learning tasks, but they have limited power to account for specific regional effects of frontal injury. Some studies simply placed all patients with frontal lesions into a 'frontal' group and compared that group with a control group of normals or subjects with another type of non-frontal injury (Jetter *et al*., 1986; Janowsky *et al*., 1989*a*; Eslinger and Grattan, 1994; Gershberg and Shimamura, 1995; Kopelman and Stanhope, 1998). Within these 'frontal' groups, lesion locations were often limited to the primarily dorsolateral lesions (left and right considered together) (Janowsky *et al*., 1989*a*; Eslinger and Grattan, 1994; Gershberg and Shimamura, 1995). In others, all frontal structures were included (Jetter *et al*., 1986; Kopelman and Stanhope, 1998). When lesion groupings were analysed with left and right frontal injuries considered separately, there were again limitations (Incisa della Rocchetta, 1986; Incisa della Rocchetta and Milner, 1993; Vilkki *et al*., 1998). No study attempted to specify exact regional locations within the frontal lobes. Two studies had a relative over-representation of superior and medial lesions (Incisa della Rocchetta, 1986; Incisa della Rocchetta and Milner, 1993). One study assessed patients with recent tumour resections (Vilkki *et al*., 1998). One study of left frontal infarctions is difficult to interpret because the only identification of the localization was in the radiology reports, and the description is unclear if only anterior cerebral artery territory strokes are included (Hildebrandt *et al*., 1998).

There is considerable disagreement among these studies about the nature of any learning impairments after frontal lesions. Some imply that semantic factors play a role in learning deficits (Incisa della Rocchetta, 1986; Incisa della Rocchetta and Milner, 1993). One explicitly rejects a role of semantic deficits (Vilkki *et al*., 1998). None of these studies used, however, a direct measure of semantic or lexical function. The studies that conclude that frontal lesions impair encoding (Janowsky *et al*., 1989*a*; Incisa della Rocchetta and Milner, 1993; Eslinger and Grattan, 1994; Gershberg and Shimamura, 1995) emphasize deficits in organization or categorization or clustering. If the distinctive effects of lesions in different frontal regions that we have demonstrated are correct, it is not surprising that studies that did not respect regional differences did not find them. In an earlier study by our group using an experimental test (Stuss *et al*., 1994), analysis of patients by regional lesion groups demonstrated that different regions were associated with different patterns of, and neural mechanisms for, impairment. Our investigation largely supports our original hypotheses, but also makes important new anatomical differentiations. Lesions in different regions of the frontal lobes affect list learning. Encoding, monitoring, discrimination and bias differ between groups. 'Strategic' deficits in learning are seen in most groups.

Recall

Left dorsolateral lesions, centred on areas 44, 9 and 46, have the most potent effects on recall, and these effects are correlated with (and perhaps embedded in) the semantic/lexical residuals of these lesions (decreased naming and verbal fluency), even when the residuals are very mild. Non-frontal left lesions that impair semantic and lexical capacities also impair verbal learning (Ween *et al*., 1996). Medial lesions that include the septum may also impair recall. The cognitive process that underlies poor memory in this group is not clear, but the anatomical basis is likely to be loss of cholinergic projections to the hippocampus.

Double recalls are another form of defective recall. In this experiment, double recalls were not significantly increased in any group. The ant. LDF ($\bar{x} = 10.6$) and the post. RDF ($\bar{x} = 9.6$) groups showed a trend to significance ($P = 0.11$), with double recall rates approximately twice those of the controls and the next highest patient group. In our earlier study (Stuss *et al*., 1994) there was a significant increase in double recalls in the right frontal group, approximately equivalent to the post. RDF group of the present study, and a trend to an increase in the left frontal group. Although the two studies do not unequivocally demonstrate propensity to double recalls in any group, the trends are consistent and the lack of significance may be due to inadequate numbers of subjects. Deficient free recall was not due to proactive interference, at least as measured by the standard comparison of list B with list A, first trial. It could also not be attributed to an abnormal serial position effect or to defective primary memory capacity. The demonstration that impaired secondary memory profiles exactly parallel the free-recall results becomes, in this context, little more than a redundant statement that there is a free-recall defect.

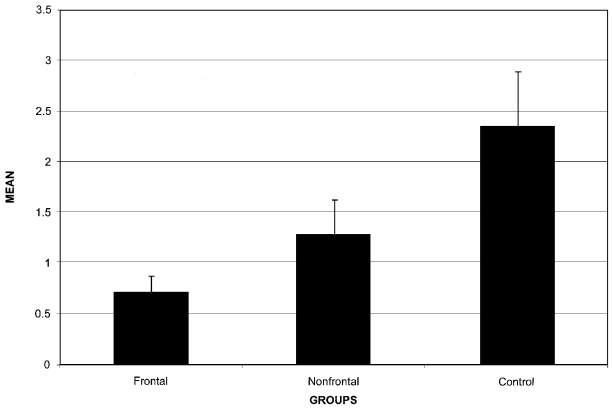

Fig. 5 Subjective organization, also known as the pair frequency score, is defined as the ability to recall two words together as a unit from one trial to the next trial, independently of any other organization factor. All the patients with frontal lesions are compared with all the patients with non-frontal (posterior) lesions, and the control group. The frontal-lesioned group is significantly impaired compared with the control group.

Inefficiencies are not due to intrusions and are not, generally, due to double recalls. Of the various options for the organization of learning, the use of fixed serial order and semantic clustering strategies was available to all patient groups and overall recall success was highly correlated with semantic clustering in all patient groups. Under-use of these strategies cannot account for impaired learning. Subjective organization is the consistent recall of words paired together across sequential trials. Patients with frontal lesions in any region except right polar had considerable difficulty maintaining subjective organization, and the rank order of impaired subjective organization paralleled recall performance: the post. LDF and PMF groups were most impaired. Poor subjective organization is also suggested by the low consistency score. Thus, the use of semantic and serial order strategies may be relatively automatic, perhaps encoded in temporoparietal semantic associations or auditory–verbal short-term memory systems. The creation and maintenance of a subjective and on-the-fly strategy requires frontal systems, perhaps those of working memory. Inefficiencies arise when that strategy is poorly implemented. When verbal material is presented around a well-organized semantic context, such as a story narrative, these various frontal impairments are, in large part, by-passed.

Recognition

In this experiment with CVLT, impairments in recognition memory were only significant in the post. LDF group. Poor encoding due to mild semantic deficits may leave the patient susceptible to bias, i.e. poor criterion setting, because the defective semantic encoding cannot specify items distinctly from the semantic gist. False-positive recognition of foils results. The rate of false-positive endorsements is highly influenced by the characteristics of the presented materials (Schacter *et al*., 1996), such as the number of items in a particular category, whether the items are blocked or unblocked, etc. False-positive frequency is also affected by the structure of the recognition component of the task: the ratio of targets to foils, and the instructions to the patient or subject (Dodson and Johnson, 1993). Depending upon the interactions of these factors, there can be considerable variability in false-positive endorsements. In the present experiment, some combination of a low proportion of items in each category in the total list (25%), unblocked presentation, highly associated targets, high foil frequency (50%) and instructions appears to have suppressed false recognition in the right frontal group and altered bias in the post. LDF group. Tasks with more manipulations and tighter distinctions of semantic foils might clarify this.

The use of empirically derived anatomical subgroups appears vindicated. The groups were reasonably homogeneous anatomically and they appeared to fit common regional distinctions of connectivity. Simple comparison of left, right and bilateral groups would have revealed none of these distinctive regional effects.

Future analyses of verbal memory in patients with frontal lesions must be driven by anatomical subgroups; simply assembling a group of 'frontal' lesions, even divided according to the hemisphere involved, does not address the functional heterogeneity of the frontal lobes. This conclusion is amply reinforced by similar findings of important regional effects on all standard neuropsychological tasks (Stuss *et al*., 1998, 2000, 2001*a*, *b*). It is also supported by recent imaging studies in normal subjects. The original demonstration of hemispheric asymmetries in memory only emphasized the left/encoding and right/retrieval differences. More recent studies have increasingly parsed the frontal lobes into smaller regions and demonstrated more specific relationships between discrete elements of memory [monitoring (Shallice, 1999), working memory (D'Esposito *et al*., 1995; Petrides 1995*a*), semantic activation (Petrides, 1995*b*), retrieval effort and retrieval success (Fletcher, 2001)] and very discrete regions of frontal activation. Lesion studies have not found the same elegant anatomical distinctions (Swick and Knight, 1996) as functional imaging, probably because lesion studies are hugely more difficult to control for many variables that affect the anatomical relationships of memory, such as the chronicity of damage and the exact site of injury. Many lesions affect multiple functional regions of the frontal lobes, and even two apparently equivalent lesions of the cortex may differ dramatically in their deep extent, producing very different patterns of regional disconnection and presumably of functional impairment. Nevertheless, this study demonstrates that careful attention to the regional anatomy of frontal lobe lesions can illuminate the processes that may be impaired in memory and learning.

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