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Qualitatively different memory impairments across frontal lobe subgroups

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Abstract

Recall impairments in patients with lesions to the prefrontal cortex (PFC) have variously been attributed to problems with organisation at encoding, organisation at retrieval and monitoring at retrieval. Neuroimaging and recent theoretical work has associated the left lateral PFC with organisation and strategy production at encoding, and the right lateral PFC with organisation, error detection and monitoring at retrieval. However few lesion studies have been anatomically specific enough to test the direct predictions made by this work. Proactive interference, response to prompting, monitoring and organisational strategies were examined in 34 patients with frontal lobe lesions and 50 healthy controls using a structured verbal recall task, and the fractionation of deficits according to specific frontal lesion site was explored. Recall impairments were observed in the Right Lateral and Medial frontal subgroups. The Medial recall impairment was unaffected by manipulations at encoding or retrieval and was attributed to a "pure" memory deficit arising from disruption of the limbo-thalamic system. The Right Lateral recall impairment was ameliorated by the provision of prompts at retrieval, indicating a strategic retrieval deficit. This intervention also resulted in an unusual pattern of intrusions, namely an increase in proactive interference responses compared with extra-list intrusions. However contrary to predictions no monitoring impairment was found. We offer two explanations for the pattern of performance in the Right Lateral group: failure of a right lateralised error detection and checking system, or an impairment in the active uncued initiation of a supervisory operation.

Keywords: Frontal lobes; Memory; Executive function; Proactive interference; Monitoring

1. Introduction

Damage to the frontal lobes does not result in the kind of severe amnesic syndrome typical of lesions to the temporal or diencephalic structures. However there is a large body of evidence suggesting that it may lead to a range of more subtle impairments of memory, particularly in recall tasks (Dimitrov et al., 1999; Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Jetter, Poser, Freeman, & Markowitsch, 1986; Shimamura, Janowsky, & Squire, 1991; Wheeler, Stuss, & Tulving, 1995). Recall tasks are relatively effortful compared to recognition tasks, requiring the participant both to initiate an effective search in memory and to evaluate the products of this search. Therefore these deficits are thought to be secondary to impairments in frontally located supervisory processes, rather than being pure memory deficits.

1.1. Evidence from lesion studies

Recall impairments in frontal lobe damaged patients have been attributed to difficulties in employing effective strategies at either encoding or retrieval. Several studies have reported that frontal patients tend not to spontaneously categorise to-be-remembered material or use other top-down processes to aid encoding (Incisa della Rochetta, 1986; Hirst & Volpe, 1988). Kopelman and Stanhope (1998) have also reported that the recall of frontal patients (in contrast to diencephalic and temporal lobe amnesics) can be improved if semantically organised rather than unrelated word lists are used, externally providing the organisation that they are unable to impose subjectively. Several other groups have reported similar results. Gershberg and Shimamura (1995) found that their frontal patients benefited

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from strategy instructions at both the study stage and at the test stage, implying that they had deficits in implementing organisational strategies at encoding and in implementing strategic processes at retrieval. Strategy deficits at retrieval in the form of impaired pair frequency have also been reported by Eslinger and Grattan (1994), Gershberg and Shimamura (1995) and Vilkki, Servo, and Surma-Aho (1998), and Incisa della Rochetta and Milner (1993) reported an improvement in recall when retrieval cues were externally provided, especially amongst left frontal patients.

Most lesion studies have used either an undifferentiated "frontal" group (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Kopelman & Stanhope, 1998), or at best have compared left frontal to right frontal subgroups (Incisa della Rochetta, 1986; Incisa della Rochetta & Milner, 1993; Vilkki et al., 1998). However more anatomically specific results have emerged from groups using functional lesion localisation techniques to assess whether different deficits might follow lesions to different subregions of the frontal lobe. Stuss et al. (1994), for example, have reported that patients with left frontal (particularly left dorsolateral) damage had the most severe recall impairments in a list learning task. More recently Alexander, Stuss, and Fansabedian (2003) confirmed marked verbal free recall deficits in patients with posterior left dorsolateral lesions, but also in those with posterior medial frontal lesions, hypothesised to result from direct disruption of the memory system arising from loss of cholinergic projections to the hippocampus.

In addition to reduced veridical recall, patients with frontal lobe damage have frequently been reported to be abnormally sensitive to proactive interference, and to produce high rates of intrusions in recall tasks (Baldo, Delis, Kramer, & Shimamura, 2002; Daum & Mayes, 2000; Delbecq-Derouesne, Beauvois, & Shallice, 1990; Melo, Winocur, & Moscovitch, 1999; Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995). However patient studies using more detailed lesion localisation procedures have failed to find any intrusion effects in their frontal groups (Alexander et al., 2003; Stuss et al., 1994) so the anatomical specificity of intrusion effects is not known. Stuss et al. (1994) did however report a specific deficit in patients with right lateral frontal lesions, who produced excess repetitions in their recall. This pattern of responding was attributed to an impairment in monitoring the output of recall, which prevented the patients from editing out words they had already recalled. Monitoring impairments have been associated with the production of false alarms in recognition memory tests (Budson et al., 2002; Curran, Schacter, Norman, & Gallucio, 1997; Delbecq-Derouesne et al., 1990; Melo et al., 1999; Schacter, Curran, Gallucio, & Milberg, 1996; Swick & Knight, 1999; Verfaillie, Rapscak, Keane, & Alexander, 2004) therefore right lateral monitoring impairments may also be related to the production of intrusions in recall.

1.2. Evidence from neuroimaging

Convergent with the patient findings, imaging studies of memory almost always show activation of the prefrontal cortex (PFC, see Fletcher & Henson, 2001, for a review). However for technical reasons related to movement artefacts, research in fMRI has tended to concentrate on recognition rather than recall. In general, greater left than right frontal activation is associated with encoding tasks, and greater right than left frontal activation is associated with retrieval tasks (the Hemispheric Encoding/Retrieval Asymmetry model: Habib, Nyberg, & Tulving, 2003; Nyberg, Cabeza, & Tulving, 1996; Shallice et al., 1994; Tulving, Kapur Craik, Moscovitch, & Houle, 1994).

Left prefrontal activation at encoding has most often been attributed to the retrieval of information from semantic memory which enables "deep" encoding to take place (Baker, Sanders, Maccotta, & Buckner, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999a; Wagner et al., 1998; Wig, Miller, Kingstone, & Kelley, 2004). More specifically this left prefrontal activation, and left *dorsolateral* activation in particular, has been associated with organisation of material at encoding on the basis of semantic relations or attributes (Fletcher, Shallice, & Dolan, 1998; Savage et al., 2001; Wagner, Maril, Bjork, & Schacter, 2001), a task at which patients with frontal lobe lesions are impaired.

Right prefrontal activation has been associated with retrieval success, or the adoption of a retrieval "mode" (Lepage, Ghaffar, Nyberg, & Tulving, 2000; Nyberg et al., 1996; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Wagner, Desmond, Glover, & Gabrieli, 1998). More specifically, one component of this right prefrontal activation, and particularly right *dorsolateral* prefrontal activation, is hypothesised to reflect monitoring and checking of the products of a memory search (e.g. Cabeza, Locantore, & Anderson, 2003; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1996; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Gabrieli, 1998; Henson, Shallice, & Dolan, 1999b; Shallice, 2001). In support of this, ERP studies have provided evidence of a late onsetting right frontal positivity in recognition tasks that follows ecphory, and this has been attributed to post-retrieval monitoring (see Allan, Wilding, & Rugg, 1998, for a review).

1.3. Shallice's error detection and checking hypothesis

Shallice (2006) has assimilated this lesion and neuroimaging evidence in proposing that the Supervisory System (the prefrontal system which controls action in non-routine situations; Norman & Shallice, 1980, 1986) may be fractionated into anatomically separable subsystems, including a left dorsolateral system which controls strategy production by means of top-down selection of schema (for example the semantic organisation of word lists), and a right dorsolateral system in charge of non-evident error-detection and checking (for example the monitoring functions discussed above). Shallice (2001, 2006) has specified the error detection, checking and monitoring functions of the right dorsolateral system by proposing that it comes into play under three conditions.

(i) *When competing stimuli are likely to lead to capture errors*. In memory paradigms, proactive interference provides the best test of the ability to reject plausible alternatives and avoid capture errors. Henson, Shallice, Josephs, and Dolan (2002), in an fMRI study, reported right dorsolateral PFC activation associated with high proactive interference in a paired associate cued recall paradigm. Despite evidence that frontal patients as a whole show abnormal sensitivity to proactive interference (Shimamura et al., 1995), the hypothesis that *right* frontal patients will be particularly sensitive to proactive interference and capture errors in a memory paradigm has not been directly tested.

(ii) *When easy retrieval is over*. The right dorsolateral error detection and checking system is proposed to come into play under conditions of uncertainty. For example, Henson, Rugg, et al. (1999) and Eldridge, Knowlton, Furmanski, Bookheimer, and Engel (2000) have both reported greater right dorsolateral PFC activation associated with "Know" rather than "Remember" responses, i.e. less certain responses that required greater checking activity. In a retrieval situation, we can assume that there are two stages: first the production of material which is easily available, and second a more effortful retrieval search for additional items which do not come easily to mind. The error detection and checking system would be most necessary at the second stage. Therefore patients with right lateral PFC damage might be expected to be more susceptible to capture errors in the later stages of retrieval.

(iii) *When on-line monitoring is required*. The non-evident error detection and checking system should be initiated especially when online monitoring is required. This is consistent with evidence that the mid-dorsolateral frontal cortex (areas 46/9) is involved in keeping track of actions and expected events so as not to repeat them (Petrides, 2000; Petrides, Alivisatos, Evans, & Meyer, 1993; Petrides, Alivisatos, Meyer, & Evans, 1993), and with the neuropsychological evidence cited above that patients with right frontal lesions produce abnormally high numbers of repetitions in their recall (Stuss et al., 1994). Therefore concurrent monitoring tasks should be particularly sensitive to right lateral PFC lesions.

1.4. The current study

A number of specific predictions deriving from theoretical and neuroimaging work can be made about the differential effects of lesions to different regions of the PFC. However few lesion studies thus far have been anatomically specific enough to test them. Most lesion studies have tended to use rather gross anatomical divisions, attributing impairments to a general "frontal" effect, and running the risk of masking more specific localised impairments. The present study employed more detailed lesion localisation methods in an attempt to localise specific recall impairments within the frontal lobe, and to close the gap between evidence from neuroimaging and lesion studies. Thirty-four patients with focal frontal lesions and 50 healthy controls were given a word list learning task, designed to assess four specific aspects of memory control.

(i) *Proactive interference and intrusions*. Lists were comprised of words drawn from four semantic categories. Semantic categories were repeated in subsequent lists, to induce proactive interference and the production of prior-list intrusions. The use of categorised lists might also induce the intrusion of unpresented semantic associates (extra-list intrusions). Previous research suggests that intrusion rates in general should be higher in patients with frontal lobe lesions (Baldo et al., 2002; Daum & Mayes, 2000; Delbecq-Derouesne et al., 1990; Melo et al., 1999; Shimamura et al., 1995). However Shallice's (2001, 2006) error detection and checking hypothesis predicts that intrusion effects, and particularly proactive interference responses, should be highest in patients with right lateral PFC lesions.

(ii) *The effects of prompting*. After initial free recall, prompts in the form of category names were provided to prompt additional recall. If poor recall performance following frontal lesions is a result of impairments at retrieval, frontal patients should show an improvement in veridical recall following this manipulation (e.g. Gershberg & Shimamura, 1995; Incisa della Rochetta & Milner, 1993), and the HERA model suggests that this improvement should be most prominent in the Right Lateral group (Habib et al., 2003; Lepage et al., 2000; Nyberg et al., 1996; Shallice et al., 1994; Tulving et al., 1994). However failure of error detection and checking systems will also be most evident following prompting, as retrieval becomes non-routine and effortful, and this would predict an accompanying increase in intrusions, and particularly proactive interference responses, in the Right Lateral group.

(iii) *Monitoring*. A concurrent monitoring task was included in which participants were asked to indicate during recall, items that had already been presented in a previous list. Failures of on-line monitoring are hypothesised to result from failure of a right lateralised error-detection and checking system so should be higher in this group.

(iv) *Organisational strategies at encoding and retrieval*. An assessment of the use of organisational strategies was made by presenting word lists either blocked by semantic category, or randomly intermixed. Blocked presentation should aid recall, whereas random presentation requires subjective organisation on the part of the participants. On the basis of the HERA model any impairments in organisation at encoding should be particularly marked in the Left Lateral group (Fletcher, Shallice, & Dolan, 1998; Savage et al., 2001; Wagner et al., 2001), whereas impairments in organisation at retrieval should be particularly marked in the Right Lateral group (Habib et al., 2003; Lepage et al., 2000; Nyberg et al., 1996; Shallice et al., 1994; Tulving et al., 1994).

2. Methods

2.1. Participants

Thirty-four patients with focal frontal lesions were recruited from the National Hospital for Neurology and Neurosurgery and tested in the Neuropsychology Department. Inclusion and exclusion criteria were: (1) the presence of a focal lesion confined to the frontal lobes, (2) English as a first language, (3) absence of childhood onset epilepsy (late onset seizures arising from the lesion were allowed), (4) absence of severe aphasia, and (5) absence of other significant neurological and psychiatric disorders. The performance of patients was

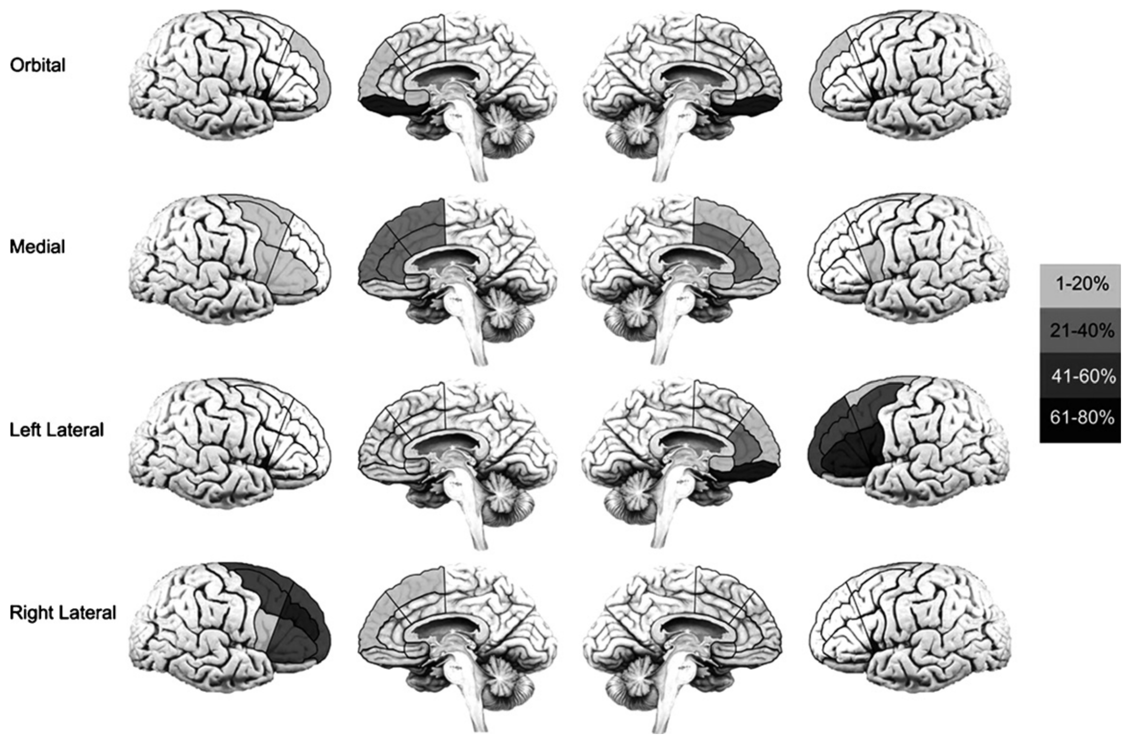

Fig. 1. Lesion location by frontal subgroup. Shaded areas represent the proportion of patients within each group who have lesions affecting at least 25% of the depicted region.

compared to that of 50 healthy controls. All participants gave informed consent before being tested, and the study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

2.2. Lesion analysis

Analysis of lesion site was conducted following an approach based on that of Stuss et al. (2002). A radiologist (TY) blind to the nature of the patient's behavioural deficit examined MRI (or CT where MRI was unavailable) scans and coded each for the presence or absence of lesion in 12 prefrontal areas in each hemisphere (24 in total). These areas were: orbital, sub genu, anterior cingulate (anterior and posterior portions), medial surface of the superior frontal gyrus (anterior and posterior portions), lateral superior frontal gyrus (anterior and posterior portions), lateral middle frontal gyrus (anterior and posterior portions), and lateral inferior frontal gyrus (anterior and posterior portions). On the medial surface the anterior/posterior border was taken as the point midway between the frontal pole and the ramus marginalis. On the lateral surface the anterior/posterior border was taken as the point midway between the frontal pole and the precentral sulcus. An area was only coded as damaged if at least 25% of that area was affected (areas of oedema were coded in the initial analysis but did not affect final groupings and were not common enough across patients to be included in the final analysis).

These 24 regions were then collapsed into four groups for group comparisons. Patients were assigned to the following groups according to the region of greatest damage: Orbital ($n = 11$), in which greatest damage was to the orbital surface of one or both lobes; Medial ($n = 8$), in which greatest damage was to the sub genu, anterior cingulate or medial surface of the superior frontal gyrus of one or both lobes; Left Lateral ($n = 8$), in which greatest damage was to the left lateral superior, middle or inferior frontal gyrus; and Right Lateral ($n = 7$), in which greatest damage was to the right lateral superior, middle or inferior frontal gyrus.

These groups were selected to be similar to those used in the work of Stuss et al. (2002) and held to be related to functional divisions within the prefrontal cortex. However the grouping methods differed in two ways. Firstly our 24 regions were defined on the basis of sulci and gyri (rather than architectonic divisions) to ensure reliable anatomical localisation across a large number of patients. Our 24 regions thus vary slightly from those employed by Stuss et al. (2002). Secondly our Orbital/Medial division differed from the Stuss et al. (2002) Superior Medial/Inferior Medial division so as to be exclusive[1] and to allow for reasonable group sizes based on the distribution of lesions in our sample (use of an exclusive version of the Stuss et al. (2002) divisions would have resulted in a very large Inferior Medial group and a very small Superior Medial group).

Fig. 1 shows the proportion of patients in each group with damage to each of the 24 coded areas. Patients were included in one group only, hence minor damage to frontal regions other than the major grouping was allowed. For example in the Orbital group one patient had minor additional damage to the sub genu and superior frontal gyrus. In the Medial group four patients had minor additional damage to lateral regions. In the Left Lateral group six patients had minor additional damage to left orbital and medial regions but no patients had damage to the right hemisphere. In the Right Lateral group one patient had minor additional damage to the right medial superior frontal gyrus, but no patients had damage to the left hemisphere. Individual details of aetiology and lesion location for each patient can be found in Appendix A.

Table 1 shows demographic data for the Control group and the four Frontal groups. No groups differed significantly in terms of age or years of education. Neither did the frontal groups differ in time since surgery. Our recruitment procedure resulted in a heterogeneous and largely acute sample. We acknowledge that acute effects can be relatively transitory; however this does not prevent them being relatively focal. Moreover, any more widespread transitory acute effects would be more likely to weaken group differences than create spurious positive results. In addition, reorganisation of function is liable to be less than in chronic samples. Any positive localisation findings from the current study should therefore provide valuable data to complement those from studies using more chronic patients. An approximate measure of potential lesion size effects was obtained by correlating the number of the 24 regions affected in each patient with all behavioural measures. None of these correlations were significant.

[1] In the Stuss et al. (2002) procedure the area covered for Superior Medial patients includes that for Inferior Medial patients, but not vice versa. Moreover impairments found in the Superior Medial subgroup in the studies of Stuss et al. are often found to involve the whole medial surface on more detailed analysis, e.g. Stuss et al. (2005).

Table 1
Demographic data

	Sex	Age	Years of education	Time since surgery (days)
Control ($n = 50$)	25M, 25F	48.62 ± 15.96	13.06 ± 3.05	N/A
Orbital ($n = 11$)	10M, 1F	45.73 ± 16.75	13.45 ± 3.64	239.50 ± 570.03
Medial ($n = 8$)	5M, 3F	41.38 ± 11.04	12.88 ± 3.36	6.67 ± 5.28
L Lateral ($n = 8$)	3M, 5F	49.88 ± 13.97	12.38 ± 2.77	19.17 ± 30.62
R Lateral ($n = 7$)	2M, 5F	51.43 ± 12.63	12.43 ± 3.74	78.43 ± 169.14

Data are presented in the form: mean ± standard deviation. The large variance in time since surgery was introduced by four re-admitted patients (three in the Orbital group and one in the Right Lateral group) who were tested between 1 and 5 years after initial surgery. With these outliers removed time since surgery was 8.57 ± 3.91 in the Orbital group and 14.67 ± 13.32 in the Right Lateral group.

2.3. Experiment

2.3.1. Stimuli

Six 16-word lists were created, each consisting of four words from four different categories drawn from the Battig and Montague (1969) norms. In each case the prime associate from each category was excluded, and the second, third, fourth and fifth most frequent associates were used to construct the lists. This manipulation ensures that reliance on semantic memory alone is not sufficient for adequate responding, particularly following a prompt, and also increases the likelihood of extra-list intrusions. The words in the first, third and fifth lists were presented in a blocked fashion, such that the words comprising each category were presented together. The words in the second, fourth and sixth lists were randomly intermixed so that although they were still drawn from four categories, semantic organisation of the material on the part of the participants was required to aid recall. In the first list, each of the four semantic categories was necessarily new. However in lists 2–6, two of the categories were new, whilst two of the categories had already appeared in a previous list. Within these repeated categories, two of the four words were new, and two had already been presented in a previous list. This manipulation was introduced to create proactive interference and encourage prior-list intrusions.

2.3.2. Procedure

For each list, words were presented individually in the centre of a computer screen for 2 s, with a further 1 s interval before presentation of the next word. Following the last word of each list, participants completed a distractor task in which they were asked to add one to a series of random numbers (between 1 and 99) that appeared on the computer screen, and report their answer out loud. After 30 s participants were prompted to verbally recall as many words from the list as they could remember. After participants reported that they had freely recalled as many words as possible, they were invited to press a key for "clues". When they did this the names of each of the four categories that comprised that list appeared individually on the computer screen for 20 s, to prompt further recall. The same procedure was repeated for the remaining lists: presentation, distractor task, free recall and cued recall. However in lists 2–6, for both free and cued recall, participants were not only prompted to recall as many words as they could, but also to complete a concurrent monitoring task in which they had to indicate after recall of each word whether it had also been presented in an earlier list. The lists were presented in the same order to each participant, and the words within each list also remained in a constant order.

2.4. Statistical analysis

Analysis of variance was used to compare the performance of the Orbital, Medial, Left Lateral, Right Lateral and Control groups. Age and years of education were included as covariates. Significant ANOVAS were followed by pairwise comparisons to look for differences between the groups. Adjustment for multiple comparisons was made using a Bonferroni correction for four comparisons. Uncorrected significance levels are reported, but results are only treated as significant if they achieve $p < 0.012$. In all cases where Levene tests showed that the error variances between the groups differed significantly, data were transformed using the arcsin transformation for proportion data, and the natural log transformation in all other cases. If error variances remained unequal after this transformation, non-parametric statistics were applied to the data (Kruskal–Wallis test). In the absence of an accepted method for making post hoc comparisons following a significant Kruskal–Wallis test, pairwise Mann Whitney U tests were conducted. This method has exactly the same logic as the LSD tests if it is only applied when the Kruskal–Wallis test gives a significant result.

3. Results

3.1. Baseline neuropsychological testing

Baseline neuropsychological testing (see Table 2) showed that the Medial group had slightly depressed general intelligence as measured by Ravens APM performance compared to Controls (Univariate ANOVA: effect of "Group" $p = 0.04$, pairwise comparisons: Medial < Control $p = 0.007$). However there were no differences in NART estimated full scale IQ, and no naming or visual perception impairments in any group.

3.2. Experimental task

3.2.1. Free recall

The free recall performance of the Control and Frontal groups on the experimental task can be seen in Fig. 2. Only the Medial and Right Lateral frontal groups had a significant

Table 2
Baseline neuropsychological testing

	Ravens APM	NART FSIQ	Graded Naming Test	Incomplete Letters
Control ($n = 50$)	11.18 ± 2.85	110.64 ± 9.78	11.04 ± 3.49	19.26 ± 0.88
Orbital ($n = 11$)	11.09 ± 2.30	105.73 ± 10.15	9.18 ± 3.89	19.64 ± 0.50
Medial ($n = 8$)	8.13 ± 3.68	96.50 ± 16.29	8.71 ± 3.20	18.63 ± 2.00
L Lateral ($n = 8$)	9.25 ± 1.58	108.38 ± 18.72	11.25 ± 2.96	19.25 ± 1.04
R Lateral ($n = 7$)	11.14 ± 2.19	110.43 ± 13.09	10.29 ± 3.50	19.29 ± 0.76

Performance of Control and Frontal groups on the following general baseline tests: Ravens Advanced Progressive Matrices (age scaled score), National Adult Reading Test: Full Scale IQ, Graded Naming Test (age scaled score) and Incomplete Letters subtest of the Visual Object and Space Perception Battery (Raw score, Maximum score = 20). Data are presented in the form: mean ± standard deviation.

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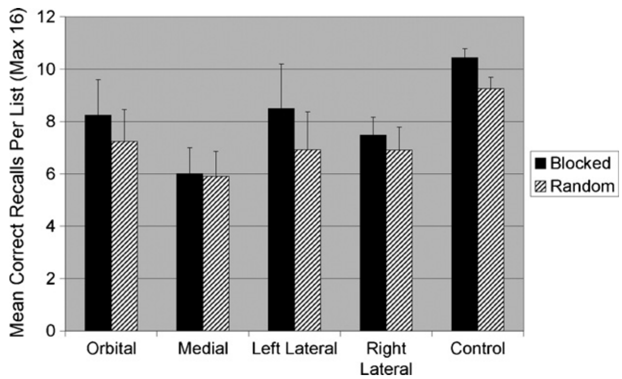

Fig. 2. Correct free recall of blocked and randomly organised lists by Orbital, Medial, Left Lateral, Right Lateral and Control groups. Bars represent mean scores and error bars represent standard error of the mean.

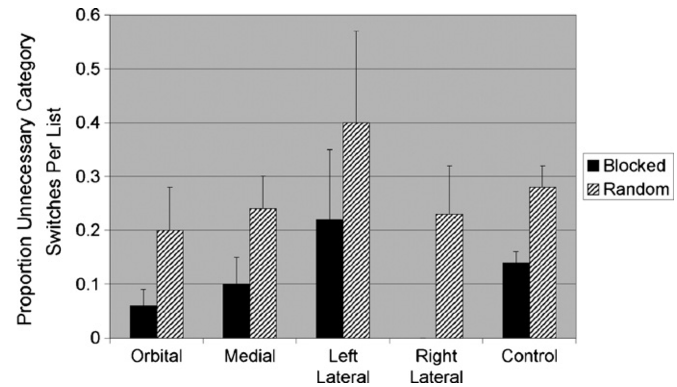

Fig. 3. Proportion of unnecessary category switches in recall of blocked and randomly organised lists by Orbital, Medial, Left Lateral, Right Lateral and Control groups. Bars represent mean scores and error bars represent standard error of the mean.

recall impairment compared to Controls (Kruskal–Wallis: effect of "Group" $p = 0.011$; Pairwise Mann Whitney U comparisons: Medial < Control $p = 0.002$; Right Lateral < Control $p = 0.011$).[2] Analysis of variance showed no effect of List Organisation (blocked vs. random), nor a Group × List Organisation interaction indicating that no group was disproportionately impaired at recalling randomly presented lists.

In order to explore deficits in organisational strategies at retrieval, we examined category clustering during recall—that is whether participants tended to recall all the words from one semantic category together, or whether they switched between categories as they recalled individual words. If four categories are recalled, it is only necessary to switch category three times. Therefore the proportion of unnecessary category switches made in the recall of each list can be calculated using the formula:

$$\frac{\text{No. category switches made} - \text{No. categories recalled} + 1}{\text{No. categories recalled} - 1}$$

However analysis revealed no differences between the Control and Frontal groups in terms of unnecessary category switches (Kruskal–Wallis: effect of "Group" $p = 0.53$). Analysis of variance again showed no effect of List Organisation (blocked vs. random), nor any Group × List Organisation interaction. Again, our results provide no evidence for impairments in the use of organisational strategies in any Frontal group (Fig. 3).

Intrusion rates in free recall are presented in Fig. 4. Contrary to predictions, no Frontal group had elevated intrusion rates compared to Controls (Mixed Model ANOVA: effect of between-subjects factor "Group" $p = 0.38$). Neither was there any effect of List Organisation (blocked vs. random), Intrusion Type (extra-list vs. prior-list), nor any significant interactions.

3.2.2. *Recall after prompting*

Fig. 5 shows the rates of additional correct recall and additional intrusions produced after the category prompts were given.

Analysis of additional correct recall obtained with prompting revealed that the Right Lateral group benefited from prompting, being the only group to produce significantly more additional correct recalls with the aid of prompting than Controls (Kruskal–Wallis effect of "Group" $p = 0.02$; Pairwise Mann Whitney comparisons Right Lateral > Control $p = 0.003$). In fact, comparison of total correct recall rates (initial free recall + prompting) revealed that after prompting, the Right Lateral and Control groups no longer differed in recall performance (independent t test: $p = 0.13$). Analysis of variance again showed no significant effect of List Organisation (blocked vs. random), nor a Group × List Organisation interaction.

Analysis of additional intrusions produced following prompting revealed several effects. First the Orbital and Medial groups both produced significantly higher rates of post-prompting intrusions than Controls (Mixed Model ANOVA: effect of between-subjects factor "Group" $p = 0.001$; Pairwise comparisons Orbital > Control $p < 0.001$, Medial > Control $p = 0.004$). There was no effect of List Organisation (blocked vs. random) or of Intrusion Type (extra-list vs. prior-list). However there was a significant Intrusion Type × Group interaction ($p = 0.04$). Follow-up analysis indicated that this was due to two factors. Firstly, the Control group produced significantly more extra-list than prior-list intrusions following prompting (paired t test:

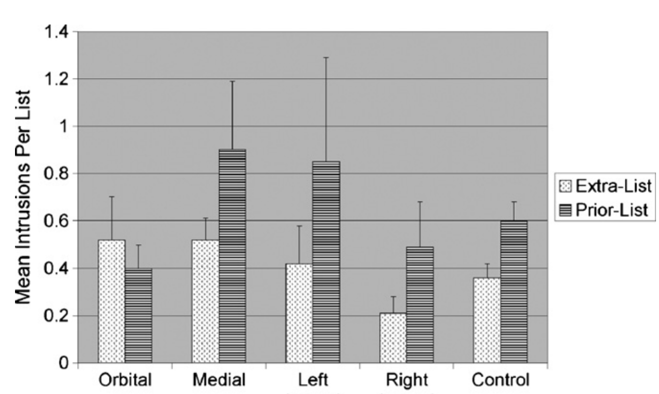

Fig. 4. Mean extra-list and prior-list intrusions produced in free recall by Orbital, Medial, Left Lateral, Right Lateral and Control groups. Bars represent mean scores and error bars represent standard error of the mean. As no effect of list presentation was found data from blocked and random lists are collapsed in these figures.

[2] In group analyses using Kruskal–Wallis due to unequal variance, data from blocked and random list presentation are combined.

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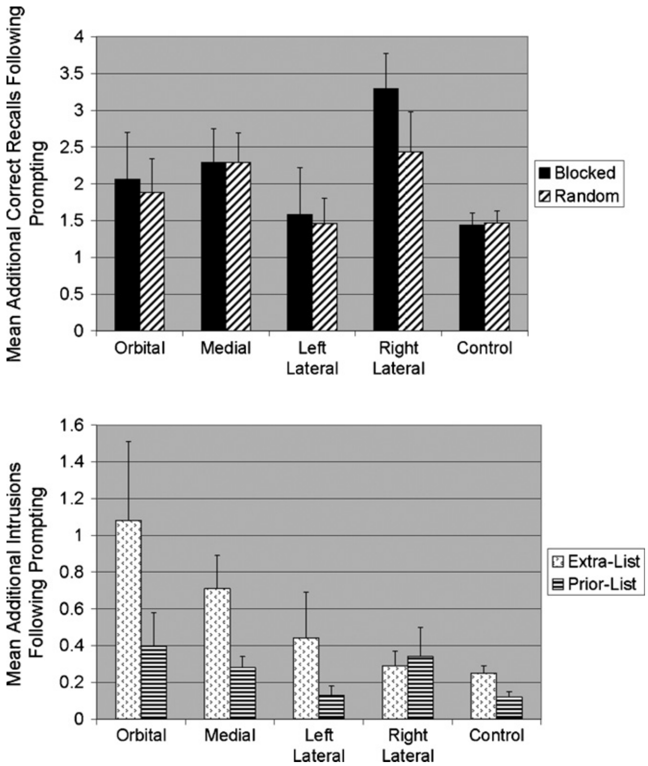

Fig. 5. Mean additional correct recalls and additional intrusions produced following prompting by Orbital, Medial, Left Lateral, Right Lateral and Control groups. Bars represent mean scores and error bars represent standard error of the mean. Data do not include rates of correct recall and intrusions from initial free recall. As no effect of list presentation was found, intrusion data from blocked and random lists are collapsed.

$p = 0.001$), whilst the Orbital, Medial, Left Lateral and Right Lateral groups' rates of extra-list and prior-list intrusions did not differ. Secondly, whilst analysis of group differences in the rates of extra-list intrusions revealed only a trend towards significance (Kruskal–Wallis effect of Group $p = 0.06$), when prior-list intrusions were analyzed the Right Lateral group were the only group found to produce significantly more prior-list intrusions than Controls (Kruskal–Wallis effect of Group $p = 0.05$; Pairwise comparisons Right Lateral > Control $p = 0.009$). In contrast to the general trend (where rates of extra-list intrusions were higher than rates of prior-list intrusions) the Right Lateral group shows a very different pattern of responding following prompting, with rates of extra-list intrusions identical to the Controls, but an elevated prior-list intrusion rate.

3.2.3. Monitoring

During recall of the word lists, an assessment of monitoring ability was made by asking participants to indicate, for each word they recalled, whether it had already appeared in a previous list, or was a new item.

Fig. 6 shows rates of misses (the percentage of repeated words that were not identified as repeated) and false positives (the percentage of new words that were incorrectly identified as repeated) in each group. However analysis revealed no difference between Orbital, Medial, Left Lateral, Right Lateral and Control groups on misses (Univariate ANOVA: $p = 0.15$), false positives (Univariate ANOVA: $p = 0.18$), or these errors combined (Kruskal–Wallis: $p = 0.30$). Contrary to predictions no monitoring impairments were found in any group.

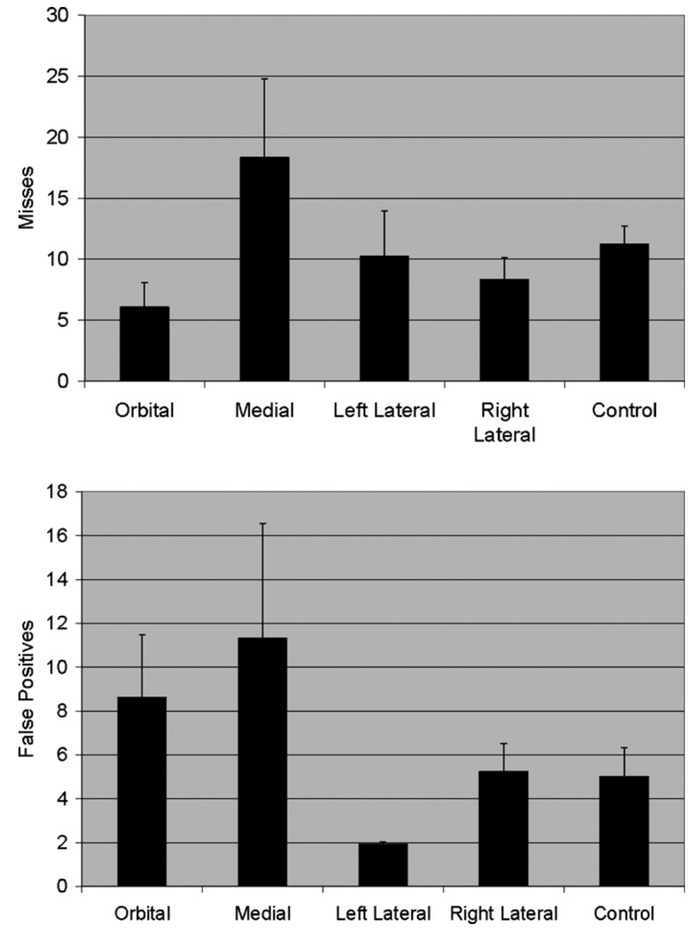

Fig. 6. Rates of misses (the percentage of repeated words that were not identified as repeated) and false positives (the percentage of new words that were incorrectly identified as repeated) by Orbital, Medial, Left Lateral, Right Lateral and Control groups in the monitoring task. Bars represent mean scores and error bars represent standard error of the mean.

4. Discussion

Our study confirms previous reports that patients with frontal lobe lesions may show impairments on verbal free recall tasks (Dimitrov et al., 1999; Janowsky et al., 1989; Jetter et al., 1986; Shimamura et al., 1991; Wheeler et al., 1995). However the use of more detailed anatomical groupings and the testing of specific predictions from neuroimaging and recent theoretical work have revealed more detailed results than previously reported. The first striking finding was that it was only the Medial and the Right Lateral frontal groups whose free recall was significantly impaired compared to Controls.

4.1. Medial impairments in recall

Medial frontal impairments in recall have not been frequently reported. However one reason for this may be the lack of anatomical specificity in previous lesion studies. The use of undifferentiated "frontal" groups, or comparison of left and right frontal groups is likely to have masked any medial effects. In fact when more detailed lesion localisation procedures were used, medial impairments in recall were reported by both Alexander et al. (2003) and Dimitrov et al. (1999). Alexander et al. (2003) reported that rather than being a general medial impairment, only those patients with *posterior* medial damage affecting the septum had a recall impairment. They concluded that this arose from direct disruption of the memory system due to loss of cholinergic projections to the hippocampus.

Examination of individual performance of patients within our Medial group showed that two patients had recall performance more than 2*SD* outside the range of the controls. The patient with the most severe memory deficit (patient 150) had damage extending across the entire medial region, including posterior medial regions. The other patient (patient 105) had a lesion affecting the left sub genu. Both patients had aneurysms of the anterior communicating artery, which are known to affect basal forebrain regions involved in cholinergic innervation of the hippocampus. Moreover, the fact that the medial recall impairment in our sample was unaffected by any manipulation (organisation at encoding or prompting at retrieval) does indeed indicate that it may be a more "pure" memory deficit than the strategic memory deficits often associated with frontal lobe damage. Our results therefore provide further evidence that memory impairments in medial frontal patients are associated with damage to posterior medial regions implicated in the limbo-thalamic circuit underlying memory (Petrides, 2000).

The other effect relating to the Medial group was an elevated rate of intrusions following prompting. This effect was also present in the Orbital group. This is the first evidence relating to the anatomical specificity of intrusion effects in frontal patients, and is reminiscent of the association between Orbital and Medial frontal damage and confabulation (Gilboa & Moscovitch, 2002; Schnider, 2003; Turner, Cipolotti, Yousry, & Shallice, in press). Although intrusions and confabulations are distinct phenomena, intrusions might be seen to reflect a failure to inhibit inappropriate responses and have frequently been considered a confabulatory-like behaviour and used as an approximate measure of confabulation. The present results imply that they may also have common anatomical substrates.

However it is noteworthy that in initial free recall no intrusion effects were found. This seems surprising in the light of previous evidence that patients with frontal lobe lesions show high rates of intrusions in unprompted recall (Baldo et al., 2002; Daum & Mayes, 2000; Delbecq-Derouesne et al., 1990; Melo et al., 1999). However it is consistent with Alexander et al. (2003) and Stuss et al. (1994) who found no increase in intrusions in their frontal groups compared to controls. This seems to be an empirically grey area. In our study, intrusions in Orbital Frontal and Medial Frontal patients only reached significance following a prompt. This seemed to induce an uncontrolled responding strategy in which the search in memory was widened and the response criterion relaxed. In particular the Orbital and Medial groups appeared to generate their responses from semantic memory rather than from episodic memory, which resulted in the production of non-presented words (extra-list intrusions) but no additional presented words (correct recalls and prior-list intrusions). This strategy, which was qualitatively different from that adopted by the Right Lateral group, seems likely to be related to the processes underlying provoked confabulation.

4.2. Right lateral impairments in recall

The recall impairment in the Right Lateral group initially seemed surprising in the light of previous studies which had associated left lateral frontal regions with verbal recall impairments (Alexander et al., 2003; Dimitrov et al., 1999; Incisa della Rochetta & Milner, 1993; Stuss et al., 1994; Vilkki et al., 1998). However right lateral recall impairments have in fact been previously reported by Stuss et al. (1994), Vilkki et al. (1998) and Alexander et al. (2003). The HERA model for verbal material would predict that right frontal damage would disrupt retrieval rather than encoding processes (Habib et al., 2003; Lepage et al., 2000; Nyberg et al., 1996; Rossi et al., 2001; Shallice et al., 1994; Tulving et al., 1994). It is possible therefore that the Right Lateral impairment reflects a strategy or "executive" deficit at retrieval. The argument for a strategic impairment in the Right Lateral group is supported by the performance of this group when category prompts were given to aid recall. In free recall this group produced significantly fewer correct recalls than Controls. However the provision of prompts enabled them to raise their recall to the level of the Controls. This represents the first lesion evidence to directly support imaging evidence linking the right PFC to retrieval processes.

Although this facilitatory effect of providing cues at retrieval to patients with frontal lobe damage has been reported many times previously (e.g. Dimitrov et al., 1999; Gershberg & Shimamura, 1995; Incisa della Rochetta & Milner, 1993) it has not previously been reported specifically with right frontal patients. However on closer inspection the results reported by Incisa della Rochetta and Milner (1993) do actually show a similar right frontal effect. Their data indicate an average advantage of prompting of about 7 words a list for their right frontal group by comparison with 3.5 words per list for controls. On closer examination Stuss et al. (1994) also report a potentially related finding. Their right frontal group had significant inadequacy in control of their recall, in that they would recall a word on one trial but then fail to recall it in the next. Analogous right frontal effects do therefore seem to have been present in previous research, but have not been specifically highlighted.

Prompting also produced an unusual pattern of intrusions in the Right Lateral group. The general trend was to produce more extra-list than prior-list intrusions. However the Right Lateral group showed a different pattern, with significantly higher rates of prior-list intrusions following prompting than the Controls, but equal rates of extra-list intrusions. In contrast to the Medial and Orbital groups (who widened their search and relaxed their response criterion), the Right Lateral group adopted a controlled responding strategy in which they produced additional recalls from episodic memory. This meant that they produced additional presented items (correct recalls and prior-list intrusions) but not extra-list intrusions. As discussed in the Introduction, this pattern of performance may indicate the failure of a right lateralised error detection and checking system (Shallice, 2001, 2006).

The failure of such a system was firstly hypothesised to disrupt the ability to reject plausible alternatives, and lead to susceptibility to capture errors (which are known to occur in right frontal patients in a problem-solving paradigm; Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005). In our paradigm capture errors were best represented by sensitivity to proactive interference and prior-list intrusions. Unlike extra-list intrusions, these words *had* previously been presented. They arose from episodic rather than semantic memory, were associated with high familiarity, and were therefore the most difficult to reject. Thus the higher rate of prior-list than extra-list intrusions is consistent with the predictions of an error detection and checking failure.

The error detection and checking system was secondly hypothesised to be most critical in conditions of uncertainty. Conditions of uncertainty in retrieval will be at their peak after initial production of easy recall is over, and when subjects are engaged in a more effortful attempt to ferret out additional words that do not come easily to mind. Therefore failures of the error detection and checking system, and an increase in proactive interference responses, should be expected to occur particularly following the prompt. Interactions in the analysis of post-prompting intrusions revealed exactly this pattern. The general trend was to produce more extra-list than prior-list intrusions following a prompt. However the Right Lateral group showed a different pattern, with significantly higher rates of prior-list intrusions following prompting than the Controls, but equal rates of extra-list intrusions.

Overall, the patients in the Right Lateral group would produce the words which came easily to mind during the initial stages of free recall, but would appear not to initiate a more effortful second stage in which a careful check is made to retrieve potentially accessible additional words that do not come easily to mind. However the provision of prompts cued the additional veridical recall which would have been produced with this second stage, raising their level of recall to that of Controls. The artificial induction of this second stage of recall also made obvious their impairment in error detection and checking processes, as they were unable to reject the prior-list intrusions also cued by the prompt.

The third prediction relating to the error detection and checking system was that it should be initiated especially when on-line monitoring is required. Therefore we expected to find a Right Lateral impairment in the ability to monitor, during recall, those words which had already been presented in an earlier list. However no Frontal group showed any impairment in their ability to monitor repeated items in their recall. This is surprising in the light of several studies that have linked the right dorsolateral region to monitoring functions (Cabeza et al., 2003; Fletcher et al., 1996; Fletcher, Shallice, Frith, et al., 1998; Henson, Shallice, et al., 1999; Shallice, 2001, 2006; Stuss et al., 1994). It is of course possible that the current procedure was not sensitive enough to detect monitoring deficits. However examination of the data does not even indicate a trend towards monitoring impairments in the Right Lateral group. If anything, they perform rather better on the monitoring task than Controls. If this null result is robust, there are two potential implications for monitoring accounts of the right dorsolateral PFC.

One possibility is that our task was tapping a different monitoring function to those previously associated with frontal lesions. In neuroimaging studies "monitoring" has been used to describe checking of single items or word pairs in recognition (Cabeza et al., 2003; Fletcher et al., 1996), keeping track of free recall (Fletcher, Shallice, Frith, et al., 1998), and identification of source (Cabeza et al., 2003; Henson, Shallice, et al., 1999). In the lesion study reported by Stuss et al. (1994) monitoring referred to the ability to keep track of items that had already been produced in recall. The monitoring task in the present experiment was slightly different in that it demanded monitoring of repetitions in *presentation*. Dobbins, Simons, and Schacter (2004) in an fMRI study reported greater right dorsolateral PFC activation associated with judgements of frequency in a memory retrieval task, a task which is conceptually similar to that in the current experiment. However their task involved estimations of frequency for items which had all been presented at least twice (a task which is known to present problems for patients with right frontal lesions, Smith & Milner, 1988). Success in their task was assumed to depend on monitoring of familiarity. The task in the current study can be done by monitoring of fairly closely contrasted familiarity for items which either had been presented once or twice, but it is also possible and probably easier to use recollection of whether an item had occurred on the previous list. As such it could involve the right frontal lobe less (Henson, Rugg, et al., 1999) This finding though, reinforces the need for a clearer specification of the monitoring account of the right dorsolateral PFC. On the base of the current findings, it does not appear that the right lateral PFC (or at least those regions affected in our sample) is *necessary* for processes such as explicitly requested determination of repetitions which occurred at presentation.

The other possibility is that the function undertaken by the right dorsolateral PFC is more general than error detection and checking. Instead it may reflect the more general possibility of an active uncued initiation of a supervisory operation (AUISO). Active checking (along with other effortful processes) requires that the subject spontaneously (without any cue or learned procedure to do it) initiates an active process to check on the solution achieved so far. It is possible that it is this spontaneous initiation of a supervisory operation which is the component of active checking that is lateralised to the right. This would explain the lack of a Right Lateral on-line monitoring impairment in the current experiment, because the monitoring task involved an explicit instruction to carry out an operation on each retrieved response and thus did not require *spontaneous* initiation of a supervisory process. The AUISO hypothesis also accounts for the Right Lateral group's decreased recall performance without prompting and the increase in veridical recall following prompting: In free recall, all groups were able to successfully complete the initial stage of retrieval in which they produced words which came easily to mind. Following this, all Frontal groups other than the Right Lateral group spontaneously initiated a second stage of retrieval in which an effortful search for extra words was conducted. The Right Lateral group was unable to initiate this stage and stopped the recall attempt. However the provision of a prompt cued this second stage externally, enabling them to increase their veridical recall to the level of controls. The downside of this was the creation of a situation where prior list intrusions were potentiated, yet there was no explicit instruction to monitor for these. Under these circumstances the Right Lateral group was unable to spontaneously initiate an error detection and checking process, resulting in an increase in false positives.

4.3. Organisational strategies at encoding and retrieval

Recall impairments in patients with frontal lobe lesions have traditionally been attributed to impairments in the use of organisational strategies at either encoding or retrieval (Eslinger & Grattan, 1994; Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rochetta, 1986; Incisa della Rochetta & Milner, 1993; Kopelman & Stanhope, 1998; Vilkki et al., 1998). However our results found no evidence for organisational impairments in frontal lobe damaged patients.

At encoding, externally provided organisation (in the form of presenting lists blocked by semantic category) conferred no recall advantage on any group compared to presenting information randomly. This is in contrast to lesion evidence suggesting that recall deficits in frontal patients may be at least in part due to a failure to organise material at encoding (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rochetta, 1986; Kopelman & Stanhope, 1998), and is also contrary to findings from neuroimaging work, which suggest that the left lateral PFC plays a key role in organisation at encoding (Fletcher, Shallice, & Dolan, 1998; Savage et al., 2001; Wagner et al., 2001).

Deficits in strategy production, including the semantic categorisation of word lists at encoding, have been specifically linked to the *left dorsolateral* PFC (Fletcher, Shallice, & Dolan, 1998; Savage et al., 2001; Shallice, 2006). It may be that our failure to find strategic deficits of this type was a result of the make-up of our left lateral group, the majority of whom had more ventrolateral lesions. However it then seems surprising that other studies using detailed lesion localisation techniques have failed to associate deficits in organisation at encoding with left dorsolateral lesions (Stuss et al., 1994).

In fact, closer examination of the previous lesion studies reveals that those studies which did report frontal impairments in the use of organisational strategies at encoding measured either verbal reports of the use of organisational strategies (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988), or tested the effects of providing instructions to use categorisation at encoding on the recall of randomly presented (but categorisable) materials (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rochetta, 1986). These studies did not compare recall of lists blocked by semantic category to recall of lists presented randomly. In fact in studies where this comparison was made, none have reported any disproportionate benefit of blocking in frontal groups compared to control groups (Incisa della Rochetta & Milner, 1993; Kopelman & Stanhope, 1998; Stuss et al., 1994). It may be that this type of measure is insensitive to organisational impairments in patients with frontal lobe lesions. However it should be pointed out that due to the repetition of words across lists, the current design was not optimal for detecting a blocked versus random effect.

An investigation of organisation at retrieval was conducted by examining category clustering in recall. However there was no evidence that any Frontal group were switching categories in their recall any more than the Control group. This is in contrast to the findings of Baldo et al. (2002) and Gershberg and Shimamura (1995) who reported that frontal patients had reduced category clustering in recall. It may be that the inclusion of blocked as well as random lists in our study made the strategy of semantic categorisation more obvious to participants, and masked any organisational deficit that may have been present. However Stuss et al. (1994) and Alexander et al. (2003) also failed to find impairments in semantic category clustering in recall in their frontal patients, and the Alexander et al. (2003) study used the CVLT, which does not contain blocked lists. The reasons for the discrepancies between these studies remain unclear. However in our sample at least, strategic organisation in the form of category clustering at retrieval is not impaired.

4.4. The lack of left lateral recall impairments

As mentioned above the lack of left frontal effects in the current experiment was surprising. There are several reasons why this might be the case. The first is the grouping methods employed in previous lesion studies. In the Dimitrov et al. (1999), Incisa della Rochetta and Milner (1993) and Vilkki et al. (1998) studies patients were only grouped by hemisphere, so any medial patients in these studies were incorporated into the lateral groups. These studies may be consistent therefore with our Medial impairment in recall. However the more anatomically specific studies of Alexander et al. (2003) and Stuss et al. (1994), also reported that their left dorsolateral patients (with lesions affecting especially areas 44, 9 and 46) had the greatest impairment in recall. In these studies the authors concluded that the underlying reason for the recall impairments in their left lateral groups was a mild language impairment. Our Left Lateral group was rather more ventrolateral (see Fig. 1), and while testing of language was limited, no language impairments were detected (see Table 2). It may be that left frontal impairments in verbal recall will only be found when a language impairment is present.

4.5. Conclusions

The use of a structured verbal recall task confirmed previous reports that patients with frontal lobe lesions may show impairments in recall tasks. However more detailed lesion grouping revealed that only those with Medial frontal or Right Lateral frontal lesions were significantly impaired compared to Controls. We propose that our results reflect the existence of two functionally distinct deficits arising from different regions of damage within the PFC: a medial frontal impairment that arises from direct disruption of projections from the ventromedial frontal cortex to the medial temporal lobe limbic system, and a right lateral frontal impairment that is secondary to a strategic or "executive" deficit at retrieval. This hypothesis is supported by the Right Lateral group's response to prompting, which resulted in an increase in veridical recalls, and also an unusual pattern of intrusions, namely an increase in proactive interference responses compared with extra-list intrusions. Contrary to predictions, monitoring impairments were not found in this group. We offer two explanations for the Right Lateral impairment. Firstly it may reflect a specific impairment of error detection and checking processes overseen by the right dorsolateral PFC (Shallice, 2006). Secondly, it may reflect a broader impairment in the active uncued initiation of a supervisory operation (AUISO).

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Appendix A. Lesion location and aetiology of individual frontal patients

		LEFT												RIGHT											
		Orbital	Medial					Lateral						Orbital	Medial					Lateral					
		Orb	SG	ACC		SFG		SFG		MFG		IFG		Orb	SG	ACC		SFG		SFG		MFG		IFG	
				ant	pos	ant	pos	ant	pos	ant	pos	ant	pos			ant	pos	ant	pos	ant	pos	ant	pos	ant	pos
Orbital Group																									
102	ACoA	●												●											
108	ACoA	●																							
110	AVM													●											
118	Meningioma													●											
123	ACoA	●																							
130	ACoA	●																							
141	ACoA	●																							
142	Haematoma													●											
143	ACoA	●												●											
148	Abscess	●						●						●	●			●		●					
155	ACoA													●											
Medial Group																									
103	Glioma			●	●	●																			
105	ACoA		●																						
115	Haematoma																●		●		●		●		
117	Glioma																	●						●	
126	Metastasis																		●						●
144	Glioma				●		●						●												
145	ACoA															●									
150	ACoA			●	●											●	●	●							
Left Lateral Group																									
106	Meningioma	●										●	●												
109	Glioma	●		●		●		●		●		●	●												
120	Haematoma	●						●		●	●	●	●												
122	ACoA	●						●																	
137	Metastasis									●	●														
138	Glioma	●										●	●												
139	Glioma										●														
154	Glioma	●	●	●				●	●	●	●	●	●												
Right Lateral Group																									
111	Meningioma																				●		●		
119	Haematoma																					●	●	●	●
121	Meningioma																			●	●	●	●		
125	Glioma																					●		●	
127	Meningioma																	●	●	●	●	●	●		
135	Glioma																			●	●	●		●	
156	Meningioma																			●					

Dots indicate that at least 25% of the region is affected by the lesion. Orb: Orbital; SG: sub genu; ACC: anterior cingulate cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; ant: anterior; pos: posterior.

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