Impaired List Learning Is Not a General Property of Frontal Lesions

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Abstract

■ **Background:** List-learning tasks are frequently used to provide measures of ''executive functions'' that are believed necessary for successful memory performance. Small sample sizes, confounding anomia, and incomplete representation of all frontal regions have prevented consistent demonstration of distinct regional frontal effects on this task. **Objective:** To confirm specific effects of lesions in different frontal regions. **Subjects:** Forty-one patients with chronic focal frontal lesions and 38 control subjects. There were no group differences in naming scores. **Methods:** Two word lists were presented, one with unblocked words from related categories and one in a preblocked format. Standard measures of learning, recall, recognition, and strategies were obtained, first for the frontal group as a whole and then for large but defined frontal regions. For all measures with significant group differences, a lesion ''hotspotting'' method identified possible specific regional injury effects. **Results:** The frontal group was impaired on almost all measures, but impairments on most measures were particularly identified with lesions in the left superior frontal lobe (approximately area 9s) and some deficits in learning processes were surprisingly more prominent on the blocked list. **Conclusion:** Difficulty with list learning is not a general property of all frontal lesions. Lesions in different frontal regions impair list learning through specific mechanisms, and these effects may be modified by manipulations of the task structure. ■

INTRODUCTION

Unless there is damage in or near the septal nuclei, frontal lesions do not produce amnesia (Stuss et al., 1994; Irle, Wowra, & Kunert, 1992; Alexander & Freedman, 1984), but lesions in other parts of the frontal lobes can cause a variety of impairments in learning and recall (Davidson, Troyer, & Moscovitch, 2006; Wheeler, Stuss, & Tulving, 1995). Although the effect of these lesions of the frontal lobes on learning and memory has been approached from several directions, a comprehensive account of these effects has been elusive. This is, in part, because there are so many effects of frontal lesions on memory: on source memory (Eslinger & Grattan, 1994; Johnson, Hashtroudi, & Lindsay, 1993), sequential memory, self-ordered versus cued learning (Petrides, 1995), learning strategies (Gershberg & Shimamura, 1995; Eslinger & Grattan, 1994; Stuss et al., 1994; Incisa della rocchetta & Milner, 1993; Janowsky, Shimamura, Kritchevsky, & Squire, 1989), sensitivity to interference (Baldo, Delis, Kramer, & Shimamura, 2002; Incisa della rocchetta & Milner, 1993), recall versus recognition memory (Alexander, Stuss, & Fansabedian, 2003; Kopelman & Stanhope, 1998; Janowsky et al., 1989), susceptibility to false recognition (Verfaellie, Rapcsak, Keane, & Alexander, 2004; Schacter, Curran, Galluccio, Milberg, & Bates, 1996), use of familiarity versus recollection (Schnyer et al., 2004; Wheeler & Stuss, 2003), confidence of recall judgments or predictions (Schnyer et al., 2004; Vilkki, Servo, & Surma-aho, 1998), and ''metamemory'' generally (Davidson, Troyer, & Moscovitch, 2006).

One tool that is often used to analyze learning in brain-injured patients is list learning (Delis, Kaplan, Kramer, & Ober, 2000; Delis, Kramer, Kaplan, & Ober, 1987). Patients with frontal lobe lesions are impaired on list learning tasks (Alexander et al., 2003; Baldo et al., 2002; Vilkki et al., 1998; Stuss et al., 1994; Incisa della rocchetta & Milner, 1993). They are more impaired on learning lists than they are on learning and recalling semantically organized material such as stories (Janowsky et al., 1989). Proposed explanations for the impairment on list learning revolve around reduced availability or recruitment of one or more strategies that might capture the supraspan list, such as subjective ordering—an idiosyncratic linking of words (Alexander et al., 2003; Eslinger & Grattan, 1994; Stuss et al., 1994); semantic clustering—linking words by meaning relationships (Gershberg & Shimamura, 1995; Eslinger & Grattan, 1994; Stuss et al., 1994); or generating semantic cues to facilitate encoding (Stuss et al., 1994; Incisa della rocchetta & Milner, 1993), and presumably, subsequent retrieval.

A completely clear account of the mechanisms by which frontal lesions might impair list learning has, nevertheless,

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been elusive for several reasons. First, all of the proposed executive strategies are explicitly or implicitly dependent on semantic or lexical functions, and even mild anomia influences their effectiveness. Second, although all reports are, by definition, of list learning, different reports have used lists with quite different properties. Third, most studies have had small patient groups with all frontal lesion sites considered a single ''frontal group'' to allow sufficient statistical power. This lumping invariably leads to a conclusion, at least implicitly, that there is a general ''frontal'' effect on learning even when post hoc analyses have sometimes identified frontal regions that play more significant roles in memory (Alexander et al., 2003; Stuss et al., 1994; Incisa della rocchetta & Milner, 1993).

In the present report, we describe the results of a list learning experiment that addressed the three limitations described above. First, a stringent cutoff for anomia was implemented. Second, two list structures were used to analyze the effects of presentation with explicit semantic ordering (blocked) as opposed to the standard clinical tests such as the CVLT-II (Delis et al., 2000) with pseudorandom ordering (unblocked). Third, we recruited 41 patients with well-defined focal frontal lesions, a very large subject group compared to most reports, and sufficient to address some potential regional effects. These are the same subjects reported in a series of studies of attention in which regional effects were demonstrated.

METHODS

Subjects

We tested 41 patients with frontal lesions and 38 nonpatient controls (controls), matched as closely as possible to the patients for sex, age, and education. All patients met the following inclusion criteria: at least 2 months (all but one past 3.6 months) post onset (mean = 22 months; range = 2 to 109 months); IQ within the normal range (patients: $M = 108$, $SD = 8.9$; controls: $M = 112$, $SD = 6.7$; all scores >90). To be included, patients had to have normal language comprehension (Token Test; De Renzi & Vignolo, 1962), no evidence of active depression (Beck Depression Inventory; Beck & Steer, 1993), and no history of any other significant neurological or psychiatric disorders. The National Adult Reading Test—Revised (NART-R) was administered as a measure of general intellectual ability. Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was a measure of lexical–semantic function. Digit span forward and backward was a measure of simple immediate verbal span. All patients and controls gave informed consent in accordance with the Institutional Review Board requirements of the University of Toronto and Baycrest Centre for Geriatric Care.

The etiologies of the lesions included infarction, hemorrhage (including ruptured aneurysms with secondary infarction or intracerebral hemorrhage), trauma, and tumors. Patients with trauma had well-defined focal contusions and no or only brief loss of consciousness. All trauma patients were more than 5 months post onset (most more than 24 months), allowing for complete recovery from acute phase factors such as edema or hemorrhage. Patients with tumors all had resection of meningiomas or low-grade gliomas, were tested more than 6 months postsurgery, and had no evidence of recurrence. None had brain radiation. Although it would be preferable to create groups differing only in lesion site, and not in etiology, it is impossible to gather patients with lesions in all frontal regions because different etiologies have predispositions for different regions (Stuss, Shallice, Alexander, & Picton, 1995), and the location of lesions is more critical than the etiology in determining cognitive deficits (Elsass & Hartelius, 1985). Etiology has had no effect on results in any of our previous reports with a similar patient population (Picton, Stuss, Shallice, Alexander, & Gillingham, 2006; Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Stuss et al., 2005).

Lesion localization was established with a standard template (Petrides & Pandya, 1994; Damasio & Damasio, 1989) using postacute CT in 61% and late MRI, relying predominantly on T1-weighted images, in 39%. Lesion size was quantified by superimposing the lesion contour for each axial slice onto a constant pixel diagram and counting the number of pixels within the lesion area. The percentage of total brain volume damaged was obtained by dividing the lesion count by the total pixel count for all axial slices.

The patients and controls reported in this study are identical to the groups in an earlier paper except for two patients (2146 and 2166) in that study who did not participate in this study due to scheduling difficulties; summaries of demographic data neuropsychological test results and lesion maps can be found in that paper (Alexander, Stuss, Shallice, Picton, & Gillingham, 2007). Patients were assigned to exactly the same region of injury groups as in the earlier study: superior medial (SM; $n = 11$), inferior medial (IM; $n = 13$), right lateral (RL; $n = 6$), and left lateral (LL; $n = 11$).

Experimental Procedure

Two 16-word lists were created. The blocked list included four exemplars from four semantic categories (footwear, flowers, tools, and vegetables) with the items from each category presented sequentially. The unblocked list had four exemplars from four different semantic categories (house parts, insects, birds, and geographic formations) presented in pseudorandom order such that no two items from the same category were adjacent. The frequencies, imageability, and familiarity ratings were equivalent for both lists and for recognition foils. Each of those measures was identical to the blocked

and unblocked lists used in an earlier study (Stuss et al., 1994).

The list-learning tasks were performed during a full day of neuropsychological and reaction time tests. The words in each list were presented in the same order five times at a rate of about one every 2 sec. At the end of each presentation, subjects were instructed to repeat as many of the words as they could recall in any order, including words repeated in earlier trials, with the explicit goal of recalling every word. All subjects then performed reaction time and other neuropsychological tasks for 20 to 25 min before they were again instructed to try to recall the words in any order (delayed free recall). They were allowed as much time as they required. A forced-choice recognition task followed immediately with the 16 targets and 16 foils from the same four semantic categories. The unblocked list was always presented first. The blocked list was presented about 2 hr later in the day after several more reaction time and neuropsychological tests and a 1-hr lunch break. The unblocked task was presented first to prevent the subjects from prematurely gaining explicit knowledge of the possibility of semantic clustering.

The key dependent measures were the number of items recalled correctly in each trial, the total correct over five trials, the difference between Trial 1 (T1) and Trial 5 (T5) and the slope across five trials as measures of learning efficiency, the total recalled after delay, and recognition hits/misses and false positives. There are numerous possible measures of learning strategies. If any strategy is repeatedly used successfully over trials, this will be captured by a consistency score. Only further analysis will pinpoint which strategy is actually implemented: semantic cluster index (words consecutively recalled from the same category) or subjective ordering index (words recalled in adjacent positions on consecutive trials)—controlled for the total number of words recalled. [These measures were used in an earlier study (Alexander et al., 2003), and details of the computations and measures can be found there.]

Analysis

For purposes of comparison to previous research, our strategy for statistical analyses followed the approaches previously used, with increasing specification of lesion analysis. For the first level of analysis, the entire group of patients was compared to the controls in the unblocked condition with a series of one-way ANOVAs for each of the memory measures. This is the analysis reported most commonly in the literature. This was repeated for the blocked condition. The second level of analysis was a series of two-way mixed-factor [group (frontal vs. control) and condition (blocked vs. unblocked)] ANOVA on each memory measure: Interactions would identify any specific effects of condition. For the third level of analysis, the same serial ANOVA strategy was applied—for the blocked and unblocked conditions separately—to the patients split into four coarse regional groups, each compared to controls.

Lesion localization effects were probed for all significant analyses using a ''hot spot'' technique described in several earlier publications. Working from standard templates (Petrides & Pandya, 1994; Damasio & Damasio, 1989) for frontal localizations in each patient, every Petrides and Pandya (1994) architectonic area was coded as damaged (greater than 25% of its area) or not. For each area, the group of patients who had lesions in that area were compared to all patients who had no damage to that area using t tests. This approach maps the full range of the behavioral variables (initial performance, learning over time, delayed recall, organizational strategies, and recognition) on to different areas of the brain and identifies ''hot spots,'' architectonic areas most related to the abnormal findings.

There are a number of limitations to this method. It is very susceptible to type 1 error because of the large number of comparisons, so we interpret the results cautiously to *suggest* more precise localizations. Using CT and T1 MRI to localize critical regions risks underestimating lesion extent, a problem that paradoxically risks hyperlocalizing lesions. Lesions are mapped onto a standardized template, but there is variation in the exact extent and local geography of Brodmann's areas. Claims for any specific Brodmann's area can only be approximate. Brodmann's areas differ considerably in size, risking overemphasizing small regions with small lesions over large regions with small lesions; this would potentially create false-positive correlations. In addition, there is variability in the number of cases with lesions in each area. To minimize these problems, effect sizes were computed for each area, and only areas that were involved in three or more subjects were included. The conventional definitions of effect size are $d = 0.8$ as large, $d = 0.5$ as medium, and $d = 0.2$ as small (Cohen, 1988).

RESULTS

All Patients versus Controls—Unblocked Condition

Acquisition

The frontal group recalled significantly fewer words than the controls for the analyses of T1, T5, and the total over five trials (Table 1).

For measures of learning, neither the slope across trials nor the T5–T1 difference was significant, although a ceiling effect may mask differences.

Learning Strategies

The frontal group had less consistency ($p = .022$), but there were no differences on the semantic clusters or subjective organization indices. These indices themselves

Table 1. Results of Learning and Delayed Recall for the Whole Frontal Group

	Blocked	*Unblocked*
Trial 1		
Frontal	7.63* (0.41)	7.71*** (0.34)
Control	9.87 (0.49)	8.63 (0.29)
Trial 5		
Frontal	13.66* (0.49)	12.02** (0.50)
Control	15.55 (0.17)	13.74 (0.37)
Trials 1 to 5		
Frontal	58.98* (1.99)	52.34** (2.18)
Control	69.18 (1.39)	59.84 (1.46)
Delayed Recall		
Frontal	10.98* (0.67)	10.22*** (0.64)
Control	14.21 (0.41)	12.21 (0.60)

*Significantly different from controls ($p < .001$).

**Significantly different from controls ($p < .01$).

***Significantly different from controls ($p < .05$).

strongly correlate (for all subjects, $r = .775$, $p = .0001$; for frontal subjects, $r = .774$, $p = .0001$). Regression analyses indicate that they may account for up to 44% of the variance in recall. A scatterplot of the relationship between semantic organization and recall on T5, when subjects should have maximal experience with test items and the possibility of organizing them, is demonstrated in Figure 1.

Delayed Recall

The frontal group recalled fewer words than controls ($p = .006$) (Table 1). The difference between the number recalled on T5 and at delay was the same in the two groups, suggesting equivalent forgetting in patients and controls.

When recall at T5 and at delay was covaried for recall at T1, there was no interaction with group. For both frontal and control groups, recall at T1 had a significant effect on recall at T5 [$F(1, 77) = 7.48$, $p = .008$].

Recognition

There was no difference in the number of subjects with more than one miss (χ^2, $p = .15$) or more than one false positive (χ^2, $p = .28$).

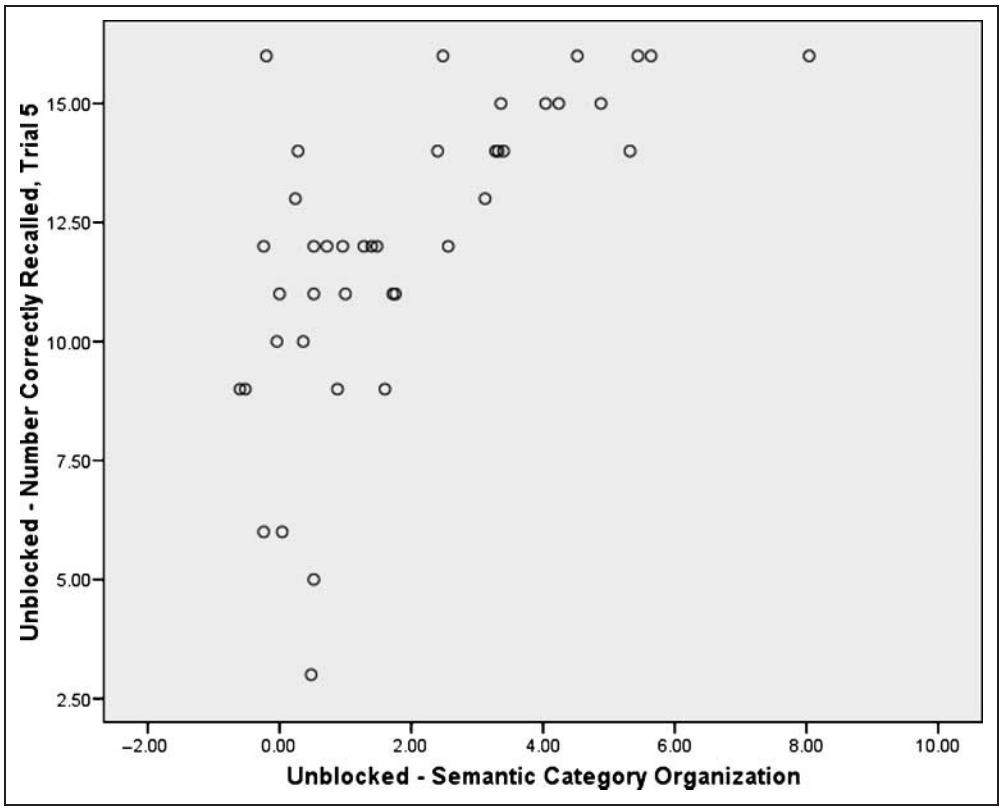

Figure 1. Scatterplot relationship between semantic organization and recall at Trial 5 of the unblocked list in the entire patient group: $r = .662$. Linear regression standardized coefficient was beta = .662, $t(39) = 5.51$, $p < .0005$.

Summary

On the unblocked list, the frontal group recalled fewer words on first exposure, total learned, and delayed recall, with no specific differences in the measures of strategic processing (''executive'' function).

All Patients versus Controls—Blocked Condition

Acquisition

The frontal group again recalled significantly fewer words than the controls for the analyses of T1, T5, and the total over five trials (Table 1).

For measures of learning, neither the slope across trials nor the T5–T1 difference was significant, but again with a ceiling effect in controls.

Learning Strategies

The frontal group had less consistency ($p < .001$), and there were significant differences on both the semantic cluster ($p < .001$) and subjective organization ($p < .001$) indices. These measures correlate even more highly on the blocked list than the unblocked list (for all subjects, $r = .837$, $p = .0001$; for frontal subjects, $r = .842$, $p = .0001$). Up to 75% of the variance may be explained by use of semantic strategy. The scatterplot for the relationship of semantic organization and recall at T5 is shown in Figure 2.

Delayed Recall

The frontal group recalled fewer words than controls ($p < .001$) (Table 1). The difference between number recalled on T5 and at delay was the same in the two groups, suggesting equivalent forgetting in patients and controls.

When recall at T5 and at delay was covaried for recall at T1, there was no interaction with group. For both frontal and control groups, recall at T1 had a significant effect on recall at T5 [$F(1, 77) = 11.73$, $p = .001$].

Recognition

There was no significant difference in the number of subjects with more than one miss (χ^2, $p = .18$). The frontal group had more false-positive responses than the control group (1.1 vs. 0.36), and significantly more frontal subjects had more than one false positive (12/41) than in the controls (4/38) (χ^2, $p = .03$).

Summary

Results are generally comparable in the two conditions, but presentation of a blocked list appeared to assist

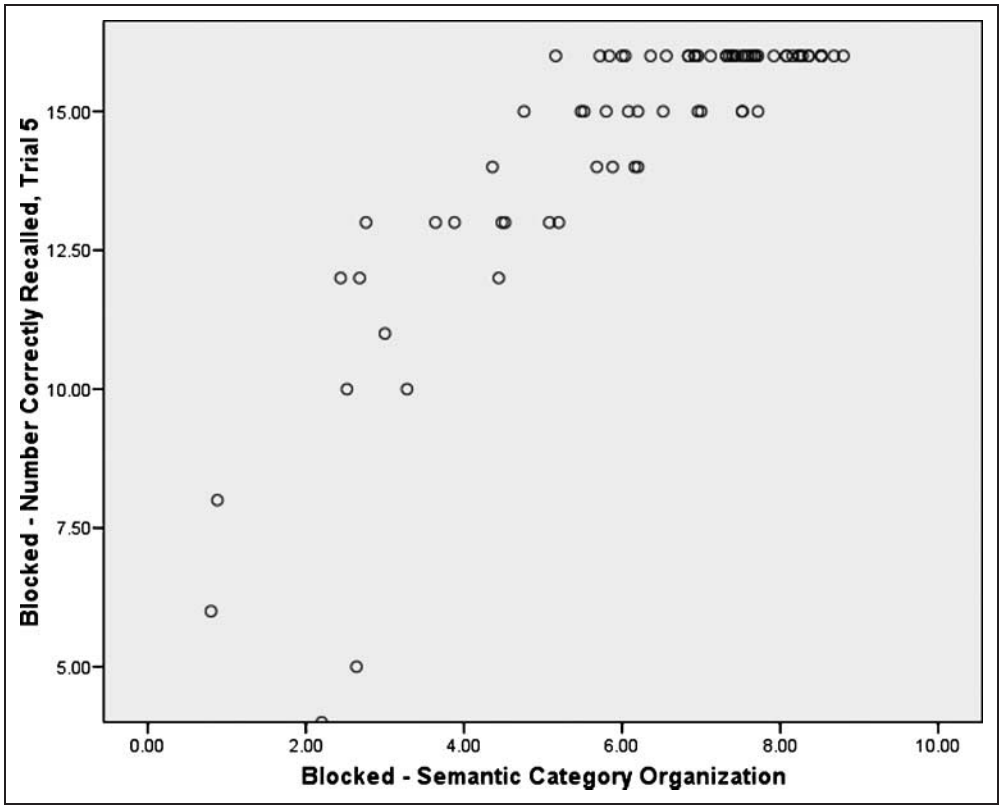

Figure 2. Scatterplot relationship between semantic organization and recall at Trial 5 of the blocked list in the entire patient group: $r = .866$. Linear regression standardized coefficient was beta = .886 $t(39) = 10.8$, $p < .0005$.

controls more than the frontal group with organization and evoked more false positives in the frontal patients than in the controls.

Direct Comparison of Conditions—Unblocked and Blocked

On all analyses of acquisition, there was a main effect of list (all ps $< .001$). More words were recalled from the blocked list. Only T1 showed an interaction effect between list and group. Controls showed greater benefit—relatively more words recalled—from the blocked list ($p = .04$).

Regarding Strategies

A three-factor ANOVA with two within-subject factors, strategy (subjective ordering or semantic) and condition (blocked or unblocked), demonstrated significant interactions: Condition × Strategy [$F(1, 77) = 18.19$, $p < .001$] and Condition × Group [$F(1, 77) = 8.72$, $p = .004$]. Although both groups used the subjective ordering strategy relatively more in the blocked condition, controls used a relatively more strategic approach on the blocked condition than the unblocked compared to frontals.

For delayed recall, there was a main effect of list ($p = .001$), fewer words recalled from the unblocked list, but no interactions.

Summary

When considered as a single, heterogeneous group, patients with frontal lesions are impaired on list learning and delayed recall and have a modest increase in false positives on recognition. Using blocked lists improves performance in patients and controls, perhaps because it explicitly allows use of semantic organization as a cue to subjective organization, but controls have relatively more benefits from the blocked presentation—better learning on first presentation and more efficient use of strategy.

Regional Frontal Groups versus Controls

There were many fewer significant results, presumably because of increased variance in the smaller groups. In both conditions, when the ANOVA indicated a significant group difference, the SM group was the only impaired group relative to the control group (see Table 2 for details.) In the unblocked condition, the SM group was impaired on T1 learning, total learned, and delayed recall, and the relationship between semantic and subjective organization was lost ($r = .553$, $p = .092$).

There were no significant group effects in recognition, but the LL and IM groups had most of the patients with excessive false positives: LL 4/11, IM 5/13, RL 1/6, SM 2/11. In the blocked condition, the SM group was impaired on T1 learning, total learned, delayed recall, semantic clusters, subjective organization, and consistency.

Table 2. Results of Learning and Delayed Recall for the Superior Medial (SM) Group

	Blocked	*Unblocked*
Trial 1		
SM	6.64** (0.66)	6.55** (0.67)
Control	9.87 (0.49)	8.63 (0.29)
Trial 5		
SM	12.36* (1.30)	10.55*** (0.93)
Control	15.55 (0.17)	13.74 (0.37)
Trials 1 to 5		
SM	53.82* (4.64)	45.64** (3.86)
Control	69.18 (1.39)	59.84 (1.46)
Delayed Recall		
SM	9*** (1.43)	7.82*** (1.35)
Control	14.21 (0.41)	12.21 (0.60)

*Significantly different from controls ($p < .001$).

**Significantly different from controls ($p < .01$).

***Significantly different from controls ($p < .05$).

Lesion Analyses

Given the finding of specific impairments in the SM group, a ''hot spotting'' procedure was carried out. This analysis is not corrected for multiple comparisons, and p values between .01 and .05 can only be considered possibly significant, and the consistency of results across tasks and functional plausibility should be weighed.

Trial 1

On the blocked list, lesions of left 9s ($p = .004$) and the right 6As ($p = .02$) were identified. On the unblocked list, lesions in a much broader area were associated with poorer performance: left 9s ($p = .001$), 9/46d ($p = .04$), 24s ($p = .04$), and right 6Ald ($p = .03$) and 9s ($p = .03$).

Trial 5

On the blocked list, lesions of left 9s ($p < .001$), 9/46d ($p = .02$) and 24s ($p = .04$), and right 6As ($p = .02$) and

9s (p = .04) were identified. On the unblocked list, lesions of left 9s (p = .003), right 9s (p = .03), and 32s (p = .03) were identified.

Total over Five Trials

On the blocked list, only lesions of left 9s (p < .001) and 9/46d (p = .03) were associated with poorer performance. On the unblocked list, lesions of left 9s (p = .004) and right 9s (p = .04) were identified (Figure 3).

Delayed Recall

On the blocked list, lesions of left 9s (p < .001), right 6As (p = .03), and 8Bd (p = .04) were associated with poorer performance. On the unblocked list, lesions of left 9s (p = .003), right 9s (p = .01), 32s (p = .01), and 24s (p = .04) were identified (Figure 4).

Subjective Organization

On both the blocked and unblocked lists, lesions of left 9s (both p = .03), 10s (both p = .04), and 10i (both p = .04) were associated with lower indices. There were no right-sided lesions identified. Trial 2 (T2) of the unblocked list was the first opportunity for subjects to demonstrate that they had noticed that were semantic categories and attempt to use them as organizing aids to learning. Only lesion in left 9s was identified as significant (p = .05).

Semantic Cluster Index

For both blocked and unblocked conditions, the same lesion sites as for subjective organization were significant.

Table 3 summarizes effect sizes for the significant results. Only regions identified in more than one analysis are included. There are scattered positive results in the prefrontal region, perhaps to be expected with this technique, but a consistent identification of left area 9s for both conditions, left area 9/46d for the learning phases of the blocked list, and for area 9s for the unblocked task.

There were no significant correlations of any experimental task with lesion size.

Correlations with Neuropsychological Tests

There were no significant differences in scores on the Boston Naming Test between any groups and controls: LDL—53 ± 4, RDL—57.2 ± 2.8, IM—56.2 ± 3.2, SM—52 ± 3.8, controls—55.5 ± 4.4. There were no correlations of naming with any result. There was an overall (patients and controls) correlation of recall on T1 with forward digit span (r = .274, p = .015).

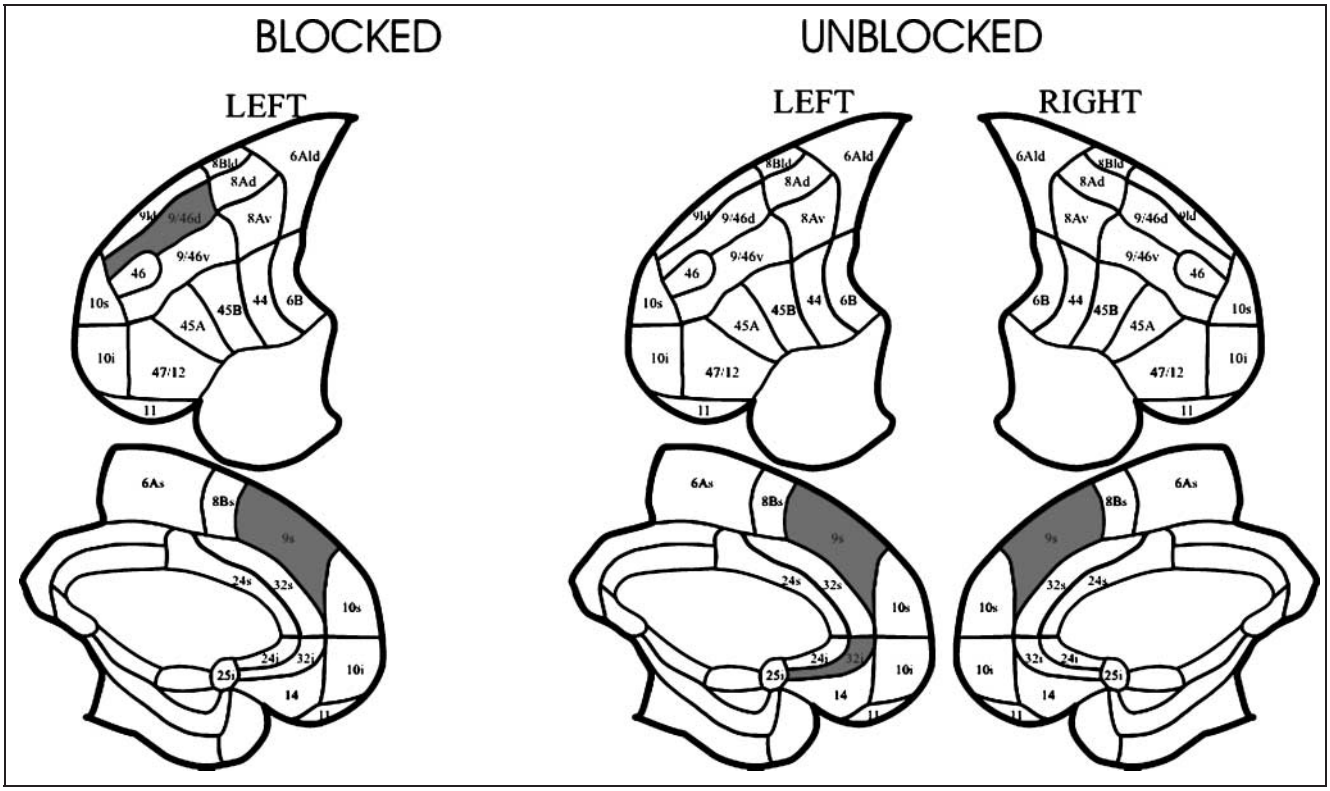

Figure 3. Regions associated with impairments in total number of words learned over five trials, blocked and unblocked lists.

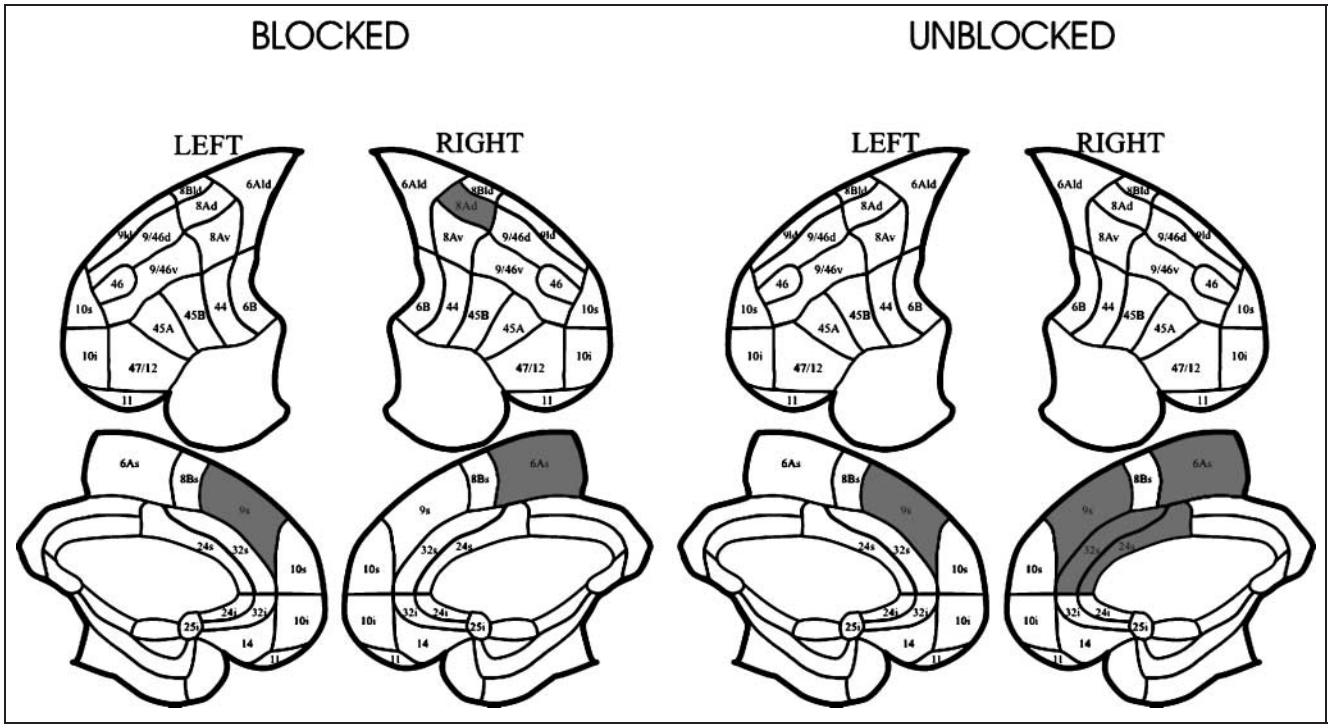

Figure 4. Regions associated with impairments in delayed recall, blocked and unblocked lists.

Table 3. Effect Sizes for All Significant ($p < .05$) Results of the Region-by-Measure "Hotspotting" Analyses

					Blocked							
	Left 10i	*Left 10s*	*Left 6Ald*	*Left 9/46d*	*Left 9s*	*Left 24s*	*Left 24i*	*Right 24s*	*Right 32s*	*Right 9s*	*Right 6As*	*Right 8B*
Trial 1					1.35						1.29	
Trial 5				1	2.68	1.09				0.69	1.23	
Trials 1–5				0.9	2.18							
Delayed					1.84		1.14				1.21	0.92
SC	0.7	0.93			0.95							
					Unblocked							
	Left 10i	*Left 10s*	*Left 6Ald*	*Left 9/46d*	*Left 9s*	*Left 24s*	*Left 25i*	*Right 24s*	*Right 32s*	*Right 9s*	*Right 6As*	*Right 8B*
Trial 1			1.07	0.08	1.81	1.07				0.75		
Trial 5					1.45	1.3			0.7	0.75		
Trials 1 to 5					1.54		0.99			0.69		
Delayed					1.44			0.73	0.88	0.93		
SC	0.7	0.93			0.95							
SC, Trial 2					0.84							

Shading indicates the regions with $p < .005$.

SC = semantic clustering index.

Summary

There may be more than one mechanism for specific frontal lesions causing impairments, but if anomic patients are excluded, a major effect is driven by lesions in the left superior frontal region.

DISCUSSION

We studied memory functioning in patients with focal frontal lesions using list learning, an artificial task although it resembles some real-life activities: memorizing facts in school, assembling and remembering items on a shopping list. Real-life tasks are supported by prior semantic and experiential knowledge and plausibility or by prior episodic experience with similar lists, such as shopping lists. List learning does, however, illuminate some of the processes underlying learning and recalling information in the absence of supporting semantic or episodic experience.

Most studies have demonstrated that a heterogeneous group of patients with chronic frontal lesions will have poor list learning, poor delayed recall, and possibly, poor recognition memory with the variably reported increases in false positives possibly due to the structure of the recognition task and to the frequency and semantic relatedness of the foils as much as to the lesion. All of these studies, including our own, have, however, significant limitations. Most report a very small number of patients. Most consolidate all patients, whatever their lesions, into a single group—''frontals''—or at most, into two groups—left and right frontals (Gershberg & Shimamura, 1995; Eslinger & Grattan, 1994; Janowsky et al., 1989; Jetter, Poser, Freeman, & Markowitsch, 1986). The range of potential lesion sites is often highly restricted (Kopelman & Stanhope, 1998; Gershberg & Shimamura, 1995; Eslinger & Grattan, 1994; Janowsky et al., 1989; Jetter et al., 1986). In patients with left frontal lesions, the severity of anomia has been quite variable (Alexander et al., 2005; Gershberg & Shimamura, 1995; Stuss et al., 1994); some subjects have been frankly aphasic. In some, lesion location is difficult to evaluate (Hildebrandt, Brand, & Sachsenheimer, 1998; Vilkki et al., 1998). These studies have used disparate comparisons—unstructured lists to structured lists, recall of lists to recall of semantically organized stories, lists with and without explicit cues to strategies, and comparing free recall to cued recall—in order to reach similar conclusions. All have concluded that patients with frontal lesions are impaired, in some way, in application of learning strategies or retrieval strategies or both that are available to control subjects (Gershberg & Shimamura, 1995; Stuss et al., 1994; Eslinger & Grattan, 1993; Incisa della rocchetta & Milner, 1993; Janowsky et al., 1989): semantic organization, categorization or clustering, or subjective organization.

Our study extends the existing literature to emphasize three factors: (1) specific lesion location is a determinant of the performance profile, (2) clinical characteristics associated with specific lesion sites influence performance, and (3) the structure of the task affects the relationship between lesion site and performance.

The demonstrated impairments are not an equivalent property of lesions anywhere in the frontal lobes. Studies that have found significant impairments in a heterogeneous group of mixed frontal lesions may have done so because they happened to have sufficient numbers of critical lesions to power overall group significance: either a large proportion of left superior lesions (area 9s) (Incisa della rocchetta & Milner, 1993) or left lateral lesions (variously areas 44, 45, 46, and 46/9) (Alexander et al., 2003; Baldo et al., 2002; Gershberg & Shimamura, 1995; Stuss et al., 1994). When the large frontal group in this study was analyzed by subregions, the critical lesion with greatest association with impairments was in the left SM region. In the eight analyses of recall, left 9s was identified in all eight with very large effect sizes. Left dorsolateral regions were intermittently identified. Lesions in right 9s were consistently associated with impairments in learning the unblocked list. The critical lesions for strategy impairments, that is, a failure to utilize semantic clustering, or subjective organization (which may be nearly identical in this task), even for the blocked condition when the words were presented ''preclustered,'' were in left 9s, and possibly in left area 10. Failure to utilize semantic clustering in the second presentation of the unblocked, that is, the first opportunity to benefit from experiencing the presence of semantic categories in the list, was also associated with lesions in left 9s.

A critical factor for left-sided lesions is the variable co-occurrence of anomia that may contribute to poor verbal learning. In an earlier study with 32 patients, we demonstrated that when patients were assigned a priori into regional groupings, only the left lateral group and the inferior medial group (which included patients with left, right, and bilateral damage) were impaired on recall of a blocked list but not an unblocked list (Stuss et al., 1994). We had not yet developed a technique to probe for a more specific critical lesion, and inspection of the images indicates patchy involvement of various ventrolateral and dorsolateral regions in the LL group. Review of the associated cognitive findings suggested two causes of poor recall. The inferior medial group included several patients who had had a ruptured anterior communicating artery aneurysm with very posterior medial lesions involving the septal region, a direct limbic mechanism of memory impairment. In that study we included patients with significantly more anomia than in the current study (LL mean BNT = 48.5; IM mean BNT = 39.7 vs. 53.4 and 56.2 in comparably grouped patients in the present study). Secondary memory, that is, words held longer in memory than immediate verbal short-term memory, was correlated with verbal fluency

(FAS test; $r = .59$, $p = .004$), suggesting a potential lexical–semantic deficit impairing some aspect of learning.

In another study, we turned the approach around—going from behavior to lesions instead of lesion sites to behavior. We used total recall across five trials of the CVLT-I as the independent variable to sort a new group of 33 patients with frontal lesions into groups determined by their performance (Alexander et al., 2003). The groups that emerged had differing and distinctive lesion anatomies that were similar to the a priori groups of the first study—posterior, inferior medial, and posterior left lateral. The group with posterior left lateral frontal damage had the lowest score on the total recalled, and impaired performance on T1 learning, delayed recall, and recognition, the last due to excessive false positives that were, in turn, due to abnormal bias in the yes/no recognition format. An anterior left lateral group was intermediate, neither significantly different than the posterior group below nor the controls above. For the posterior lateral group, total recall correlated with verbal fluency (FAS test; $r = .97$, $p = .04$) and recognition hits correlated with the Boston Naming Test ($r = .93$, $p = .02$). In that study, we also included patients with more significant anomia than in the current study (posterior left lateral mean BNT = 39.4 vs. 53.4 in the left lateral patients in the present study; $p = .009$). No other group in the earlier study had significantly different BNT scores than any group in the present study, and the posterior left lateral group was significantly lower than all of the subgroups in the present study (ps ranged from .000 to .032). Inspection of the images reveals that the important distinction in the left frontal lobe was anterior–posterior, not ventral–dorsal, but there were relatively few examples of superior dorsal lesions.

The conclusion that impaired lexical–semantic function might impede learning and recall is supported by a variety sources. Patients with partly recovered aphasia but with mild residual anomia, whatever the lesion location, show similar impairments on list learning (Ween, Verfaellie, & Alexander, 1996). More significantly, aphasic patients with lesions in left lateral frontal regions show poor recall and poor use of available strategies (Risse, Rubens, & Jordan, 1984).

The effects of specific left frontal lesions may then be more complex and varied than just left versus right. Our attempt to define possible specific regional effects has gone through methodological change, moving from behaviorally clear but anatomically diffuse conclusions (left—due to semantic deficits) toward more specific behaviors and less diffuse anatomy (left ventrolateral—semantic organization). Our tentative conclusion is that there are four factors involved in the effects of left frontal lesions on list learning and that each effect may speak to more general properties of regional frontal functions.

Left ventrolateral lesions may affect learning by impairing the lexical–semantic associations that underlie encoding or that focus retrieval set. The dominant connectivity of the ventral frontal region is in the ''ventral stream''—the organization, generation, and retrieval of semantic associations. The critical marker for damage to this system sufficient to disrupt learning is straightforward impairment in lexical retrieval independent of any verbal learning task.

Left dorsolateral lesions may affect verbal learning by impairing working memory, thus the effect of dorsolateral lesions during the learning phases of the present study, poor secondary memory and difficulty recalling words from the middle of the lists in our study (details not reported) and in the reports of more overtly aphasic patients with anterior lesions (Risse et al., 1984). That this operation is supported by dorsal frontal structures is supported by meta-analysis (Gilbert et al., 2006), although the statistical properties of fMRI certainly contribute to hyperlocalization and surely underestimate the role of broad prefrontal regions in maintenance of working activation of frontal and posterior regions.

Left superior lesions may affect verbal learning through failure to implement action structures that should optimize learning. Even in the absence of overt anomia or fluency deficits, patients in this study with superior lesions had defective use of on-line organizational strategies that paralleled the defective learning. Temporary ''lesions'' in Brodmann's area 9s produced by transcranial magnetic stimulation impair capacity to organize verbal encoding (Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). Of the contending options for managing the task of learning in real time (serial order, subjective ordering, semantic ordering, etc.), this region may be critical for consistent strategy.

Left polar lesions may affect learning in a subtle manner by failure to establish a specific goal-oriented strategy that is effective, a strategy that the superior dorsal region must implement, the lateral dorsal region must keep active, and the lateral ventral region actually effect through lexical–semantic operations. Recent meta-analyses of functional imaging studies of area 10 in goal-oriented behaviors support this strategic role, although it is not clear where the current paradigm fits into the stimulus-oriented or stimulus-independent dichotomy proposed in that analysis (Burgess, Gilbert, & Dumontheil, 2007).

This mechanism is supported by a computational model (Becker & Lim, 2003) that was tested on the word lists (blocked and unblocked) from our earlier study (Stuss et al., 1994). Prefrontal ''lesions'' in this model disrupt the rapid development of learning codes that arise based on the task demands—in this case, lexical–semantic, thus poorer semantic clustering, poorer total recall, and better performance in the blocked list in this model. This model for the various roles of distinct left frontal regions matches the proposals of others (Nadeau & Heilman, 2007). They distinguished between the roles of dorsomedial frontal and lateral frontal regions. Dorsomedial regions—approximately comparable to our superior localization—in that model ''formulate and sequence generic forms of

plans . . . {choose} among multiple available plans and {initiate and sustain} the volitional execution of these plans.''

The mechanisms for the more modest effect of right frontal lesions are more speculative. The task—list learning—is completely verbal and the weak effect of right frontal lesions could be simply related to the domain-specific demands of the task. Right superior lesions—primarily 9s—emerged as significant primarily on the unblocked list, suggesting an additional mechanism for impairment for a task—even a verbal one—requiring greater active strategy. In other tasks in the same patient group as this study, we have demonstrated impairments in response monitoring (Picton et al., 2006; Stuss et al., 2005) after right dorsal lateral lesions and in response inhibition (Picton et al., 2007) after right superior lesions. These impairments suggested that, in this study, right-sided lesions might have generated an excess of perseverated recalls (monitoring) or semantically related intrusions (inhibition), but these were not observed. In one study, we demonstrated impaired monitoring of recall in patients with right-sided lesions, but we have not been able to reproduce this effect consistently (Stuss et al., 1994). Perhaps coincident amnesia is usually required for false positives to emerge (Verfaellie et al., 2004) or perhaps when recall is from minimally constrained remote, personal memory confabulations will emerge after right-sided lesions (Davidson et al., 2006). In a recent study of patients with mostly acute frontal lesions using a very complex list learning paradigm, intrusions could be induced in patients with right frontal lesions under conditions of high proactive interference or in cued conditions when prompts at recall induced a shift from episodic recall to semantic familiarity (Turner, Cipolotti, Yousry, & Shallice, 2007).

A role for the right dorsolateral frontal lobe in monitoring cognitive activities has emerged from functional imaging (Cabeza, Locantore, & Anderson, 2003; Henson, Shallice, & Dolan, 1999). The definition of monitoring varies considerably from study to study and does not typically apply to error detection in a recall task.

Another possible role for the right superior dorsolateral region is maintenance of sustained attention. The unblocked task was more difficult; both frontal patients and controls had lower recall scores, less use of specific strategies, and lower correlations of semantic with subjective organization on the unblocked task. The extra difficulty may be the demand to divide attention between holding recent words in working memory while maintaining preparation of attention for upcoming words. We have demonstrated deficits in sustaining attention over short intervals in this group of patients on other tasks (Stuss et al., 2005).

The structure of the task will modify the results and careful attention must be paid to the specific methodology when comparing studies. The CVLT-II has replaced the earlier version, and it is unknown if it will demonstrate the same range of regional lesion effects. The initial report from its authors is not definitive (Baldo et al., 2002). Only 11 patients were tested. They were very chronic (mean = 10 years), and right- and left-sided lesions were placed into a single test group. Inspection of the published lesion schematics reveals that the patients overwhelmingly had lateral lesions and that involvement of superior frontal regions was modest, especially in the left lateral group. That study (with the CVLT-II) and the current study (unblocked condition) had comparable results. Our results indicate that, although it may be counterintuitive because it is easier, the blocked condition may provide additional insight into frontal impairments in learning, much as we found to our surprise several years ago. The blocked condition provides explicit guideposts for organization that controls can utilize but some frontal patients cannot. On T1, there is already a Group × Condition interaction indicating that the frontal group has not benefited from the categorical ordering in the list. From that point, the frontal group never catches up to controls. There are additional measures of organization that were only significant (frontal impaired) on the blocked list—subjective organization and perhaps semantic clustering index—that suggest that the frontal group was less able to benefit from the built-in structure of the blocked list. On all eight measures that were significant for both conditions, the p value was lower for the blocked condition. The blocked list may have some specificity for left superior and polar regions reflected in the large number of significant correlations with left area 9s and clustering correlation with area 10. The unblocked list may be sensitive to right or left frontal lesions reflected in the broader regional injuries that correlate with performance on the unblocked list. This difference between blocked and unblocked lists was not seen in the other recent study of list learning after frontal lesions (Turner et al., 2007), but the overall demands of the task in that study were very different than the CVLT-II or our lists.

These studies of list learning may illuminate the executive mechanisms that control complex supraspan learning, but they are not very informative about other aspects of ''metamemory'' (Davidson et al., 2006). They do not speak to source memory (Johnson et al., 1993), memory for temporal order (Butters, Kasniak, Glisky, Eslinger, & Schacter, 1994; Eslinger & Grattan, 1994), judgment of accuracy (Schnyer et al., 2004), monitoring retrieval from remote autobiographical memory, or sensitivity to interference (Baldo et al., 2002).

List learning is a useful measure of the effects of frontal lesions on memory and learning, but the effects of lesions in different regions should not be blended into a single ''executive'' account. Lesions in different regions have different mechanisms. If interventions are to be developed to improve memory function, they will need to respect the distinctive contributions of discrete lesions.

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REFERENCES

Alexander, M. P., & Freedman, M. (1984). Amnesia after anterior communicating artery aneurysm. *Neurology, 34,* 752–757.

Alexander, M. P., Stuss, D. S., & Fansabedian, N. (2003). California verbal learning test: Performance by patients with focal frontal and non-frontal lesions. *Brain, 126,* 1493–1503.

Alexander, M. P., Stuss, D. T., Shallice, T., Picton, T. W., & Gillingham, S. (2005). Impaired concentration due to frontal lobe damage from two distinct lesion sites. *Neurology, 65,* 572–579.

Alexander, M. P., Stuss, D. T., Shallice, T., Picton, T. W., & Gillingham, S. (2007). Frontal injuries cause distinct impairments in cognitive control. *Neurology, 68,* 1515–1523.

Baldo, J. V., Delis, D., Kramer, J., & Shimamura, A. P. (2002). Memory performance on the California Verbal Learning Test—II: Findings from patients with focal frontal lesions. *Journal of the International Neuropsychological Society, 8,* 539–546.

Beck, A. T., & Steer, R. A. (1993). *Beck Depression Inventory*. San Antonio, TX: Psychological Corporation.

Becker, S., & Lim, J. (2003). A computational model of prefrontal control in free recall: Strategic memory use in the California Learning Task. *Journal of Cognitive Neuroscience, 15,* 821–832.

Burgess, P. W., Gilbert, S. J., & Dumontheil, I. (2007). Function and localization within rostral prefrontal cortex (area 10). *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 362,* 887–899.

Butters, M. A., Kasniak, A. W., Glisky, E. L., Eslinger, P. J., & Schacter, D. L. (1994). Recency discrimination deficits in frontal lobe patients. *Neuropsychology, 8,* 343–353.

Cabeza, R., Locantore, J. K., & Anderson, N. D. (2003). Lateralization of prefrontal activity during episodic memory retrieval: Evidence for the production monitoring hypothesis. *Journal of Cognitive Neuroscience, 15,* 249–259.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Mahwah, NJ: Erlbaum.

Damasio, H., & Damasio, A. R. (Eds.) (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.

Davidson, P. S., Troyer, A. K., & Moscovitch, M. (2006). Frontal lobe contributions to recognition and recall: Linking basic research with clinical evaluation and remediation. *Journal of the International Neuropsychological Society, 12,* 210–223.

De Renzi, E., & Vignolo, L. A. (1962). The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain, 85,* 665–678.

Delis, D., Kaplan, E., Kramer, J., & Ober, B. (2000). *California Verbal Learning Test—II*. San Antonio, TX: Psychological Corporation.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (1987). *California Verbal Learning Test*. San Antonio, TX: Psychological Corporation.

Elsass, P., & Hartelius, H. (1985). Reaction time and brain disease: Relations to location, etiology and progression of cerebral dysfunction. *Acta Neurologica Scandinavia, 71,* 11–19.

Eslinger, P. J., & Grattan, L. M. (1993). Frontal lobe and frontal–striatal substrates for different forms of human cognitive flexibility. *Neuropsychologia, 31,* 17–28.

Eslinger, P. J., & Grattan, L. M. (1994). Altered serial position learning after frontal lobe lesion. *Neuropsychologia, 32,* 729–739.

Gershberg, F. B., & Shimamura, A. P. (1995). Impaired use of organization strategies in free recall following frontal lobe damage. *Neuropsychologia, 13,* 1305–1333.

Gilbert, S. J., Spengler, S., Simons, J. S., Lawrie, S. M., Frith, C. D., & Burgess, P. W. (2006). Functional specialization within the rostral prefrontal cortex (area 10): A meta-analysis. *Journal of Cognitive Neuroscience, 18,* 932–948.

Henson, R. N., Shallice, T., & Dolan, R. J. (1999). Right prefrontal cortex and episodic memory retrieval: A functional MRI test of the monitoring hypothesis. *Brain, 122,* 1367–1381.

Hildebrandt, H., Brand, A., & Sachsenheimer, W. (1998). Profiles of patients with left prefrontal and left temporal lobe lesions after cerebrovascular infarctions on California Verbal Learning Test-like indices. *Journal of Clinical and Experimental Neuropsychology, 20,* 673–683.

Incisa della rocchetta, A., & Milner, B. (1993). Strategic search and retrieval inhibition: The role of the frontal lobes. *Neuropsychologia, 31,* 503–524.

Irle, E., Wowra, B., & Kunert, H. (1992). Memory disturbance following anterior communicating artery rupture. *Annals of Neurology, 31,* 473–480.

Janowsky, J. S., Shimamura, A. P., Kritchevsky, M., & Squire, L. R. (1989). Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behavioral Neuroscience, 103,* 548–560.

Jetter, W., Poser, U., Freeman, R. B., Jr., & Markowitsch, H. J. (1986). A verbal long term memory deficit in frontal lobe damaged patients. *Cortex, 22,* 229–242.

Johnson, M. K., Hashtroudi, S., & Lindsay, D. S. (1993). Source monitoring. *Psychological Bulletin, 114,* 3–28.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia: Lea and Febiger.

Kopelman, M. D., & Stanhope, N. (1998). Recall and recognition memory in patients with focal frontal, temporal lobe and diencephalic lesions. *Neuropsychologia, 36,* 785–796.

Nadeau, S. E., & Heilman, K. M. (2007). Frontal mysteries revealed. *Neurology, 68,* 1450–1453.

Petrides, M. (1995). Impairments on spatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *Journal of Neuroscience, 15,* 359–375.

Petrides, M., & Pandya, D. N. (1994). Comparative architectonic analysis of the human and macaque frontal cortex. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 9, pp. 17–57). Amsterdam: Elsevier.

Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (2007). Effects of focal picton frontal lesions on response inhibition. *Cerebral Cortex, 17,* 826–838.

Picton, T. W., Stuss, D. T., Shallice, T., Alexander, M. P., & Gillingham, S. (2006). Keeping time: Effects of focal frontal lesions. *Neuropsychologia, 44,* 1195–1209.

Risse, G. L., Rubens, A. B., & Jordan, L. S. (1984). Disturbances of long-term memory in aphasic patients: A comparison of anterior and posterior lesions. *Brain, 107,* 605–617.

Sandrini, M., Cappa, S. F., Rossi, S., Rossini, P. M., & Miniussi, C. (2003). The role of prefrontal cortex in verbal episodic memory: rTMS evidence. *Journal of Cognitive Neuroscience, 15,* 855–861.
Schacter, D. L., Curran, T., Galluccio, L., Milberg, W. M., & Bates, J. F. (1996). False recognition and the right frontal lobe. *Neuropsychologia, 34,* 793–808.
Schnyer, D. M., Verfaellie, M., Alexander, M. P., LaFleche, G., Nicholls, L., & Kaszniak, A. W. (2004). A role for right medial prefrontal cortex in accurate feeling-of-knowing judgements: Evidence from patients with lesions to frontal cortex. *Neuropsychologia, 42,* 957–966.
Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L., & Pogue, J. (1994). Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology, 8,* 355–373.
Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43,* 396–417.
Stuss, D. T., Shallice, T., Alexander, M. P., & Picton, T. W. (1995). A multidisciplinary approach to anterior attentional functions. *Annals of the New York Academy of Sciences, 769,* 191–211.
Turner, M. S., Cipolotti, L., Yousry, T., & Shallice, T. (2007). Qualitatively different memory impairments across frontal lobe groups. *Neuropsychologia, 445,* 1540–1552.
Verfaellie, M., Rapcsak, S. Z., Keane, M. M., & Alexander, M. P. (2004). Elevated false recognition in patients with frontal lobe damage is neither a general nor a unitary phenomenon. *Neuropsychology, 18,* 94–103.
Vilkki, J., Servo, A., & Surma-aho, O. (1998). Word list learning and prediction after frontal lobe lesions. *Neuropsychology, 12,* 268–277.
Ween, J. E., Verfaellie, M., & Alexander, M. P. (1996). Verbal memory function in mild aphasia. *Neurology, 47,* 795–801.
Wheeler, M. A., & Stuss, D. T. (2003). Remembering and knowing in patients with frontal lobe injury. *Cortex, 39,* 827–846.
Wheeler, M. A., Stuss, D. T., & Tulving, E. (1995). Frontal damage produces episodic memory impairment. *Journal of the International Neuropsychological Society, 1,* 525–536.