Right Frontal Lobe Mediation of Recollection- and Familiarity-based Verbal Recognition Memory: Evidence from Patients with Tumor Resections

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Abstract

■ Medial-temporal, parietal, and pFC regions have been implicated in recollection and familiarity, but existing evidence from neuroimaging and patient studies is limited and conflicting regarding the role of specific regions within pFC in these memory processes. We report a study of 20 patients who had undergone resection of right frontal lobe tumors and 20 matched healthy control participants. The location and extent of lesions were traced on the patients' scans. A process dissociation procedure was employed to yield estimates of the contributions of recollection and familiarity in verbal recognition performance. Group comparisons revealed deficits in recollection but not familiarity in the patient group relative to their healthy counterparts. We found a positive relationship between estimates of familiarity and lesion sizes in the right inferior pFC (BA 11, 47) which was significant upon bootstrap resampling. These results are discussed in terms of prior work linking this area to an overextended sense of familiarity. ■

INTRODUCTION

An increasingly common view is that recognition memory is supported by two independent processes: (1) recollection (conscious, controlled retrieval of prior events in their context) and (2) familiarity (a feeling that a particular event has been experienced before, unaccompanied by contextual details; Jacoby, 1991; Mandler, 1980; but see Wixted, 2007). Results from ERP, fMRI, and focal lesion studies converge in finding that, in nonfrontal regions, the medial-temporal lobes and parietal lobes play a role in both processes, although there still exists considerable disagreement about whether each region can be subdivided into different areas playing more specialized roles (for reviews, see Wixted & Squire, 2010; Spaniol et al., 2009; Vilberg & Rugg, 2008; Eichenbaum, Yonelinas, & Ranganath, 2007; Skinner & Fernandes, 2007). For example, many fMRI studies report that the hippocampus supports recollection, whereas perirhinal cortex supports familiarity (e.g., Daselaar, Fleck, & Cabeza, 2006; Ranganath et al., 2003; but see Wais, Squire, & Wixted, 2009). Medial and lateral parietal cortices, especially in the left hemisphere, have been associated with recollection processes (e.g., Ciaramelli, Grady, & Moscovitch, 2008; Davidson, Anaki, et al., 2008; Vilberg & Rugg, 2007; Henson, Hornberger, & Rugg, 2005; Yonelinas, Otten, Shaw, & Rugg, 2005; Wheeler & Buckner, 2004), whereas Yonelinas et al. (2005) reported that more superior parietal regions are activated coincident with familiarity-based responses.

The focus of the current study is on the possible role(s) of distinct regions within pFC in recollection and familiarity. Some investigators argue that pFC regions support both recollection and familiarity. This view rests primarily on functional neuroimaging data. Recollection-based activations have been identified most consistently in frontal polar and lateral pFC in both hemispheres (e.g., Montaldi, Spencer, Roberts, & Mayes, 2006; Yonelinas et al., 2005; Bunge, Burrows, & Wagner, 2004; Duarte, Ranganath, Winward, Hayward, & Knight, 2004; Kahn, Davachi, & Wagner, 2004; Wheeler & Buckner, 2004; for reviews, see Spaniol et al., 2009; Skinner & Fernandes, 2007). Familiarity-based activations have been most consistently identified in the right dorsolateral pFC (Bunge et al., 2004; Dobbins, Simons, & Schacter, 2004; Wheeler & Buckner, 2004), although left frontal regions have also been implicated (Woodruff, Hayama, & Rugg, 2006; Kahn et al., 2004). At least part of the variability across studies may be attributable to differences among the particular tasks employed (e.g., Spaniol et al., 2009).

Other investigators have argued based on neuropsychological studies that the frontal lobes are not required for familiarity but are recruited along with the posterior regions listed above to support recollection (e.g., Knowlton & Squire, 1995; Wheeler, Stuss, & Tulving, 1995). Consistent with this view, in a meta-analysis of earlier patient

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studies, Wheeler et al. (1995) found that, although patients with circumscribed frontal lobe lesions were impaired relative to healthy controls on free recall, cued recall, *and* recognition memory, the impairments were greatest in free recall, a finding which they suggested reflects a preferential role of the frontal lobes in recollection over familiarity. Recollection is also required for intact remembering of the source of information, and patients with frontal lobe lesions have been reported to have source memory impairments for perceptual information (Duarte, Ranganath, & Knight, 2005; Johnson, O'Connor, & Cantor, 1997; but see Thaiss & Petrides, 2003), for remembering temporal order (Duarte, Henson, Knight, Emery, & Graham, 2010; Daum & Mayes, 2000; Swain, Polkey, Bullock, & Morris, 1998; Kopelman, Stanhope, & Kingsley, 1997; Mangels, 1997; Butters, Kaszniak, Glisky, Eslinger, & Schacter, 1994; Kesner, Hopkins, & Fineman, 1994; McAndrews & Milner, 1991; Milner, Corsi, & Leonard, 1991; Shimamura, Janowsky, & Squire, 1990; Janowsky, Shimamura, & Squire, 1989; but see Thaiss & Petrides, 2003), and sometimes also for remembering spatial context (Daum & Mayes, 2000; Janowsky et al., 1989; but see Kopelman et al., 1997; Smith & Milner, 1984). Their source memory impairment is also evident beyond the laboratory, in the real world (Davidson, Cook, Glisky, Verfaellie, & Rapcsak, 2005). Functional neuroimaging studies converge with the lesion data (for reviews, see Mitchell & Johnson, 2009; Spaniol et al., 2009).

Many neuroimaging studies have focused on laterality differences, such as semantically guided production in the left pFC versus postretrieval monitoring and verification in the right pFC (Cabeza, Locantore, & Anderson, 2003) or systematic retrieval in the left pFC versus heuristic retrieval in the right pFC (Nolde, Johnson, & Raye, 1998). Others have focused on component processes of retrieval, associating setting a retrieval mode with frontal polar regions (e.g., Velanova, Lustig, Jacoby, & Buckner, 2003), retrieval attempt with polar and anterior pFC (e.g., Kahn et al., 2004), and retrieval monitoring and verification with dorsolateral pFC (e.g., Henson, Rugg, Shallice, & Dolan, 2000). In a recent meta-analysis, Spaniol and colleagues (2009) reported that objective recollection (e.g., source memory) is associated with left ventrolateral and dorsolateral pFC activations, whereas subjective recollection (e.g., a "Remember" response in a Remember/Know paradigm) is associated with anterior and medial pFC activations.

Surprisingly few studies have investigated recollection and familiarity directly in patients with pFC damage, and these have provided conflicting results. Duarte et al. (2005) presented pictures of objects in either the ipsi- or contralateral visual field to nine patients with unilateral focal pFC lesions and matched controls and tested object memory using a remember/know procedure (c.f., Tulving, 1985) to estimate recollection and familiarity (cf. Yonelinas & Jacoby, 1995). Recollection was intact in the patients relative to controls regardless of the visual field in which the objects had been presented, although source memory (i.e., correct memory for which of two encoding tasks participants had performed with each object) was impaired in the patients with left pFC lesions. By contrast, familiarity was impaired only when the objects had been presented in the contralesional visual field, and this effect was stronger for patients with left pFC lesions than it was for their counterparts with right pFC damage. The latter results suggest that pFC is critical for familiarity but not recollection when based on subjective report. Similar results were reported by MacPherson et al. (2008), who had 24 patients with focal pFC lesions encode photographs of buildings. During a recognition test, participants gave confidence ratings, allowing the investigators to use the receiving operating characteristic method to estimate recollection and familiarity. The patients showed reduced familiarity, but not recollection, compared with 33 healthy controls, with familiarity deficits evident in patients with medial and lateral, but not orbital, pFC lesions.

In contrast to the first two studies, Wheeler and Stuss (2003) reported that a group of five patients with frontopolar damage was impaired on recollection on a verbal remember/know task, although five patients with dorsolateral damage were no different from normal. Finally, Hay, Moscovitch, and Levine (2002) employed a verbal process dissociation procedure (Jacoby, 1991) that places recollection and familiarity in opposition to one another to estimate their separate contributions to performance (this procedure is described in greater detail below). Their study included five patients, four with right hemisphere pFC lesions and one with a left hemisphere pFC lesion. Compared with matched controls, the patients' familiarity was intact, whereas the four patients with right-sided damage had impaired recollection. Interestingly, the one patient with left-sided damage had intact recollection, suggesting a potential right pFC mediation of recollection, even when using verbal materials.

In summary, the role of specific regions within pFC in recollection and familiarity remains ambiguous. The neuroimaging data are conflicting, and few patient studies have attempted to link changes in memory processing to specific subregions within the frontal lobes. Conclusions from them must be qualified, however, because in these studies anatomical divisions have been large (e.g., right vs. left pFC in Duarte et al., 2005; Hay et al., 2002; medial, lateral, or orbital pFC in either hemisphere in MacPherson et al., 2008) or restricted (dorsolateral vs. frontopolar in Wheeler & Stuss, 2003). These limitations prevent a better understanding of the role of multiple subregions within the lateral or medial frontal cortex in these recognition memory processes.

The goal of the current study was to explore the effects of damage to specific regions within pFC on recollection and familiarity in a relatively large sample of patients. To this end, we report a study comparing 20 adult patients who had undergone resection of a right frontal brain tumor with 20 matched healthy control participants. Patients with lesions in the left frontal lobe were excluded from this study because of potential language disorders

or impairments in encoding or semantic retrieval that can confound estimates of recollection and familiarity. All participants performed a verbal "repetition lag" paradigm (Jennings & Jacoby, 1997) consisting of two phases. In the study phase, participants learned a list of 30 words. In the recognition phase, studied words were intermixed with new words (i.e., lures); each lure was presented twice, after 0, 5, or 10 intervening words (the "lag"). This task was performed twice by all participants, once under *Exclusion* instructions wherein participants were to respond "yes" to studied words only and once under *Inclusion* instructions wherein participants were to respond "yes" to studied words *and* to repeated lures. The critical items are the repeated lures. A "yes" response to a repeated lure under Inclusion instructions would be a correct response and could be supported by recollection or familiarity, but under Exclusion instructions it would be an incorrect response influenced by familiarity in the absence of recollection. The process dissociation procedure, therefore, relies on comparisons of veridical and false "yes" responses to derive estimates of the contributions of recollection and familiarity to recognition memory and not on subjective reports of these underlying processes (Jacoby, 1991).

Our primary goal was to relate estimates of recollection and familiarity[1] to the location and extent of focal lesions within the frontal lobes. We selected six ROIs within the right frontal lobe. The selection of four of these regions was guided by the Moscovitch and Winocur's (2002) model of how subregions within the frontal lobe in support of episodic memory: premotor (BA 3, 4, 6) linked to response selection and inhibition, anterior (BA 10) implicated in context-dependent "feeling of rightness" for endorsement, inferior (BA 11, 47) associated with cue specification, which minimizes an unwarranted sense of familiarity, and dorsolateral (BA 8, 9, 46) linked to monitoring and manipulation of information held in working memory. With the goal of surveying the entire right frontal lobe, we additionally selected the right hemisphere homologue of Broca's area (BA 44, 45) as well as ACC (BA 24, 25, 32, 33). Guided by this model of Moscovitch and Winocur (2002), we predicted that lesions in premotor, anterior, or dorsolateral regions of the right frontal lobe would disrupt recollection because of deficits in response selection and inhibition, a context-dependent "feeling of rightness," or monitoring, whereas damage to inferior regions of the right frontal lobe would disrupt familiarity because of deficits in cue specification.

To assess group differences, we compared the performance of patients and controls on the neuropsychological tasks, on the inclusion and exclusion tasks, and on estimates of recollection and familiarity. Correlations between the memory processes (recollection and familiarity) and lesion sizes within each ROI were calculated, including only those patients with lesions greater than zero in each ROI. Because small sample sizes in lesion research limit the ability to meet assumptions of and the power of parametric statistical tests (cf., Kimberg, Coslett, & Schwartz, 2007), we further assessed the significance of these results using bootstrap resampling (Good, 2005; Efron & Tibshirani, 1986; Edgington, 1980).

METHODS

Participants

Inclusion criteria for participation were English fluency, no serious sensory or motor impairments that would prevent participation, no uncontrolled seizure disorders, and no history of a medical or neurological condition known to affect cognitive functioning (other than a right prefrontal brain tumor). Twenty-one individuals who had been treated for a primary brain tumor participated in this study. One patient discontinued testing midsession because of anxiety; the data from the remaining 20 patients are reported here.

Twenty healthy control participants were also tested. They were matched to the patients for age ($p = .90$), education ($p = .62$), sex, handedness, and age at which English was learned. Demographic information for the controls and patients and details about the patients' tumor types and treatment are provided in Table 1. The three patients who were undergoing chemotherapy at the time of the study were tested in between cycles when side effects were minimal.

Materials and Design

A short battery of neuropsychological tests and the experimental Inclusion and Exclusion recognition memory tasks were administered. The neuropsychological tests were the Wechsler Abbreviated Scale of Intelligence (WASI), the Hopkins Verbal Learning Test (HVLT), the WAIS-III Digit Span, the WAIS-III Digit Symbol, the WCST, the Trail-Making Test (TMT), and phonemic and semantic verbal fluency. Patients also received the North American Adult Reading Test (NAART) to estimate premorbid level of intellectual functioning. Because of an administrative error, only 11 of the patients received the WAIS-III Digit Span task.

For the recognition memory tasks, 216 nouns were selected from the MRC Psycholinguistic Database (www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). Of these, 180 were split into 12 sets of 15 words each, matched for word length, imageability, concreteness, and Kucera and Francis word frequency [all $F(11, 168) < 1$]. The other 36 words were split into two practice lists of 18 words each.

For each task (Inclusion and Exclusion), three sets (i.e., 45 words) were assigned to the study phase, and those three sets plus an additional three sets of new words were assigned to the test phase. The new words were each presented twice during the recognition tests (see Figure 1). Words from one set (i.e., 15 words) were presented sequentially (i.e., the "0 lag" condition), words from another

Table 1. Demographic, Tumor, and Treatment Information

	Controls					*Patients*									
Patient No.	*Age*	*Sex*	*Hand*	*Educ*	*Lang*	*Age*	*Gender*	*Hand*	*Educ*	*Lang*	*Tumor Type*	*Tumor Grade*	*Time Since Surgery (months)*	*Time Since RT (months)*	*Time Since Chemo (months)*
1	45	M	R	11	NE	46	M	R	8	NE	Oligodendroglioma	2–3	27	23	n/a
2	33	F	R	18	21	35	F	R	15	24	Oligoastrocytoma	2	74	69	n/a
3	56	F	R	12	NE	55	F	R	11	NE	Multiple Meningiomas		52	34	n/a
4	44	M	L	12	NE	40	M	L	12	NE	Oligoastrocytoma	3	44	42	30
5	48	M	R	15	NE	52	M	R	15	NE	Chondrosarcoma	2	83	79	n/a
6	37	M	R	17	5	35	M	R	19	NE	Astrocytoma	2	34	32	n/a
8	39	M	R	13	NE	37	M	R	15	NE	Astrocytoma	3	28	26	n/a
9	43	M	R	19	9	41	M	R	16	12	Oligodendroglioma	3	3	n/a	n/a
10	42	F	R	14	6	41	F	R	12	4	Oligodendroglioma	2	28	25	n/a
11	64	M	L	12	NE	57	M	L	12	NE	Oligodendroglioma	2	71	68	n/a
12	49	M	R	16	NE	51	M	R	15	NE	Glioblastoma	4	33	31	30
13	31	M	R	17	NE	29	M	R	15	NE	Oligoastrocytoma	2–3	7	7	0
14	45	M	R	13	NE	48	M	R	12	NE	Oligodendroglioma	2	2	n/a	n/a
15	62	F	R	10	NE	59	F	R	10	NE	Glioblastoma	4	14	14	0
16	55	M	R	12	NE	51	M	R	13	NE	Astrocytoma	2	18	39	0
17	69	M	R	15	5	71	M	R	12	19	Oligodendroglioma	2	3	n/a	n/a
18	31	F	R	17	NE	32	F	R	17	NE	Oligodendroglioma	2–3	9	2	10
19	38	F	R	10	NE	40	F	R	12	NE	Oligodendroglioma	2	31	29	3
20	46	F	L	12	NE	48	F	L	15	NE	Oligodendroglioma	2	9	n/a	n/a
21	32	M	R	16	NE	32	M	R	17	NE	Astrocytoma	3	34	32	25
Mean	**45.5**			**14.1**		**45.0**			**13.7**				**30.2**	**34.5**	**12.3**

Educ = years of formal education; Lang = age at which English was learned, NE = native English speaker; RT = radiation treatment. Patient 7 withdrew from the study.

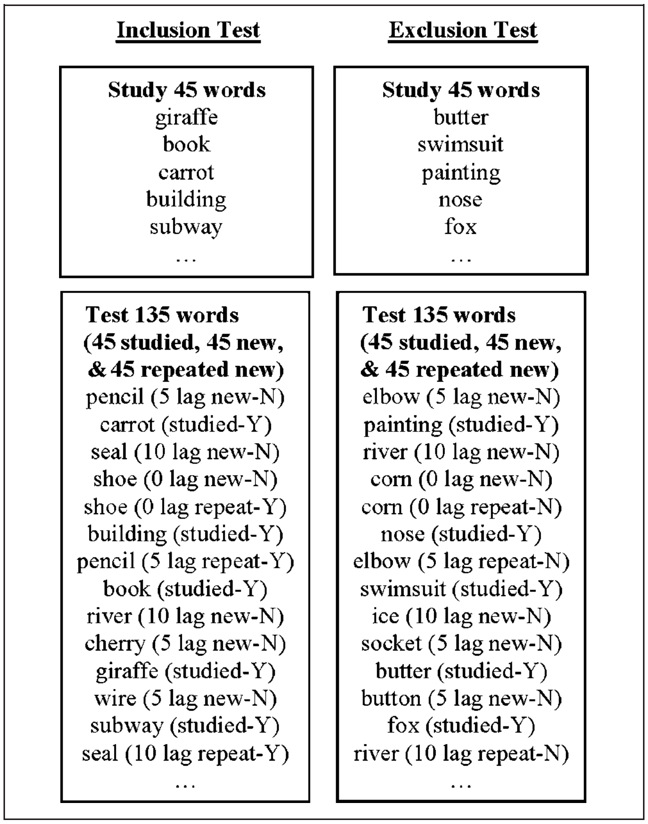

Figure 1. Schematic of the inclusion and exclusion memory tasks.

set were repeated after five intervening words (i.e., the "5 lag" condition), and words from another set were repeated after 10 intervening words (i.e., the "10 lag" condition). The assignment of task order (Inclusion or Exclusion first) was counterbalanced across participants. The assignment of word set to task (Inclusion or Exclusion), item type (studied or new), and new item lag condition (0, 5, or 10) was counterbalanced across participants. The words were presented in a random order during the study phase. A single order of test conditions across trials (i.e., old words, new words shown the first time, and new words shown the second time at their appropriate lags) was created and used for both the Inclusion and Exclusion tasks, but the order of the words within each condition was random. For the practice lists, nine words were presented in the study phase and 18 words (nine old and nine new) were presented in the test phase, with three new words in each of the lag conditions.

Procedure

After obtaining informed consent and conducting a short interview with the participants about their demographic and medical background, we administered tasks in a single session lasting about 3 hr, in the following order: HVLT Learning Trials, WASI Block Design and Matrix Reasoning, HVLT Delayed Trials, WASI Vocabulary and Similarities, NAART (patients only), Inclusion or Exclusion, TMT, WCST, WAIS-III Digit Symbol, Inclusion or Exclusion, WAIS-III Digit Span, and verbal fluency.

For the Inclusion and Exclusion tasks, stimulus presentation and response collection were managed using SuperLab Pro v2.0. Words were presented in lowercase black against a white screen in 72 point Times New Roman font. In the study phase of each task, words were presented for 2000 msec with a 500-msec blank screen ISI. Participants were instructed to read each word out loud as it appeared on the computer screen and to use mental imagery to help learn the words. Strategy instructions were provided to keep encoding strategy constant across participants and to keep performance off the floor (very low performance was obtained from patients who were pilot tested without such instructions).

In the test phase of each task, words remained on the screen until a response was recorded. For the Inclusion test, participants were instructed to read each word out loud and then say "yes" to studied words and to repeated new words and "no" to new words presented for the first time. For the Exclusion task, participants were instructed to read each word out loud and then say "yes" to studied word and "no" to new words both times they were presented. The experimenter entered the participants' responses.

Neuroimaging Analyses

Details of the neuroimaging protocols and lesion analyses can be found in Davidson, Gao, et al. (2008). Briefly, 16 patients had axial T1-weighted MRI with Gadolinium contrast, 1 had a 3-D T1-weighted MRI, and the remaining 3 had CT. All scans were postoperative. Lesions were manually traced slice-by-slice, using ANALYZE AVW Software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Two experienced operators (blinded to participants' scores) agreed on boundaries of lesions, which consisted of hypointense or hypodense residual tumor and surrounding resected regions, and any abnormal hyperintense areas in MRI (enhanced tumor tissue) or hyperdense areas in CT (enhanced or calcified tumor tissue). Most patients had one large, circumscribed, well-defined lesion encompassing one or more of our ROIs (see Figure 2). Individual volumes were fit to the MNI-ICBM single-subject *Colin* brain template (available in MRIcro; Rorden & Brett, 2000) to compare the size and locus of lesions while accounting for individual differences in brain size and shape using Automatic Image Registration version 5.2.5 software (bishopw.loni.ucla.edu/AIR5/). Visual inspection of the raw images and the transformed lesion maps suggested good correspondence between the two.

The number of voxels in each Brodmann's area containing lesion was calculated using the *Colin* template in MRIcro. Brodmann's areas were grouped into larger regions (based on anatomy and/or putative function; see Moscovitch & Winocur, 2002) to (1) minimize individual differences in gyral anatomy, (2) reduce the number of

correlations performed and consequently the likelihood of obtaining false positives, and (3) minimize multicolinearity as the amounts of tissue damage in neighboring Brodmann's areas were highly correlated. The clusters defined premotor (BA 3, 4, 6), anterior (BA 10), inferior (BA 11, 47), dorsolateral (BA 8, 9, 46), right hemisphere homologue of Broca's (BA 44, 45), and cingulate (BA 24, 25, 32, 33) regions. The number of lesioned voxels in each ROI was then divided by the total number voxels in each ROI in the *Colin* template to produce a percent lesion size for each ROI. These percentages in each ROI for each patient can be found in Davidson, Gao, et al. (2008).

RESULTS

Neuropsychological Task Performance

The performance of patients and control participants on the neuropsychological tasks is shown in Table 2. Group differences were assessed using independent *t* tests (with alpha set to .05, two tailed). The control participants outperformed the patients on most neuropsychological measures, including VIQ [$t(38) = 2.75, p = .009$], FSIQ [$t(38) = 2.11, p = .04$], HVLT total learning [$t(38) = 2.39, p = .02$], HVLT recognition discrimination [$t(38) = 2.39, p = .02$], Digit Symbol [$t(38) = 3.67, p = .001$], Trail Making Part A [$t(38) = 2.82, p = .008$], phonemic fluency [$t(38) = 2.09, p = .04$], and semantic fluency [$t(38) = 2.38, p = .02$]. Marginal group differences were found on Digit Span [$t(29) = 1.44, p = .08$] and HVLT delayed recall [$t(38) = 1.79, p = .08$]. The two groups did not differ on PIQ [$t(38) = 0.79, p = .44$], Trail Making Part B [$t(38) = 1.61, p = .12$], WSCT categories [$t(38) = 1.59, p = .12$], or WSCT percent perseverative errors [$t(38) = 0.90, p = .37$]. Relationships between performance on WSCT, Trail Making, and phonemic fluency and focal lesion sizes are reported by Davidson, Gao, et al. (2008).

Inclusion Task

Recognition hit rates (correctly saying "yes" to studied words) were higher for the controls than for the patients, $t(38) = 3.15, p = .003, \eta^2 = 0.21$ [*M* (*SD*): controls = 0.84 (0.13), patients = 0.71 (0.13)], but false alarm rates to new words the first time they were presented did not differ between groups, $t(38) = 1.09$ [*M* (*SD*): controls = 0.09 (0.09), patients = 0.13 (0.11)]. Similarly, both groups responded "yes" to repeated new words at an average rate of 95% (lag 10) to 100% (lag 0) of trials. These ceiling effects made ANOVA an inappropriate statistical approach and, furthermore, restricted the range of recollection estimates, hence rendered familiarity estimates unsolvable in a number of cases when standard calculations were used (cf. Jennings & Jacoby, 1997). However, as described below, the data from the exclusion task did not suffer these same problems, and we were able to estimate recollection and familiarity from the exclusion task alone.

Exclusion Task

Hit rates on the exclusion data were higher for the controls than for the patients, $t(38) = 2.27, p = .03, \eta^2 = 0.12$ [*M (SD)*: controls = 0.78 (0.15), patients = 0.68 (0.14)], but false alarm

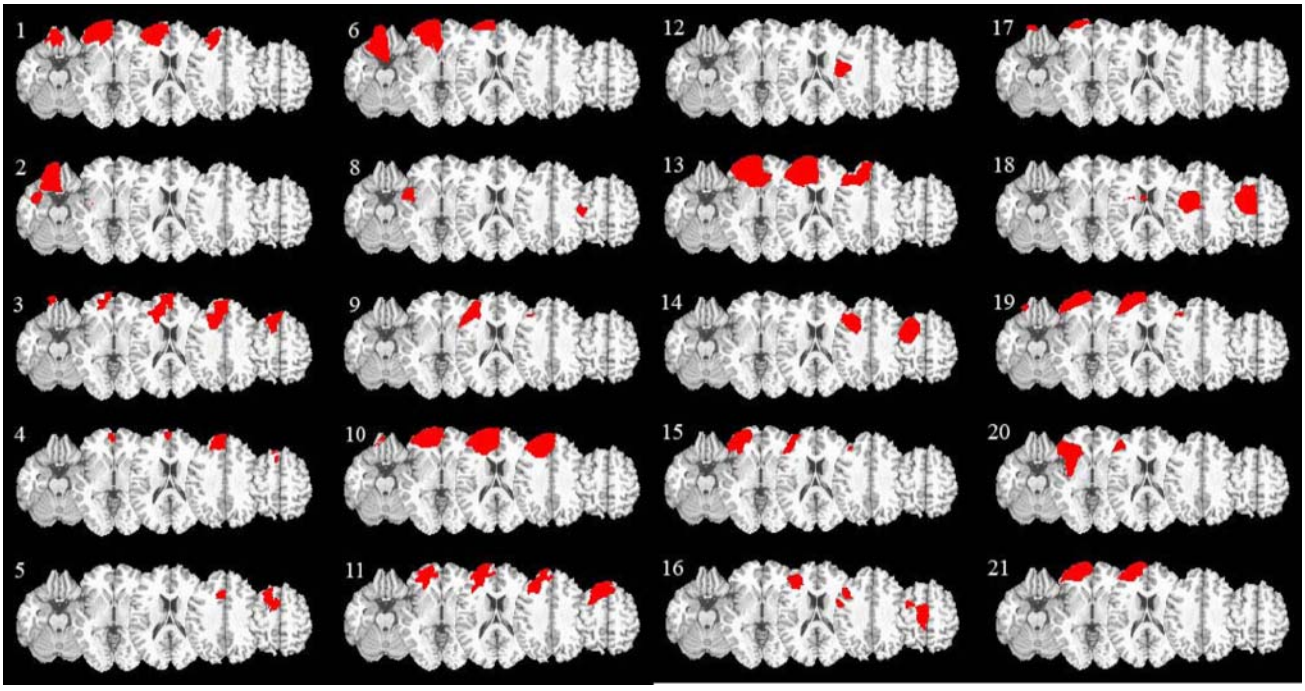

Figure 2. MR or CT images for each patient normalized to the MRIcro template. Shading shows lesion in the right frontal lobe for each patient (note that Patient 7 discontinued participation). Reprinted from Davidson, Gao et al. (2008) by permission of Taylor & Francis, Ltd. (http://www.informaworld.com).

Table 2. Neuropsychological Test Performance

	Controls			Patients			
	Mean	*SD*	*Standard Score*	*Mean*	*SD*	*Standard Score*	*p*
General intellectual ability							
NAART premorbid FSIQ				103.1	10.9		
VIQ	107.2	12.6		95.3	14.7		.01
PIQ	106.6	12.6		103.4	13.2		.44
FSIQ	107.9	12.4		99.2	13.6		.04
Memory							
Digit span	18.9	4.4	SS = 11.7	16.6	4.3	SS = 9.8	.16
HVLT							
Trials 1–3 total (/36)	26.7	3.6	39%ile	23.6	4.6	22%ile	.02
Delayed recall (/12)	9.7	2.0	37%ile	8.6	2.0	24%ile	.08
Recognition hits–FA (/12)	11.9	0.3	48%ile	11.4	0.9	39%ile	.02
Psychomotor speed/executive abilities							
Digit symbol	75.3	12.1	SS = 11.2	58.9	16.0	SS = 8.0	<.01
TMT-A	28.0	10.1	T = 50.5	37.8	12.0	T = 41.7	.01
TMT-B	56.0	24.4	T = 58.6	68.6	25.1	T = 51.2	.12
Phonemic fluency (FAS)	43.0	11.0	49%ile	35.9	10.6	33%ile	.04
Semantic fluency	21.0	5.5	49%ile	17.2	4.6	28%ile	.02
WCST							
Categories	4.9	1.8		3.9	2.2		.12
% Perseverative errors	14.9	9.9	T = 46.1	17.6	9.4	T = 42.7	.37

p values are for independent *t* tests with 38 degrees of freedom excepting Digit Span where there were 29 degrees of freedom (20 controls, 11 patients).

rates to new words the first time they were tested did not differ between groups, $t(38) = 1.35$, $p = .19$ [*M (SD)*: controls = 0.09 (0.08); patients = 0.14 (0.13)]. The probability of erroneously responding "yes" on the Exclusion task to repeated items as a function of lag is shown in Figure 3. These data were analyzed using a 2 (Group) × 3 (Lag) mixed ANOVA. False alarms to repeated new items increased across lags, $F(2, 76) = 27.94$, $p < .001$, $\eta^2 = 0.42$, but did not differ between groups, $F(1, 38) < 1$, and the interaction between group and lag was not reliable, $F(2, 76) < 1$. Importantly, these false alarm rates to repeated new words were not restricted by floor (or ceiling) effects, as they were for the Inclusion data.

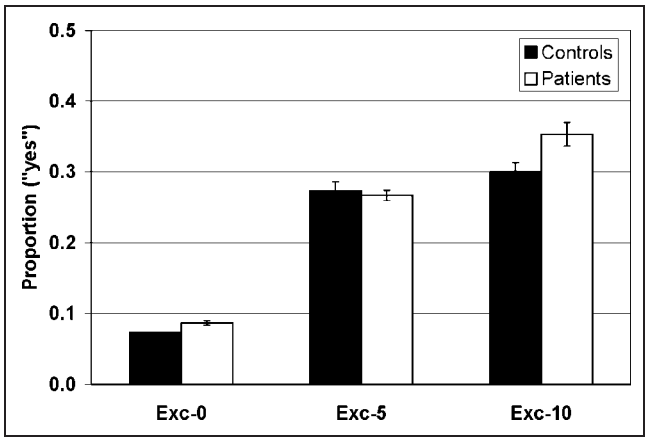

Figure 3. Mean proportion "yes" responses to repeated new items (±*SE*) in the Exclusion task as a function of group and lag.

Estimates of Recollection and Familiarity

Application of the principles of independent, dual-process retrieval theory (Jacoby, 1991; Mandler, 1980) to the data from the Exclusion task allowed us to derive estimates of

recollection and familiarity. We reasoned that studied words could be correctly recognized on the basis of recollection of the items in their context (that is, as studied words), R, and/or familiarity of the items in the absence of recollection of their context, $F(1 - R)$, or on the basis of a pure guess, G, whereas repeated new words would be erroneously responded "yes" to on the basis of familiarity of the items in the absence of recollection of their context (as new words), $F(1 - R)$, or on the basis of a pure guess, G. Erroneous "yes" responses to new words the first time they were presented could only be supported by pure guesses, as there is no opportunity (within the study) for those items to be familiar or recollected. Accordingly, to obtain an estimate of recollection, we subtracted the probability of responding "yes" to repeated new words, $F(1 - R)$, and to new words the first time they were presented, G, from the probability of responding "yes" to studied words, $R + F(1 - R) + G$. An estimate of familiarity was obtained by dividing the probability of erroneous "yes" responses to repeated new items, $F(1 - R)$, by $1 - R$. To increase the reliability of our estimates, we averaged the data at Lags 5 and 10. Erroneous "yes" responses to repeated words at Lag 0 were rare, hence, were omitted because including data from that lag would have artificially constrained our estimates of recollection.

Estimates of recollection and familiarity for controls and patients are shown in Figure 4. Group differences in these values were assessed with independent t tests and with bootstrapping (Good, 2005; Efron & Tibshirani, 1986; Edgington, 1980). Bootstrapping involved randomly resampling the data of 20 controls and 20 patients with replacement 1000 times and recalculating the t for each of the new data sets to determine if the bias-corrected and accelerated (BCa; Efron, 1987) 95% confidence intervals (95% CI) of the mean group differences included 0. Estimates of recollection were marginally higher for controls than patients, $t(38) = 1.59$, $p = .12$, $\eta^2 = 0.06$, with the BCa bootstrapped 95% CI of the mean group difference (−0.03 to 0.33) also suggesting a marginal effect. By contrast, familiarity estimates did not differ between the two groups, $t(38) < 1$ (BCa 95% CI for the mean group difference of −0.16 to 0.11). In the patient group, neither estimate was influenced by whether the patients had received radiation or chemotherapy, months since surgery, or whether their tumor had been low or high grade (all ps $> .5$).

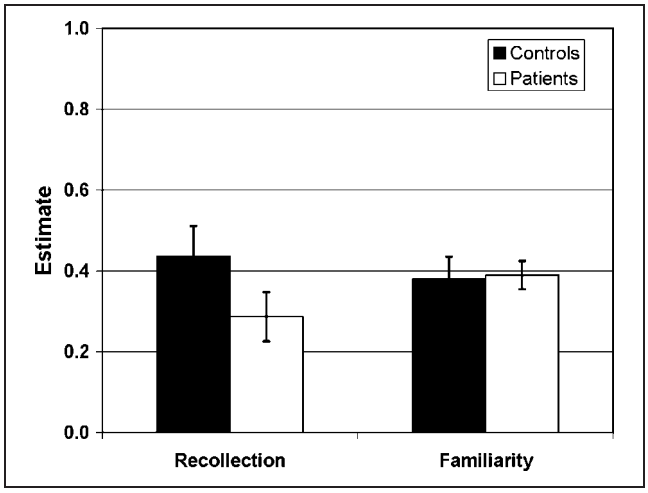

Figure 4. Mean recollection and familiarity estimates (±*SE*) as a function of group.

ROI Analyses

The ages of the patients with nonzero lesion sizes in each ROI varied. Previous research has shown that recollection and familiarity may be differentially affected by age, whereby recollection estimates are reliably lower among older than younger adults, whereas estimates of familiarity are either similar or lower in older relative to younger adults, depending on the study and methods used to derive the estimates (e.g., Anderson et al., 2008; Prull, Crandell Dawes, McLeish Martin, Rosenberg, & Light, 2006; Davidson & Glisky, 2002; Jennings & Jacoby, 1997). To account for potentially varying age effects, we first regressed recollection and familiarity estimates on age in the control group and then used those regression parameters to calculate standardized residuals with which to correlate with lesion size in each ROI. Only patients with nonzero lesion sizes were included in each correlation, as the zero values would have unduly influenced the correlation values. We also correlated the residualized estimates with total lesion size to investigate whether total brain injury contributed to these memory estimates. These correlations are shown in Table 3, which also shows the range and mean percent lesion size in each ROI, the number of patients with lesions in each ROI, and the lower and upper cut points of the BCa 95% CI from bootstrap resampling. Bootstrapping involved randomly resampling intact pairs of data with replacement 1000 times and recalculating the correlation for each of the new data sets to determine if the BCa 95% CIs of those r values include 0.

One correlation was marginally significant using traditional asymptotic p values, that relating estimates familiarity and inferior right pFC lesion size, $r(13) = .47$, $p = .10$, and it was significant on bootstrap resampling (95% CI = 0.21 to 0.76). Recollection and familiarity estimates were not significantly related to lesion size in any other ROI, nor to total lesion size.

DISCUSSION

This study compared the performance of 20 patients who had undergone resection of right frontal lobe tumors and 20 matched healthy control participants. The patient group performed worse than the control group on most tests in a battery of neuropsychological tests, in line with expectations of brain damage caused by the tumors (and possibly

Table 3. ROI Lesion Size (in Percent) Descriptives and Correlations with Age-corrected Estimates of the Contribution of Recollection and Familiarity

	Lesion Characteristics			*Correlation (p) [Min, Max of 95% CI]*	
ROI	*Size (%) Range*	*Size (%) Mean*	*% > 0 n*	*Recollection*	*Familiarity*
Premotor	0–12	3	8	.03 (.94) [−.82, .94]	.17 (.69) [−.27, .60]
Anterior	0–61	19	12	.01 (.99) [−.48, .62]	.43 (.17) [−.06, .79]
Inferior	0–36	11	13	−.29 (.34) [−.81, .24]	**.48 (.10) [.21, .76]**
Dorsolateral	0–37	11	15	−.18 (.53) [−.64, .21]	−.16 (.58) [−.54, .40]
Broca HL	0–17	6	12	−.32 (.31) [−.74, .22]	.36 (.26) [−.26, .75]
Cingulate	0–27	5	13	.02 (.95) [−.55, .58]	.13 (.67) [−.50, .59]
Total brain	1–16	7	20	.00 (.99) [−.43, .47]	.08 (.73) [−.36, .46]

Premotor = BA 3, 4, 6; Anterior = BA 10; Inferior = BA 11, 47; Dorsolateral = BA 8, 9, 46; Broca HL (homologue) = BA 44, 45; Cingulate = BA 24, 25, 32, 33. *p* values are asymptotic.

their treatment, although we saw no obvious effects of radiation or chemotherapy). Of main interest to us were the results of a process dissociation procedure that we used to estimate recollection and familiarity in a verbal recognition test. Recollection estimates were marginally lower in the patient than the control group, whereas estimates of familiarity did not differ between groups. These results are consistent with prior literature identifying greater frontal lobe memory impairments on tasks that emphasize recollective retrieval processes (e.g., Wheeler et al., 1995). Bootstrap evaluation of the correlation coefficients between the proportion of each of six right frontal ROIs and recollection and familiarity estimates revealed one significant result: Familiarity estimates were positively related to lesion size within right inferior (BA 11, 47) pFC. These results suggest that when the right inferior pFC is damaged, recognition judgments are more reliant on familiarity-based processing. This result confirmed our hypothesis that damage to inferior regions of the right frontal lobe would disrupt retrieval cue specification, making patients more vulnerable to a heightened sense of familiarity. What was not supported was our hypothesis that deficits in recollection would be associated with lesions in premotor, anterior, or dorsolateral regions of the right frontal lobe. It is possible that the presence of recollection deficits requires more than one confluent disruption of response inhibition, a "feeling of rightness" tied to a specific context, and monitoring. Our ability to carry out such conjoint analysis (i.e., correlating recollection estimates with lesion sizes among patients with damage to two or all three of these regions) was prevented by our sample size. However, this idea is consistent with the fact that, as a whole, the patient group had greater difficulties with recollection than did their matched controls, as the patients' lesions spanned various regions within the right frontal lobe.

To our knowledge, this is only the fifth study to examine recollection and familiarity in patients with focal pFC lesions. Of the previous studies, two found that pFC damage was associated with deficits in familiarity but not recollection (MacPherson et al., 2008; Duarte et al., 2005), whereas two reported isolated recollection deficits but differed in ascribing them to frontopolar (Wheeler & Stuss, 2003) or right frontal lesions (Hay et al., 2002). Of these, only MacPherson et al. and Wheeler and Stuss examined the regional specificity of recollection and familiarity within the frontal lobes. MacPherson et al. assigned each of their 24 patients to one of three groups (medial, lateral, and orbital) based on the region of greatest damage and reported that, compared with controls, patients with damage to medial and lateral pFC had deficits in familiarity, but not recollection. We argue that this approach is limited for two reasons. First, it is not possible to determine from their data the functional specificity of subregions within these areas (e.g., dorsal vs. ventral regions of lateral pFC). Second, we can arguably learn more by correlating cognitive measures with the extent of lesion within an ROI than by comparing cognitive performance of controls with patients with various degrees of damage in a particular region. This argument was supported by the nonsignificant relationships in the current data between total lesion size and the memory estimates and is based on the assumption that if a particular region is critical in a cognitive process, then the more that region is damaged, the greater the impairment should be. Of course, subregions within any ROI may be especially critical for recollection or familiarity, and calculations of percent lesion size do not capture this. Although the quality of the images available to us and indeed the current state of knowledge both lack the spatial sensitivity to explore this question more thoroughly at present, undoubtedly we will be able to do so in the future.

Another unique approach that we took was to use bootstrap resampling. Patient studies are typically limited in sample size; although we had the largest sample of patients with right frontal lesions that has ever been reported in a study of recollection and familiarity, the sample size

nevertheless limited the power of our parametric statistics, and the observed correlations may have been unduly influenced by outliers. We did not conduct an analysis-wide correction for multiple comparisons because of the limited power. However, the influence of potential outliers is mitigated in bootstrap resampling where outlying data points are selected only a subset of the time. Bootstrap resampling permitted us to conclude that the relationship between familiarity estimates and lesion size in the right inferior pFC was significant. In this context, it is worth asking how many associations between lesions and cognitive processes were not published because they failed to meet significance thresholds using traditional parametric methods. The present study suggests that resampling approaches can be a fruitful way to determine significance in small samples.

The current study was restricted to patients with lesions to the right frontal lobes because the role of the left frontal lobe in recollection and familiarity at retrieval would be confounded by language impairments and difficulties with encoding and semantic retrieval. Some investigators have suggested alternative approaches to dissociate these functions (cf., Bastin, Van der Linden, Lekeu, Andrés, & Salmon, 2006; Alexander, Stuss, & Fansabedian, 2003; Stuss et al., 1994) but we felt that such approaches would be too tenuous in this particular endeavor. Nevertheless, our results could reflect in part the effects of right pFC damage on encoding. Indeed, it is interesting to note that the patients' deficits on the HVLT were pronounced on both recall and recognition, which suggests that their right prefrontal lobe damage may have interfered with the encoding of the words in the first place, possibly contributing to the recollection and familiarity effects reported here. The patients also had significant psychomotor slowing relative to their healthy counterparts, as shown by the TMT-A and the Digit Symbol test; the study phase presentation rate (2 sec per word) may have been too high to allow patients to encode words at a level that would support recollection. However, additional analyses (available upon request) ruled out a significant relationship between speed on these measures and lesion size or recollection and familiarity estimates.

Our finding of larger right ventrolateral pFC lesions yielding increased familiarity is generally consistent with neuroimaging studies that reported recollection-based activations in anterior medial and ventrolateral pFC (e.g., Montaldi et al., 2006; Yonelinas et al., 2005; Bunge et al., 2004; Duarte et al., 2004; Kahn et al., 2004; Wheeler & Buckner, 2004). For example, in an fMRI study, Bunge et al. presented visual pattern pairs either 11 (strong) or 4 (weak) times during an encoding phase. At test, one of the patterns was presented along with two alternatives, and participants had to select which of the alternative patterns had been studied with it. Activity associated preferentially with retrieval of strong over weak items was identified in the right ventrolateral pFC and hippocampus, which Bunge et al. interpreted as reflecting the recollection of visual associative information. Although we did not find a significant relationship between recollection and lesion size in this area, it is possible that greater damage to the right ventrolateral pFC rendered patients more susceptible to the sometimes misleading influence of familiarity.

Indeed, in the Moscovitch and Winocur's (2002) model, which is based on animal, patient, and neuroimaging data, the ventrolateral pFC is involved in making use of distinctive cues during retrieval. Damage to this region is associated with an overreliance on gist (Melo, Winocur, & Moscovitch, 1999) and an overextended sense of familiarity during retrieval (Rapcsak et al., 2001; Schacter, Curran, Galluccio, Milberg, & Bates, 1996). Moscovitch and Winocur further point out the difficulty in separating BA 47 from medial aspects of the ventral pFC, and indeed for this study, we combined BA 47 and BA 11, because BA 11 encompasses both lateral and medial aspects of pFC. Damage to ventromedial pFC, including BA 11, can result in confabulation, a condition that Moscovitch and Winocur argue stems from a damaged sense of "feel rightness" for erroneous information retrieved from memory. Our results are consistent with these ideas: Although our patients did not suffer from confabulation, those with greater damage to BA11/BA47 were more prone to falsely endorse repeated lures, leading to higher estimates of familiarity.

Many studies have reported elevated false alarm rates in patients with frontal lobe lesions relative to controls (e.g., Daum & Mayes, 2000; Schacter, Norman, & Koutstaal, 1998; Parkin, Bindschaedler, Harsent, & Metzler, 1996), but this effect did not appear in the current data. Verfaellie, Rapcsak, Keane, and Alexander (2004) found that, compared with controls, a group of patients with frontal lobe tumors but no amnesia produced normal false alarm rates, although some individual patients had excessive false alarm rates (see also Bastin et al., 2006). Our data were similar, with control false alarm rates ranging from 0.00 to 0.22 excepting one outlying control with a false alarm rate of 0.31, and patient false alarm rates ranging from 0.00 to 0.44 with four patients exceeding 0.22. On the basis of the variability across patients with frontal lobe lesions, Verfaellie et al. suggest that false alarm rates may reflect more than one underlying mechanism. The current data suggest that one such mechanism is the heightened familiarity associated with greater damage to right ventrolateral pFC, although it should be noted that some patients with considerable damage to this region had relatively low false alarm rates.

A final point is that our patients showed abnormal performance on the memory test despite our providing them with an explicit strategy to use during encoding. Had we not provided these instructions, patients' performance would undoubtedly have been worse (e.g., Gershberg & Shimamura, 1995; Hirst & Volpe, 1988). Recently, however, Cohn, Moscovitch, and Davidson (2010) found that the degree to which people with Parkinson's disease appear to be impaired in recollection versus familiarity is highly sensitive to encoding strategies. Mapping the neural

bases of component processes underlying recollection, familiarity, and false recognition will require us to be sensitive to the specific cognitive processes employed during encoding and retrieval, and to seek converging evidence by combining different neuroscience techniques, for example, TMS interference or focal lesion studies with functional neuroimaging.

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Note

1. We use the terms "estimates of recollection" and "estimates of familiarity" as short-hand for "estimates of the contribution of recollection (or familiarity) to recognition memory".

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