

“Brain Is to Thought as Stomach Is to ??”: Investigating the Role of Rostrolateral Prefrontal Cortex in Relational Reasoning

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Abstract

■ Brain imaging studies suggest that the rostrolateral prefrontal cortex (RLPFC), is involved in relational reasoning. Functional magnetic resonance imaging (fMRI) studies involving Raven's Progressive Matrices or verbal propositional analogies indicate that the RLPFC is engaged by tasks that require integration across multiple relational structures. Several studies have shown that the RLPFC is more active when people must evaluate an analogy (e.g., Is shoe to foot as glove is to hand?) than when they must simply evaluate two individual semantic relationships, consistent with the hypothesis that this region is

important for relational integration. The current fMRI investigation further explores the role of the RLPFC in reasoning and relational integration by comparing RLPFC activation across four different propositional analogy conditions. Each of the four conditions required either relation completion (e.g., Shoe is to foot as glove is to WHAT? → “hand”) or relation comparison (e.g., Is shoe to foot as glove is to hand? → “yes”). The RLPFC was engaged more strongly by the comparison subtask relative to completion, suggesting that the RLPFC is particularly involved in comparing relational structures. ■

INTRODUCTION

Central to the performance of many complex cognitive tasks is the ability to reason with structured or relational information. Understanding how the brain accomplishes relational processing is an important question in cognitive neuroscientific research on high-level cognition. Here, we use functional magnetic resonance imaging (fMRI) to investigate neural activation associated with one kind of relational processing, involving solution of propositional analogy problems. Brain imaging studies have pointed to one region in particular, located in the rostrolateral prefrontal cortex (RLPFC), as playing a central role in analogical reasoning and complex relational processing (Bunge, Wendelken, Badre, & Wagner, 2005; Christoff et al., 2001; Waltz et al., 1999). The precise regional boundaries associated with this functionality remain an open question, but current evidence supports inclusion of both the lateral aspect of the frontopolar cortex (Brodmann's area [BA] 10) along with the most anterior parts of the lateral PFC (possibly including parts of areas 11, 46, and 47).

fMRI studies have shown that the rostral PFC is activated when people solve verbal analogy problems. This region is more active when people evaluate prop-

ositional analogies than when they evaluate either semantic (Bunge et al., 2005) or categorical relationships (Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006). In our prior study (Bunge et al., 2005), participants were presented with two pairs of words separated by a short delay. In the analogy condition, participants indicated whether the pairs of words were analogous, whereas in the semantic condition, they indicated if the words in the second pair were semantically related. The strength of association between words in each pair was varied across trials, so that comparison could be made between trials involving high associative strength versus those involving low associative strength.

This initial study revealed that the left RLPFC was more active on analogy than semantic trials but did not show an effect of associative strength. In contrast, the ventrolateral PFC (VLPFC) was more active when participants had to retrieve weaker than stronger semantic relationships, but did not show as strong of an analogy > semantic effect as the RLPFC (Bunge et al., 2005). These results were interpreted as evidence that the VLPFC is involved in retrieving semantic relations between words in a pair, whereas the RLPFC is involved in the integration of relational information required to perform the propositional analogy task. The present study follows up on this finding by further examining RLPFC involvement in relational integration during the solution of analogy problems.

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There are a number of hypotheses regarding functions of the RLPFC (see Discussion). With respect to the current experiment, the hypothesis that this region supports relational integration, or the joint processing of multiple relations (Bunge et al., 2005; Kroger et al., 2002; Christoff et al., 2001), is most relevant. This hypothesis stems from brain imaging experiments involving a visuospatial reasoning task called Raven's Progressive Matrices (RPM), in which participants must identify relevant visual features based on the spatial organization of an array of visual stimuli, and then select from among several alternatives a stimulus that matches one or more of these identified features (Raven, 1941). Performance of the two-relational RPM task is thought to require relational integration, because one must jointly consider horizontal and vertical relationships between stimuli in the array to identify the missing stimulus that would complete the array. In multiple studies, the RLPFC has been shown to be more active during the solution of two-relational than one-relational and zero-relational RPM trials (Crone et al., in press; Christoff et al., 2001). In another study involving the RPM task, RLPFC activation was positively correlated with relational complexity but was unaffected by level of distraction from the incorrect choice stimuli (Kroger et al., 2002). Further supporting prefrontal involvement in relational reasoning, studies of patients with damage to the PFC have revealed deficits in the ability to integrate relations in both deductive and inductive reasoning tasks (Morrison et al., 2004; Waltz et al., 1999).

Here we consider the relatively simple form of analogical reasoning required to solve propositional analogy problems (e.g., "Is painter to brush as writer is to pen?" and "Hat is to head as glove is to *what*?"). We assume that solution of a problem with the structure "A:B::C:D?" (i.e., gIs A to B as C is to D?" as in the first example above) requires that one retrieve the semantic relationship that links each pair of terms and *compare* those relationships (i.e., to map or integrate across the retrieved relational structures; Bunge et al., 2005). In contrast, solution of a problem with the structure "A:B::C:?" (i.e., gA is to B as C is to what?") is hypothesized to require that one retrieve the semantic relationship for the first word pair and to use this retrieved relation to *complete* the second word pair. Completion of the second relation involves a kind of integration—transfer of the relationship defined over the attributes of A and B to the relevant attributes of C—and also involves generation (i.e., retrieval) of an appropriate role-filling item (cf. Jani & Levine, 2000).

Variations of the *compare* task are encountered commonly in real-world situations, whenever one needs to decide if some previous experience, insight, or solution is applicable to a current situation. For example, one may seek to determine whether the situation of being a teacher's pet at school corresponds to that of being the boss's favorite at work, or to determine if knowing the

properties of ocean waves is helpful for understanding electromagnetism. The *complete* task also has a real-world counterpart: the determination of what element of a novel situation best fits with previous experience. For example, if one knows about a pattern of relationships common to a school environment (teacher favors teacher's pet, etc.) then one might try and apply these to a new work environment ("Who is the boss's favorite?"), or if one knows that ocean waves have peaks and troughs, one might seek out these patterns in a mathematical description of light.

If RLPFC activation, as seen in our previous study of propositional analogies, is specific to the comparison of relational structures, then we can predict that this region will show a preference for compare trials over complete trials. The opposite pattern would suggest that the RLPFC is involved in the transfer and/or generation processes required for complete trials. Finally, increased RLPFC activity across all conditions would suggest that this region plays a more general role in different kinds of integration, whereas an across-the-board decrease in activity would disconfirm this hypothesis.

In addition to the compare versus complete manipulation, we also included two different forms of the initial retrieval cue. Some trials (*example* trials), as presented above, included a pair of related words, whereas others (*term* trials) included an initial word or short phrase denoting a relation (e.g., guses," "worn on"). This manipulation allows us to test whether the RLPFC is selectively engaged when comparing two pairs of related items, or whether it is also engaged when comparing one pair of related items with a relational term. Including *term* as well as *example* trials should allow for further insight into the types of representational structures that drive the RLPFC.

Other experiments that have examined RLPFC involvement in the management of multiple pieces of information have involved working memory delays (Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Sakai & Passingham, 2003; Braver & Bongiolatti, 2002). In this study, we sought to determine whether the need to hold information in mind over a delay constitutes a prerequisite for RLPFC involvement in the task. As such, we further modified our prior task design in such a way as to minimize maintenance demands. By comparing RLPFC activation across these different problem types, we sought to better understand the nature of this region's involvement in analogical reasoning.

METHODS

Participants

Twenty healthy, right-handed native English speakers were included in this study (9 women, 11 men; 18–28 years old, mean age = 21 years). Two additional participants were scanned but excluded from the study

due to excessive movement in the scanner; the criterion for excluding a participant was the presence in every session of movement spikes in excess of 2 mm. One additional participant was excluded due to poor task performance (specifically, 0% accuracy on one condition and less than 50% accuracy overall.). Participants were recruited from the University of California (UC) at Davis and were paid for their participation. Informed consent was obtained from all participants, and all procedures were approved by the internal review board at UC Davis.

Task Conditions

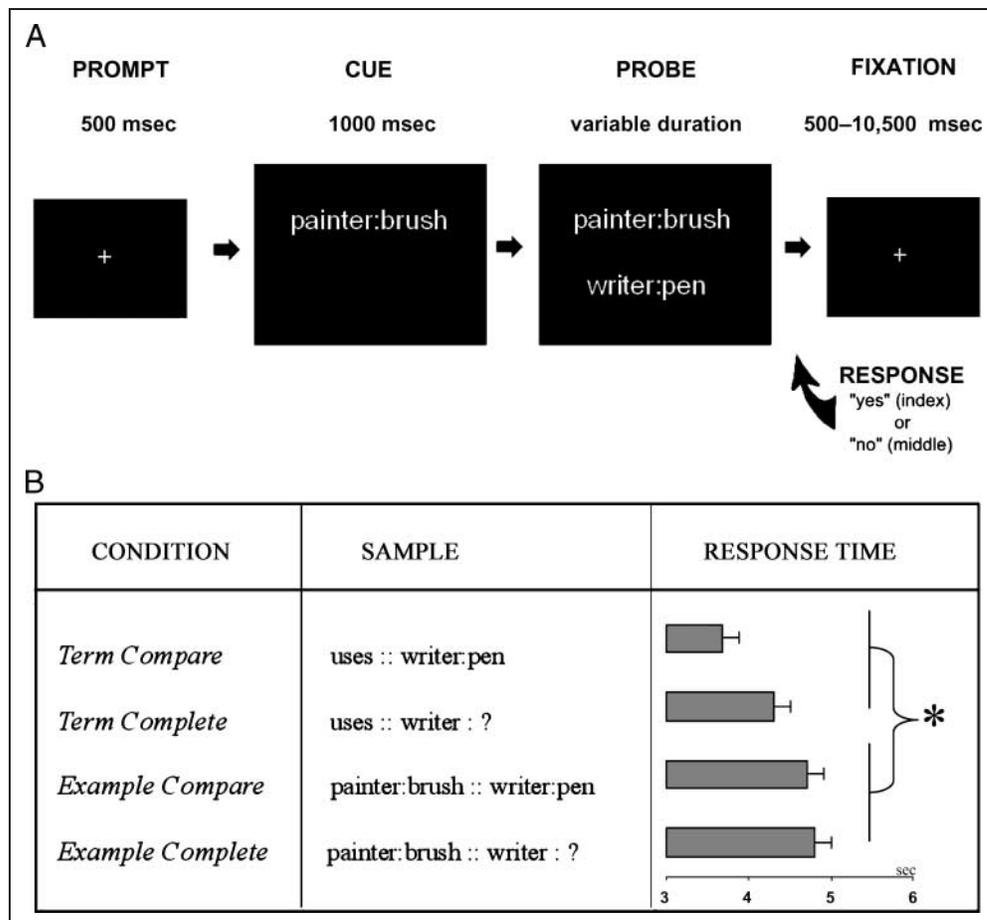
Participants performed four different kinds of analogical reasoning problems (Figure 1B). These problems differed with respect to the initial relational retrieval cue (a pair of related items such as “boots:foot” or a relational term like “wear”) and also in the type of relational task that was required (relation comparison or relation completion). In Condition 1 (*Term Compare*), participants were presented with a relational word or short phrase followed by a pair of words, and their task was to evaluate whether or not this relational term accurately summarized the semantic relationship between the two words. In Condition 2 (*Term Complete*), participants were presented with a relational term followed by a

single word. Their task here was to think of a word that related to the first word in a manner consistent with the relation term. In Condition 3 (*Example Compare*), participants saw a pair of words followed by a second pair of words. They were asked to think of a relational word or short phrase that linked the first two words and to use that term to determine whether the second word pair was analogous to the first word pair. In Condition 4 (*Example Complete*), participants saw a pair of words followed by a single word. They were asked to retrieve the relation associated with the pair of words and to use that relation to come up with a fourth word that would complete the analogy.

Experimental Procedure

For all four conditions, a trial began with a short (500 msec) prompt, consisting of a green fixation cross on a black background (Figure 1A). The first word or word pair (the cue) appeared alone on the screen for 1 sec, and was then joined by a second word or word pair (the probe) for the remainder of the stimulus presentation. When the probe appeared, participants were to make a response as quickly yet as accurately as possible. There was no time limit for responding, and each trial ended only once the participant had responded. Participants were instructed to

Figure 1. (A) Experimental and analytical paradigm. Each trial consisted of a brief prompt, followed by a 1-sec cue, and then by a probe that remained onscreen until the participant’s response. Between trials, there was a variable intertrial interval. (B) The four experimental conditions, with response time results. Trials that began with an example relation took significantly longer than those that started with a relation term. There were no significant differences in accuracy across the four conditions (not shown).



make a yes or no response on each trial by pressing one of two buttons with the index or middle finger of their right hand.

For the two conditions involving relation comparison, participants were to respond “yes” whenever the relation given by the probe matched the relation given by the cue, and to respond “no” otherwise. For the two conditions involving relation completion, participants were to respond yes when they believed that they had come up with a correct answer, and to respond no otherwise. Prior to the start of the next trial, there was a variable interval of up to 12 sec during which time a white fixation cross was displayed. Trial presentation was synchronized with the scanner, such that each trial began at the start of a volume acquisition. After scanning, participants were shown a computerized presentation of each of the Complete-task problems to which they had responded yes, and were asked to enter into the computer the word or phrase that they had come up with in the scanner.

Trials were presented according to a rapid event-related design, and the order of trials within each scan was determined using an optimal sequencing program (optseq2) designed to maximize the separability of different conditions in a rapid event-related fMRI study (Dale, 1999). Functional scanning involved four 8-min scans. Trials of different conditions were pseudorandomly intermixed within a scan, but only two conditions were presented during each scan. The reason for including only two conditions per scan was to limit effects of task switching and to minimize confusion about which task to perform on a given trial. Conditions were paired in the following manner: 1 and 2, 3 and 4, 1 and 3, and 2 and 4. Scan order was counterbalanced across participants. On average, 41 repetitions of each condition were presented across scans. This number varied from participant to participant due to differences in average response time within this self-paced design of fixed scan duration.

fMRI Data Acquisition

Scanning was performed on a 1.5T MRI scanner (General Electric Signa Advantage, Medical Advances Inc, Milwaukee, WI) at the UC Davis Imaging Research Center, using a standard whole-head coil. Visual stimuli were back-projected onto a screen that was viewed through a mirror mounted above the MRI head coil. Head motion was restricted by foam inserts that surrounded the head. Stimulus presentation and response acquisition were controlled by the Presentation software system (nbs.neuro-bs.com). Participants held a button box in their right hand and a microphone tube for communication in their left hand.

Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2.0 sec, TE = 40 msec, 24 axial slices, $3.44 \times 3.44 \times 5$ mm, 240 volumes per

run). The first four volumes of each scan were discarded to allow for T1-equilibration effects. In addition to the functional scans, high-resolution T1-weighted (spoiled gradient recalled) coronal anatomical images were collected, as well as coplanar anatomical images.

Data Preprocessing

Data were preprocessed and analyzed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were corrected for differences in slice acquisition timing and were realigned to the first volume by means of rigid-body motion correction with sinc interpolation. Structural and functional images were spatially normalized to T1 and EPI templates, respectively. These templates are based on the Montreal Neurological Institute (MNI) stereotaxic space (Cosco, Kollokian, RK, & Evans, 1997), an approximation of the Talairach space (Talairach & Tourneaux, 1988). The normalization algorithm involved a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization, the volumes were resampled to $3 \times 3 \times 3$ -mm cubic voxels. Functional images were spatially smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel. The smoothed, normalized images were then submitted to statistical analyses.

fMRI Data Analysis

A general linear model (GLM) incorporating task effects, session effects, and a linear trend was used to analyze each participant's data. For each subject, this model was used to compute the least squares parameter estimate of the height of the best-fitting synthetic response function for each condition at each voxel. Only correct trials were considered for each task condition: All incorrect trials were modeled together as a separate condition. In the primary analysis, task-related neural activity was modeled as a series of zero duration events aligned to each midpoint between trial onset and response; this series then convolved with SPM's canonical hemodynamic response function (HRF) to produce a model of the predicted blood oxygenation level dependent (BOLD) response. This analysis is designed to be maximally sensitive to neural activity that occurs in the middle of a trial and that is not specifically tied to the visual input of the cue period or the motor output of the response period. This analytic approach conforms to our general hypothesis about relational integration in the RL PFC: Integration is a process that occurs after initial processing of a stimulus and before generation of a response. High-pass temporal filtering with an upper limit of 120 sec was applied to eliminate low-frequency noise from the data. Contrasts images were computed within subjects for each comparison of interest. Random effects analyses were performed on the individual participants'

contrast images to generate group contrast maps. Except where otherwise noted, group maps were thresholded using an uncorrected p value of .001 and an extent threshold of 10 contiguous voxels.

Event-related time courses were obtained from selected activation clusters via selective averaging of data from the first 14 sec following each trial onset. This analysis involved averaging first across voxels in the region, then across repetitions of each trial type, and finally across participants.

Region-of-interest (ROI) analyses were conducted on selected prefrontal activation clusters from the primary analysis and also on 5-mm spheres centered at RLPFC activation peaks from several previous studies of relational integration. ROIs were constructed and analyzed with the Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002; marsbar.sourceforge.net). Mean contrast values for each participant and condition were extracted for each ROI and submitted to analyses of variance (ANOVAs) and post hoc comparisons. All functional ROIs were obtained from the general contrast of all correct trials versus baseline, where baseline refers to the signal that remains once modeled condition effects have been removed. The baseline estimate is predominantly based on the variable-duration periods of fixation interspersed between trials through the use of optseq2, as described previously. The left-side RLPFC activation peak ($-45, 45, 6$) from our previous study of analogical reasoning (Bunge et al., 2005) formed the basis of one ROI. Because several studies involving relational integration have demonstrated activation of a similar cluster on the right side (e.g., Braver & Bongiolatti, 2002; Prabhakaran, Smith, Desmond, Glover, & Gabrielli, 1997), we also analyzed the mirror image ROI on the right side. ROIs based on activation peaks from two other studies (Christoff et al., 2001; Prabhakaran et al., 1997) were examined as well; details of these ROIs are provided along with the results.

A secondary analysis was also performed, in which response times were included as part of the model. For this analysis, task-related neural activity was modeled as a series of epochs, which were then convolved with the canonical HRF. The epoch associated with each trial had its onset at the appearance of the second stimulus (word pair) and had a duration equal to the response time for that trial. The purpose of this secondary analysis was to control for activation differences that might emerge as a result of differences in response time; the drawback of this analysis, relative to the first, is that it is relatively insensitive to neural activity that is not sustained for the duration of the trial.

Behavioral Performance

Because we planned to exclude incorrect trials from the fMRI analysis, we sought to achieve relatively high accuracy among pilot participants while the task was first being developed. To this end, any item for which

more than 2 of the 10 pilot participants gave poor answers was not included in the experiment. There is some subjectivity in the evaluation of responses, particularly with regard to completion problems. The approach taken here, for the purpose of reporting accuracy and determining whether a trial should be included in the fMRI analysis, was to count as correct any response judged reasonable by the experimenter. On average, 83.1% of fMRI trials were counted as correct, with accuracies (± 1 standard deviation) across Conditions 1–4, of $82.2 \pm 11\%$, $84.1 \pm 11.8\%$, $83.9 \pm 10.2\%$, and $82.0 \pm 13.7\%$, respectively. There were no significant differences in accuracy between conditions, $F(3,57) < 1$.

However, as shown in Figure 1B, response times (RTs) did differ across conditions, $F(3,57) = 7.67$, $p = .0002$. Post hoc comparisons revealed that participants responded more slowly to trials that required initial retrieval of a relationship between two words (Conditions 3 and 4; 4.8 ± 1.5 sec) than those that started with a relational term (Conditions 1 and 2; 4.0 ± 1.2 sec). There were no other significant RT differences between conditions.

In an effort to verify that participants were actually performing the relation completion problems as instructed, we conducted a separate behavioral study ($n = 13$) that involved only these types of problems but under two different response conditions: silent and verbal. In both tasks, participants were instructed to press the yes button as soon as they had come up with a response that they thought to be correct. For *silent* trials, actual responses were collected in written form at the end of the experiment (as in the fMRI study). For *verbal* trials, the button press was followed by a response window during which participants stated their response out loud. There was no difference in accuracy, $F(1,12) < 1$, or RTs, $F(1,12) < 1$, between these two conditions, suggesting that subjects performed the two tasks similarly.

fMRI RESULTS

Exploratory Analysis

Contrasts between conditions were examined to identify brain regions associated with relation comparison and relation completion. Greater activation associated with comparison than completion was observed in the right RLPFC (see Figure 2 and Table 1). Although left-side RLPFC activity was not revealed at the standard threshold, a similar activation cluster within the left RLPFC did appear at the weaker threshold of $p < .005$ (uncorrected). In addition to the RLPFC, several other activation clusters were revealed for this contrast, most notably in the right DLPFC and bilateral premotor cortex. At the standard statistical threshold, no regions were identified as more active for the tasks involving completion than comparison. At a weaker threshold ($p < .005$), greater activation was observed for completion than comparison

Figure 2. (A) Axial and coronal slices from the whole-brain contrast image for compare (1, 3) > complete (2, 4), thresholded at $p < .005$ (uncorrected). Activation foci in left and right RLPFC are revealed. (B) BOLD activation time courses for each condition extracted from the left and right RLPFC activation clusters, plotted in terms of percent signal change. Note that solid lines are compare conditions and dashed lines are complete conditions.

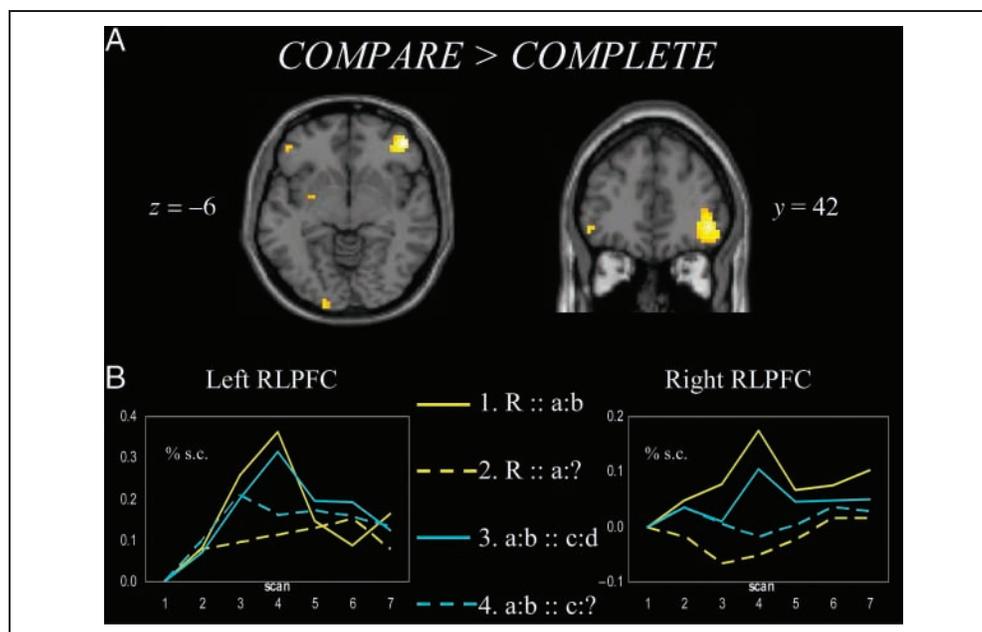


Table 1. Activation Foci for Whole-brain Contrasts

	x, y, z	k	T	Z	P
<i>Primary analysis</i>					
A. Compare – complete					
R. RLPFC (BA 10, 47)	45, 45, -3	48	5.28	4.09	<.001
L. RLPFC (BA 10, 47)	-48, 42, -6	8	3.34	2.92	<.005
R. DLPFC (BA 9)	57, 9, 33	88	4.89	3.89	<.001
Superior frontal gyrus (BA 8)	9, 27, 48	17	4.45	3.64	<.001
Supplementary motor area (BA 6)	45, 3, 60	14	4.70	3.78	<.001
R. premotor cortex (BA 6)	39, -12, 60	36	4.95	3.92	<.001
L. premotor cortex (BA 6)	-30, -21, 60	20	4.49	3.66	<.001
L. superior parietal cortex (BA 7)	-30, -60, 66	10	3.83	3.45	<.001
B. Complete – compare					
L. middle frontal gyrus (BA 8)	-30, 33, 51	35	3.77	3.22	<.005
L. medial frontopolar cortex (BA 10)	-6, 63, 9	13	3.45	3.00	<.005
<i>RT analysis</i>					
C. Compare – complete					
R. RLPFC (BA 10)	45, 45, -3	12	4.44	3.60	<.001
R. supplementary motor area (BA 6)	45, 6, 60	31	6.38	4.56	<.001
R. angular gyrus (BA 40)	39, -54, 39	11	3.78	3.20	<.001

Depicted here are the peak foci for contrasts between conditions involving comparison (1, 3) versus completion (2, 4). For compare > complete, all activation clusters that met the standard threshold ($p < .001$, five voxel extent) in either the primary or RT analysis are shown. In addition, because RLPFC was our primary ROI, a left RLPFC cluster that only appeared at the weaker threshold of $p < .005$ in the primary analysis is also included. For the complete > compare contrast, no significant voxels were observed at the standard threshold in either analysis; the two regions reaching significance at the less conservative threshold ($p < .005$, five voxels) in the primary analysis are listed here. R. = right; L. = left.

in the left medial frontopolar cortex (BA 10) as well as left middle frontal gyrus (BA 8). The medial BA 10 region was deactivated relative to baseline across all four task conditions (see Figure 3B).

The whole-brain map of task-related activation (all correct trials vs. baseline) reveals activation predominantly in left PFC, left motor cortex, and bilateral occipital cortex (Figure 3A). Functional ROIs were obtained from all prefrontal regions that were activated in this general contrast thresholded at $p < .005$, including left RLPFC, left DLPFC, and left VLPFC. t Tests performed on ROI parameter estimates revealed a significant increase in activation for compare (1, 3) versus complete (2, 4) in RLPFC, and also a significant increase for term (1, 2) versus example (3, 4) in VLPFC. No significant differences were observed in the DLPFC cluster ($F < 1$), and no significant interactions were observed between the two factors in any of the three regions (all F s < 1). In separate activation maps for each condition versus

baseline (Figure 3C), clusters of activation in VLPFC and DLPFC appear across all conditions, and an additional activation cluster in RLPFC appears for the two comparison conditions (Table 2).

For the secondary analysis, in which response times were included in the GLM, the pattern of results was largely similar to the main analysis. At the standard threshold, the right RLPFC and bilateral premotor cortex were again observed for compare versus complete. In contrast to the primary analysis, DLPFC activation was not present in this contrast at the standard threshold. Again, no activation was present at the standard threshold for complete relative to compare.

Examination of RLPFC Activation Peaks from Previous Studies

For RLPFC ROIs obtained from our previous study of verbal analogy problem solving, a comparison of parameter

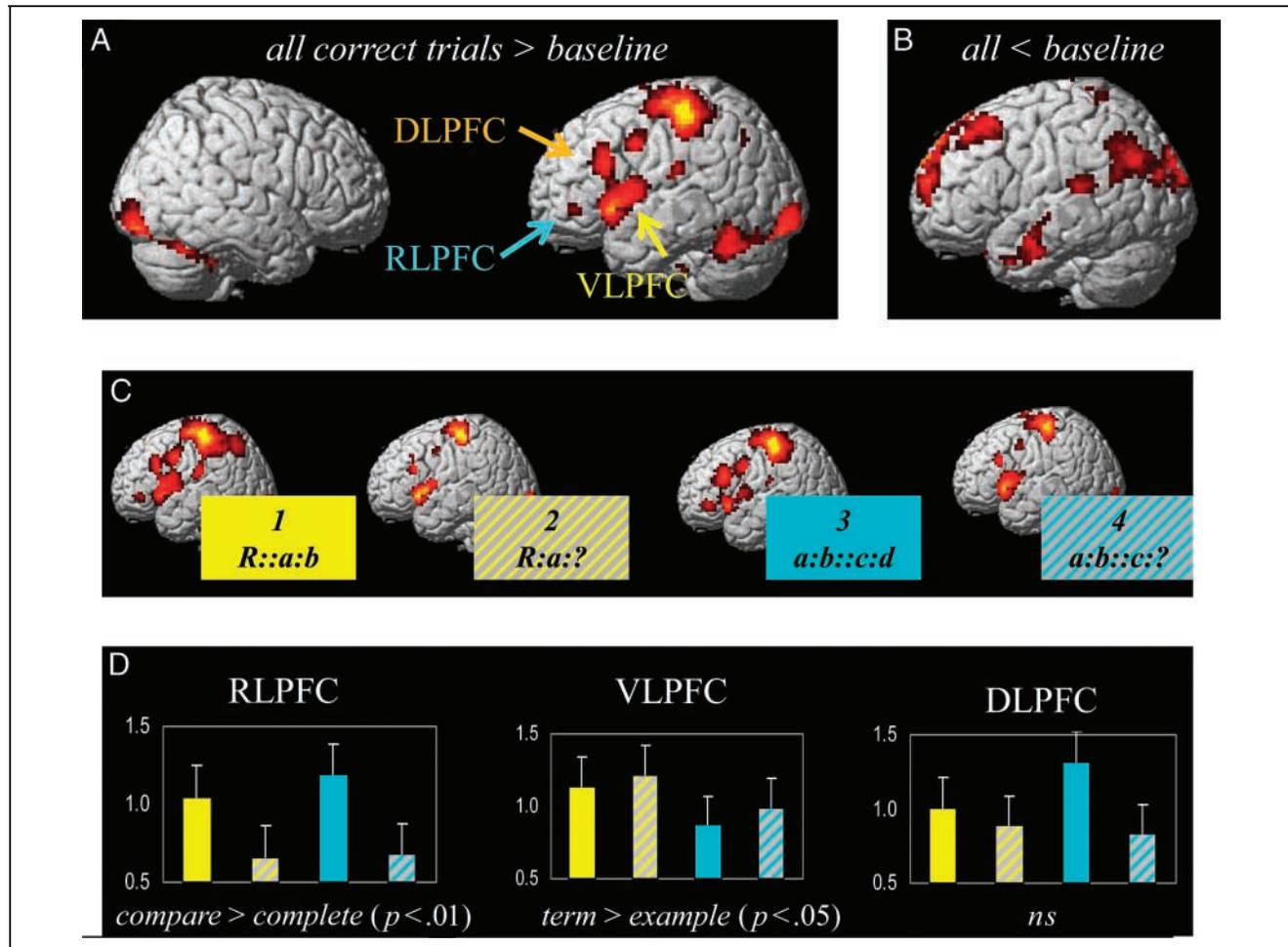


Figure 3. (A) The activation map for all correct trials > baseline (thresholded at $p < .005$ uncorrected) reveals task-related activation in prefrontal, parietal, and occipital cortices. Prefrontal ROIs were obtained from this contrast. (B) Areas of deactivation during task performance include frontopolar cortex and cingulate cortex. (C) Activation maps for each condition versus baseline reveal activation within left RLPFC for the two comparison conditions (1 and 3) but not for the two completion conditions (2 and 4). (D) Parameter estimates for each condition, within each ROI, are plotted for RLPFC, DLPFC, and VLPFC. Significant main effects are compare > complete in RLPFC ($p < .01$) and term > example in VLPFC ($p < .05$). Note that labels in (C) correspond to bar colors here.

Table 2. Activations versus Baseline

	x, y, z	k	T	Z	P (<i>unc</i>)
<i>A. All correct trials > baseline</i>					
L. DLPFC (BA 9, 46)	−45, 24, 27	62	5.11	4.00	<.001
Putamen, thalamus, globus pallidus	−30, −12, 0	554	5.87	4.38	<.001
Inferior frontal gyrus, insula	−48, 0, 9	*	5.68	4.29	<.001
L. precentral, postcentral, and parietal lobe	−33, −21, 72	406	4.49	3.66	<.001
Premotor cortex (BA 6)	−3, −6, 57	49	5.83	4.36	<.001
R. cerebellum	27, −48, −39	167	6.19	4.53	<.001
L. cerebellum	−45, −63, −27	89	5.12	4.01	<.001
R. occipital lobe (BA 18)	21, −93, −12	84	4.79	3.83	<.001
L. occipital lobe (BA 18)	−24, −90, −18	77	4.53	3.68	<.001
<i>B. Term compare > baseline</i>					
L. RLPFC (BA 10, 47)	−45, 42, −3	28	3.88	3.29	<.001
<i>C. Term complete > baseline</i>					
No additional regions.					
<i>D. Example compare > baseline</i>					
L. RLPFC (BA 10, 47)	−45, 42, −3	56	4.51	3.67	<.001
<i>E. Example complete > baseline</i>					
No additional regions.					
<i>F. Baseline > all correct trials</i>					
Frontopolar cortex (BA 20, 9)	−3, 51, 21	1610	8.98	5.55	<.0001
Anterior cingulate cortex (BA 24)	12, 51, 8	*	8.66	5.45	<.0001
Posterior cingulate, parietal lobe	6, −60, 24	1670	9.69	5.75	<.0001
R. temporal gyrus (BA 20, 21)	60, −12, −15	191	6.38	4.61	<.0001
R. parietal, temporal (BA 40, 39, 22)	60, −57, 33	541	8.53	5.41	<.0001
L. parietal, temporal (BA 39, 40)	−54, −69, 33	70	7.61	5.09	<.0001

Activations versus baseline for (A) all correct trials, (B) term compare condition, (C) term complete condition, (D) example compare condition, and (E) example complete condition; thresholded at $p < .001$ (uncorrected). Note that B–E show only regions that were active for the individual condition versus baseline but not for the more general contrast (all correct vs. baseline) at $p < .001$. (RLPFC was observed for this general contrast at $p < .005$). (F) Deactivations versus baseline are shown at $p < .0001$ (uncorrected).

*The current activation cluster is contiguous with the previously listed cluster.

estimates revealed that both left and right RLPFC were more active for the two comparison conditions (Conditions 1 and 3) than for the two completion conditions (Conditions 2 and 4). This main effect was highly significant in both left and right RLPFC, $F(1,19) = 17.5$, $p < .0001$; $F(1,19) = 47.3$, $p < .0001$, respectively. There was no effect of initial retrieval (*term* vs. *exemplar*) and no interaction between this factor and

the comparison versus completion factor (in all cases, $F < 1$).

The RLPFC activation peaks observed in both the previous study of analogical problem solving and in the current experiment are located very near one another. To gain a better understanding of how the specific brain location in which we observe analogy-related activation relates to results from other studies

of relational integration, we surveyed RLPFC activation peaks from studies of verbal analogy problem solving with those obtained from studies involving the RPM task (see Table 3 for a list of studies/peaks). Although the number of data points is insufficient for a formal analysis, an informal survey of the data reveals that the activation peaks associated with analogy problems are all ventral relative to the set of peaks associated with the RPM task.

Due to the apparent difference in the location of RLPFC activation peaks between studies of analogical problem solving and studies of the RPM task, it was an open question whether the more dorsal region identified in the RPM studies would show the same pattern of modulation across conditions in our experiment. Additional analyses were thus performed on two 5-mm spherical ROIs centered on RLPFC activation peaks (MNI coordinates [41,45,6] and [-31,45,10]) from two previous studies of the RPM task (Christoff et al., 2001; Prabhakaran et al., 1997). The same pattern across conditions, matching that seen in our analogy study ROI, was observed for both regions. The main effect of compare > complete was, however, significant only for the first of these two regions, $F(1,19) = 8.5, p < .01$. In addition, whereas positive parameter estimates were obtained for both compare conditions from the analogy study ROIs, parameter estimates obtained for both of these more dorsal regions were almost uniformly negative.

DISCUSSION

This study reveals that the RLPFC is specifically involved in the comparison of relational information in a verbal analogical reasoning task, and not in the retrieval of

relationships or in the integration of relation and item to complete an analogy. More important, maintenance demands in this task were minimal, and RLPFC activation was not directly related to behavioral measures of task difficulty. The implications of these and other findings will be discussed below.

RLPFC and Relational Integration

The current study shows that RLPFC involvement in analogical reasoning is linked specifically to the comparison of relational information rather than to relation completion. We have shown that one kind of integration, the type involved in comparing two relations, activates the RLPFC, whereas a different sort of integration, the insertion of a single item into a relation required for relation completion, does not. This finding builds on our prior study (Bunge et al., 2005), which had demonstrated RLPFC involvement during the evaluation of an analogy (the relation comparison condition in this study), but not for semantic retrieval.

One possible interpretation of the current experiment, considered in isolation, is that RLPFC activity is related to evaluation (yes/no judgment). However, when the current results are considered alongside those from our previous study, the evidence points towards RLPFC involvement in the specific integration processes that support relation comparison, and not specifically in yes/no evaluation, because the earlier experiment showed that the RLPFC was not strongly engaged for yes/no evaluations of global semantic relatedness between two words. Neither study speaks to the question of whether the RLPFC is involved in the comparison of structured, relational information in particular or to comparison of other types of information as well. However, evidence from other researchers suggests that the RLPFC is particularly involved in the consideration of relational information (Smith, Keramatian, & Christoff, 2007; Christoff, Ream, Geddes, & Gabrieli, 2003; Waltz et al., 1999). In one connectionist model of relational reasoning called SHRUTI (Shastri & Ajjanagadde, 1993), a specific type of connectionist circuit, distinguished by its capacity to bring together information from multiple relational instances, is required to perform comparisons (Wendelken, 2003). It is plausible, given current results, that the RLPFC is an important component of this comparator circuit.

One theory states that the rostral PFC is part of a resting state or default network. Resting-state activation has been most strongly associated with the medial aspect of the rostral PFC (Gusnard & Raichle, 2001), but some evidence implicates the lateral aspect as well (Christoff, Ream, & Gabrieli, 2004). It is possible that the negative parameter estimates associated with RLPFC in some cases might be attributable to resting-state activation associated with the between-trial fixation. Certainly, the widespread deactivation seen across all conditions

Table 3. RLPFC Activation Peaks in Neuroimaging Studies of Propositional Analogy Solving and RPM

<i>Study Type</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Reference</i>
Analogy	-45	45	-6	Bunge et al., 2005
Analogy	-42	48	-12	Bunge et al., 2005
Analogy	45	45	-3	Current study
Analogy	-48	42	-6	Current study
RPM	24	47	23	Prabhakaran et al., 1997
RPM	35	45	20	Prabhakaran et al., 1997
RPM	41	45	6	Prabhakaran et al., 1997
RPM	-31	45	10	Christoff et al., 2001
RPM	-32	40	22	Kroger et al., 2002
RPM	-29	54	18	Crone et al., in press
RPM	30	51	15	Crone et al., in press

MNI coordinates are shown.

in medial BA 10 is highly consistent with the idea that this region is part of a resting-state network. Our rapid event-related design was appropriate for discerning relative differences in activation levels between conditions, but is not ideal for interpreting deactivations relative to baseline.

Given that the RLPFC activations observed in our studies of verbal analogy problem solving appear to be located more ventrally than those observed in studies of the visuospatial RPM task, one must ask to what extent these represent similar functional regions. Current evidence suggests that relational integration may be common to both the more dorsal and ventral RLPFC candidate subregions. However, relative to the more dorsal RLPFC subregion that has been engaged by the visuospatial stimuli of the RPM task, the ventral RLPFC subregion was more strongly engaged by the verbal stimuli of the analogy task. The dorsal RLPFC ROIs that were tested, in fact, showed overall deactivation on our task. This differential pattern of engagement may reflect a material-type gradient within the RLPFC; however, the evidence for this point is far from conclusive because the two tasks differ on many more dimensions than just verbal/visuospatial.

Left VLPFC and Retrieval of Semantic Relations

The left VLPFC was engaged across all four conditions (Figure 3D) and was marginally more engaged by term trials, where the initial retrieval cue was a relationship term, than by example trials, where the initial cue was a sample relationship. Many researchers have linked the left VLPFC (Cabeza & Nyberg, 2000), and especially an anterior and inferior portion of the left VLPFC (Bunge et al., 2005; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001; Poldrack et al., 1999), to semantic retrieval. Because all conditions in our experiment involved multiple instances of semantic retrieval—including relation retrieval, relational role retrieval, and simple item retrieval—our VLPFC results are broadly consistent with previous findings. If the VLPFC does indeed play a key role in semantic retrieval, and if the difference that we observe here between term and example trials is reliable, then this would suggest that the retrieval of a relational concept, given the name of the relation, places greater demands on semantic retrieval than does the retrieval of that concept given an exemplar.

A connectionist model of lateral PFC (Wendelken, 2002) suggests that the role played by the VLPFC in working memory maintenance is intimately related to its role in semantic retrieval. Specifically, the VLPFC serves to selectively activate, enhance, or maintain the activation state of semantic representations that reside in posterior cortical areas. According to this model, the role of the VLPFC in the analogy task is to influence the activation state of semantic representations; it could thus facilitate relation retrieval by manipulating activa-

tion of source item representations, by enhancing activation of target relational representations, or by doing both. Similarly, it could facilitate role generation/retrieval by enhancing activation at source relations or at potential roles (item representations).

As far as we know, the RLPFC interacts primarily with other PFC subregions, rather than with the posterior cortical regions implicated in long-term memory representation (Ramnani & Owen, 2004; Petrides & Pandya, 1999). As we have previously argued, the RLPFC may operate on the products of the VLPFC by working with semantic relations retrieved by this latter region (Bunge et al., 2005). One plausible model of neural activity in the comparison task holds that, first, simple item representations become active in posterior cortical areas; next, VLPFC mediates extraction of relationships between items (for the cue and probe) and maintains dynamic links to, or temporary representations of, the extracted relational information. Finally, the RLPFC uses this VLPFC connection to perform a comparison or evaluation of the two separate pieces of information. The idea that the RLPFC may operate on the outputs or contents of the VLPFC is entirely consistent with the broader hypothesis that the primary role of the RLPFC is to integrate information within the PFC (Ramnani & Owen, 2004).

Alternate Theories of RLPFC Function

The idea that the RLPFC performs relational integration is only one of several competing hypotheses regarding RLPFC, and more generally, anterior PFC, function. We consider below how the results of our experiment address predictions of these alternative hypotheses.

Multitasking

The anterior PFC has been implicated in multitasking operations such as cognitive branching (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999), prospective memory (Burgess, Quayle, & Frith, 2001), and subgoal processing (Braver & Bongiolatti, 2002). These conceptualizations all involve maintaining information about one subtask while a second subtask is performed. Subgoal processing has the additional requirement that the maintained item and the outcome of a second task must be considered together (integrated). Notably, whereas the anterior prefrontal activations associated with cognitive branching and prospective memory are anterior to the RLPFC region that we observe, the activation seen for subgoal processing, which involves integration, is nearly identical. This observation suggests that the anterior PFC may be subdivided into a region (RLPFC) that supports integration and a more anterior region that supports multitasking. Indeed, Gilbert et al. (2006) have conducted a meta-analysis indicating that the foci associated with

task coordination lie at the most rostral part of the anterior PFC.

Mnemonic Control

The anterior PFC, including RLPFC, has been commonly associated with mnemonic control processes, especially monitoring or postretrieval evaluation (Rugg, Henson, & Robb, 2003; Ranganath, Johnson, & D'Esposito, 2000; Buckner et al., 1998; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). If we carefully consider the sort of memory retrieval situations that are likely to engage the RLPFC, it is not difficult to make the case that its role in memory retrieval is similar to the role it plays in solving analogy problems (see also Christoff & Gabrieli, 2000). RLPFC activation is often seen in cases of retrieval success versus retrieval failure (McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Buckner et al., 1998; Rugg et al., 1996) and in experiments that require participants to carefully compare an observed probe item to a similar or identical item stored in memory, either to make a recognition judgment (Rugg et al., 2003) or to describe how the two items differ (Ranganath et al., 2000). Thus, it seems likely that the RLPFC implements a comparison operation following successful retrieval (e.g., it compares a retrieved item with a current stimulus). Moreover, if we assume that the actual retrieval is mediated by other prefrontal regions, then the RLPFC is again seen to be operating on the outputs of other prefrontal regions. A systematic comparison of the coordinates of RLPFC foci across long-term memory and reasoning studies would help to clarify whether the region involved in comparing analogies is in fact the same as that involved in long-term reasoning.

Internally Generated Information

Another theory of rostrolateral function is that its primary role is in the manipulation of internal or self-generated information (Christoff et al., 2003; Christoff & Gabrieli, 2000). According to this view, the RLPFC sits atop a hierarchy of prefrontal regions and contributes mainly to the highest order cognitive transformations (Christoff et al., 2003). To the extent that self-generated information can be considered equivalent to information that is accessed or generated through prefrontal control mechanisms, this theory has much in common with the theory that the RLPFC integrates information across PFC subregions (Ramnani & Owen, 2004). The lack of interaction between cue type and integration demand in the current study suggests that relational integration operates on an internal representation of relations, and not directly on the external stimulus representations. Current results support the idea that the RLPFC is important for the higher order operations that are commonly performed on internally generated information, such as the comparison of retrieved relations.

Summary and Conclusion

In summary, we have shown that the RLPFC (or more precisely, ventral RLPFC) is engaged in verbal analogy trials that require relation comparison, relative to those that involve relation completion. These findings indicate that the RLPFC supports a specific type of integration, namely, the comparison of relational representations. The capacity to compare relational representations—supported by the RLPFC—is a key element of relational processing, and thus is one of the fundamental building blocks of high-level cognition.

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