Analogical Reasoning and Prefrontal Cortex: Evidence for Separable Retrieval and Integration Mechanisms

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The present study examined the contributions of prefrontal cortex (PFC) subregions to two component processes underlying verbal analogical reasoning: semantic retrieval and integration. Event-related functional magnetic resonance imaging data were acquired while subjects performed propositional analogy and semantic decision tasks. On each trial, subjects viewed a pair of words (pair 1), followed by an instructional cue and a second word pair (pair 2). On analogy trials, subjects evaluated whether pair 2 was semantically analogous to pair 1. On semantic trials, subjects indicated whether the pair 2 words were semantically related to each other. Thus, analogy — but not semantic — trials required integration across multiple retrieved relations. To identify regions involved in semantic retrieval, we manipulated the associative strength of pair 1 words in both tasks. Anterior left inferior PFC (aLIPC) was modulated by associative strength, consistent with a role in controlled semantic retrieval. Left frontopolar cortex was insensitive to associative strength, but was more sensitive to integration demands than was aLIPC, consistent with a role in integrating the products of semantic retrieval to evaluate whether distinct representations are analogous. Right dorsolateral PFC exhibited a profile consistent with a role in response selection rather than retrieval or integration. These findings indicate that verbal analogical reasoning depends on multiple, PFC-mediated computations.

Keywords: analogies, anterior prefrontal, frontopolar cortex, inferior frontal, semantic memory

Introduction

Analogical reasoning, or the ability to find correspondences between the structures of distinct mental representations (Gentner, 1983; Hummel and Holyoak, 1997), is central to our ability for learning and abstract thought (e.g. Holyoak and Thagard, 1995). The ability to form an analogy between distinct sets of mental representations allows us to glean general principles from specific examples, as well as to establish links between previously unconnected information. From an early age, we learn new words and concepts by analogy to ones previously learned (e.g. Gentner, 1983). As adults, we use analogies to concrete entities as currency for discussing abstract ideas. For example, we think of time through reference to space (Boroditsky, 2000), geneticists refer to DNA as a 'blueprint' for building an organism and physicists think of the probability density distribution of an electron as a 'cloud'. Thus, analogical reasoning is rightly considered a key component of higher cognitive function.

Theorists have built computational models in an effort to understand the cognitive processes underlying the representation of and reasoning about complex relational structures (Gentner, 1989, Hummel and Holyoak, 1997). These putative processes include both the retrieval of associations from long-term memory and integration (referred to as 'mapping' or 'transfer') across sets of representations (Hummel and Holyoak, 1997). Note that 'integration' here does not refer to the binding of different features of a single stimulus, as in Prabhakaran *et al.* (2000). For example, in Jani and Levine's (2000) proposed neural network model of reasoning about propositional analogies (e.g. 'BRAIN is to THOUGHT as STOMACH is to ?'), reasoning was hypothesized to initially require the retrieval and maintenance of the relation between the first pair of words and, subsequently, the transfer of this relation to the third word.

A large body of neuropsychological evidence (e.g. Luria, 1966; Stuss and Benson, 1984; Shallice and Burgess, 1991; Duncan *et al.*, 1995; Waltz *et al.*, 1999) and an emerging neuroimaging literature (e.g. Baker *et al.*, 1996; Prabhakaran *et al.*, 1997; Osherson *et al.*, 1998; for reviews, see Cabeza and Nyberg, 2000; Christoff and Gabrieli, 2002) have implicated prefrontal cortex (PFC) in reasoning and problem-solving. For example, Waltz *et al.* (1999) showed that frontotemporal dementia patients with prefrontal, but not anterior temporal, damage have difficulty integrating across multiple relations on the Raven's Progressive Matrices (RPM; a visuospatial analogy task; Raven, 1941).

Several brain imaging studies have used the RPM or RPM-like visual analogy tasks to examine the neural systems that support relational integration (Prabhakaran *et al.*, 1997; Wharton *et al.*, 2000; Christoff *et al.*, 2001; Kroger *et al.*, 2002). On one-relational RPM problems, subjects must process vertical or horizontal changes (or spatial relations) across figures in a 3 × 3 matrix to infer the missing figure at the bottom right of the matrix. On two-relational RPM problems, by contrast, subjects must jointly consider changes in the vertical and horizontal dimensions to correctly choose the missing figure. Thus, two-relational (but not one-relational) problems require subjects to integrate across several spatial relations. In an event-related functional magnetic resonance imaging (fMRI) study, bilateral frontopolar cortex (FPC) and right dorsolateral PFC (DLPFC) were shown to be sensitive to the number of relations (0, 1 or 2) across which subjects had to integrate (Christoff *et al.*, 2001). Because the response latencies varied substantially across levels of relational complexity (being nearly 3 s longer during 2 versus 0 relational problems), Christoff and colleagues covaried out reaction times (RTs) and found that only left FPC remained sensitive to relational complexity. Other results further suggest that FPC activation cannot be explained as resulting from longer RTs (Braver and Bongiolatti, 2002). On this basis, they argued that, in the visuospatial domain, left FPC plays a key role in relational integration or in the simultaneous processing of

multiple relations. They further suggested that left FPC is aided by right FPC and DLPFC, but that activation in these regions was not specific to relational integration.

Using event-related fMRI, Kroger *et al.* (2002) independently manipulated relational complexity and distractor demands in a RPM-like task and observed that bilateral DLPFC activation, extending into FPC in the left hemisphere, increased with relational complexity. Consistent with Christoff *et al.* (2001), they further noted that the most anterior extent of the left DLPFC/FPC activation [Brodmann area (BA) 10, 46, 9] was (i) specifically sensitive to relational complexity, being recruited primarily at the highest levels of complexity; and (ii) insensitive to the number of distractors. Based on this pattern, Kroger *et al.* (2002) argued that this region is selectively engaged by tasks that require explicit representation and manipulation of relational knowledge.

The aim of the present study was to explore the neural substrates underlying analogical reasoning using a simple propositional analogy task. In an effort to extend previous findings, we operationalized relational integration in a different manner from previous studies, and examined this cognitive process in the semantic rather than the visuospatial domain. In this task, subjects had to evaluate whether an analogous relation existed between two pairs of words (Fig. 1). Consistent with extant computational models (Hummel and Holyoak, 1997; Jani and Levine, 2000), we posited that analogical reasoning would require several, separable processes. Within the context of the present propositional analogy task, in which subjects had to evaluate an analogy as valid or invalid, these processes include (i) controlled retrieval of the semantic relation between each pair of words; and (ii) integration across the retrieved semantic relations. Although previous neuroimaging studies have suggested that distinct subregions within PFC might make differential contributions to analogical reasoning (Christoff *et al.*, 2001; Kroger *et al.*, 2002), we sought to provide strong evidence for dissociations between subregions of PFC that mediate the retrieval of semantic knowledge and the integration of this knowledge.
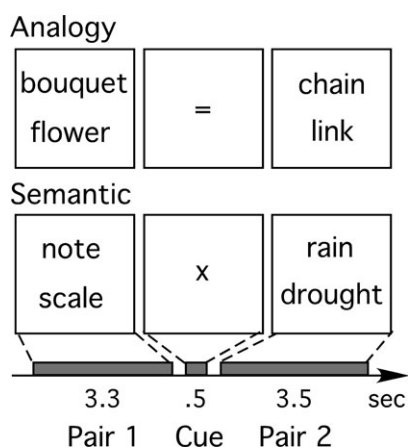

Figure 1. Shown here is the trial structure for the analogy and semantic tasks. For both tasks, subjects were instructed to determine how the words in pair 1 are related to one another. On analogy trials, cued by a '=', they were then instructed to evaluate whether the words in pair 2 are related to one another along the same dimension as the words in pair 1. On semantic trials, cued by a 'x', subjects were then instructed to determine whether the words in pair 2 are related to one another along any dimension.

To this end, we included factors that varied semantic retrieval and integration demands. In order to identify regions involved in analogical reasoning, we compared event-related fMRI activation during performance of an analogy task with that during performance of a semantic decision task (Fig. 1). Subjects viewed a pair of words (pair 1), followed by an instructional cue that signaled which task should be performed, and then a second pair of words (pair 2). On analogy trials, subjects pressed one of two buttons to indicate whether pair 2 was semantically analogous to pair 1. On semantic decision (semantic) trials, subjects indicated whether the two words in pair 2 were semantically related to one another. Thus, while both conditions required retrieval of semantic relations between words, the analogy condition required the additional operation of integrating the retrieved relations to evaluate whether an analogy could be drawn between them. That is, similar to the two-relational RPM problems discussed above, on analogy trials subjects must jointly consider two relations (in this case semantic rather than spatial relations) in order to arrive at the correct response.

To identify regions involved in controlled semantic retrieval, on both analogy and semantic trials we varied the strength of the semantic association between the words in pair 1. Reliance on controlled semantic retrieval has been hypothesized to vary with the strength of association between words when making a Relatedness decision; weaker word–word associations presumably demand increased controlled retrieval (Wagner *et al.*, 2001b; Badre and Wagner, 2002). Retrieval of the pair 1 relation is required for accurate performance of the analogy but not the semantic task, and previous findings suggest that subjects may not engage in deep semantic elaboration on verbal items unless required to do so (Bjork, 1975). However, we anticipated that subjects would retrieve the semantic relation between pair 1 words during both tasks, because subjects did not know whether they would need to use this relational knowledge until after the offset of pair 1, when the instructional cue indicated which task they were to perform. To the extent that subjects retrieve the semantic relation of pair 1 words — even on semantic trials, when knowledge about the semantic relation is ultimately not required for successful task performance — activation in regions involved in controlled semantic retrieval should vary with the associative strength of pair 1 words during both analogy and semantic trials.

On the basis of neuroimaging findings from studies of semantic memory (for reviews, see Fiez, 1997; Poldrack *et al.*, 1999; Martin and Chao, 2001; Badre and Wagner, 2002), we predicted that anterior left inferior prefrontal cortex (aLIPC) would be involved primarily in the controlled retrieval of knowledge about the semantic relations between words (Wagner *et al.*, 2001b). In contrast, we predicted that FPC and/or DLPFC would be involved primarily in integrating between retrieved semantic relations and would not mediate semantic retrieval per se. Specifically, one might expect involvement of DLPFC in comparing semantic relations between word pairs and evaluating whether the relations match, because this region is thought to play a role in monitoring and manipulating representations held in working memory (Owen *et al.*, 1996b; Petrides, 1996; D'Esposito *et al.*, 1999; Postle *et al.*, 2000; Wagner *et al.*, 2001a). Consistent with this perspective, DLPFC has been hypothesized to mediate reasoning by supporting analogical mappings (e.g. Holyoak and Kroger, 1995). Alternatively, one might expect that FPC would play a predominant

role in semantic integration. As noted above, this region appears to be particularly sensitive to relational integration demands in visuospatial reasoning tasks (Christoff *et al.*, 2001; Kroger *et al.*, 2002). Further, in the episodic memory literature, FPC and DLPFC have been implicated in post-retrieval processes such as monitoring and evaluation (for reviews, see Rugg and Wilding, 2000; Fletcher and Henson, 2001). This conceptualization of FPC function is broadly consistent with a role in post-retrieval integration and evaluation of a potential analogical mapping.

Materials and Methods

Subjects
Twenty right-handed native English-speaking volunteers (14 males; aged 19–34 years, mean = 23) received a $50 remuneration for their participation. Four additional subjects were scanned, but excluded due to poor performance (exclusion criterion: <65% accuracy on the analogy or semantic task). A second, unrelated experimental paradigm was also conducted during the scanning session. This second paradigm, which tested subjects' ability to remember pairs of non-verbal stimuli, has been reported elsewhere (Bunge *et al.*, 2004). Informed consent was obtained in a manner approved by the Human Studies Committee of the Massachusetts General Hospital and the Committee on the Use of Humans as Experimental Subjects at MIT.

Task Design
On each experimental trial (Fig. 1), subjects viewed a pair of words (pair 1) for 3.3 s, followed by a blank screen for 50 ms. An instructional cue that indicated which task should be performed (= for analogy trials, *x* for semantic trials) was then presented for 500 ms, followed by a blank screen for 50 ms. A second pair of words (pair 2) was then presented for 3.5 s, followed by a fixation period of 600 ms. Additional periods of visual fixation lasting between 1 and 9 s, jittered in increments of 2 s, were interspersed between trials as determined by a design optimization algorithm (Dale, 1999). Subjects were required to make a yes/no response during the presentation of pair 2 by pressing one of two buttons with their left hand. On analogy trials, subjects indicated whether pair 2 was semantically analogous to pair 1. On semantic trials, subjects indicated whether the two words in pair 2 were semantically related.

On analogy trials, the relation between the words in pair 2 was analogous to that between the words in pair 1 for half of the trials (related-analogy) and was not analogous for the other half (unrelated-analogy). On semantic trials, the words in pair 2 were related to one another for half of the trials (related-semantic) and were not related to one another for the other half (unrelated-semantic). On semantic trials, the relation between pair 2 words was never analogous to that between pair 1 words so as to discourage subjects from attempting to form analogies in this condition. In order to assess controlled retrieval demands — independent of the task manipulation (analogy versus Semantic) — we manipulated the level of associative strength (high, medium or low) between pair 1 words as described below.

Materials
Propositional analogy problems were drawn and modified from practice books for the Scholastic Assessment Test (Macmillan General Reference, 1997; College Entrance Examination Board, 2000; Research and Education Association, 2000). For each multiple choice problem, the sample word pair (pair 1) and either the analogically related or one of the analogically unrelated pairs (pair 2) were selected.

Associative Strength Manipulation
To vary demands on controlled semantic retrieval, we classified trials based on the strength of semantic association between the words in pair 1. A pilot behavioral study was conducted to measure the semantic Relatedness between the words in each pair drawn from the analogy problems. Two groups of 10 subjects made responses on the basis of distinct sets of word pairs. Ten subjects viewed each word pair on a computer screen and pressed the space bar as soon as they were able

to articulate the semantic relation between the two words. It was assumed that the strength of association would differ across pairs and that this difference would be reflected in response times (RTs) to retrieve the nature of the relation. That is, weaker word–word associations should yield longer RTs. Accordingly, for each subject, the word pairs were ranked by response latency; average rank, computed across subjects, was calculated for each word pair. The pair 1 stimuli were split into three groups according to average rank (high, medium and low associative strength pairs). These groups did not significantly differ in mean word frequency, number of syllables, or word length.

Two stimulus sets, consisting of the same pairs of words, were created for counterbalancing purposes. Half of the subjects were tested on one set, and half on the other. Each set consisted of 120 analogy trials and 120 semantic trials. Problems assigned to the analogy condition in the first set were assigned to the semantic condition in the second set, and vice versa. Analogy and semantic trials did not significantly differ in mean word frequency, number of syllables or word length.

Scan Session
Prior to scanning, subjects received practice on the non-verbal associative learning task (not reported here), and then received instructions for and had an opportunity to practice the analogy and semantic tasks featured in the present study. Once in the scanner, subjects participated in a 7 min scan testing memory for the non-verbal paired associates, and then advanced to the presently reported scans that indexed neural activation during performance of the analogy and semantic tasks.

Data Acquisition
Visual stimuli were projected onto a screen that was viewed through a mirror. Subjects performed 240 experimental trials over the course of four 10 min event-related fMRI scans. The design crossed Task (analogy/semantic) × Associative Strength of the pair 1 words (high/medium/low), and included 40 trials in each of the resulting six conditions. The trials from a condition were distributed evenly across the scans. Each of the six conditions consisted of an equivalent number of related (i.e. related-analogy or related-semantic) and unrelated (i.e. unrelated-analogy or unrelated-semantic) trials. The order of trial types within each scan was determined using a sequencing program that maximized design efficiency (Dale, 1999).

Scanning was performed on a 1.5 T Siemens system using a standard whole-head coil. Functional data were acquired using a gradient-echo echo-planar pulse sequence (T_R = 2 s, T_E = 40 ms, 21 axial slices, 3.125 × 3.125 × 5 mm, 1 mm inter-slice gap, 300 vols per run). Prior to each scan, four volumes were discarded to allow for T1-equilibration effects. High-resolution T1-weighted (MP-RAGE) anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head.

fMRI Data Analysis
Data were preprocessed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction (using sinc interpolation). Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to 3 mm cubic voxels. Templates were based on the MNI305 stereotactic space (Cocosco *et al.*, 1997), an approximation of Talairach space (Talairach and Tourneaux, 1988). Functional volumes were spatially smoothed with an 8 mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed using the general linear model in SPM99. The fMRI time series data were modeled by a series of 8 s epochs (corresponding to the trial duration) convolved with a canonical hemodynamic response function (HRF). The resulting functions were used as covariates in a general linear model, along with a basis set of cosine functions that high-pass filtered the data and a covariate for session effects. The least squares parameter estimates of height of the HRF for each condition were used in pairwise contrasts, and the

resulting contrast images computed on a subject-by-subject basis were submitted to group analyses. Incorrectly performed analogy and semantic trials were modeled separately from correctly performed trials, and were not included in the statistical analyses.

At the group level, contrasts between conditions were computed by performing one-sample t-tests on the contrast images, treating subjects as a random effect. The primary analysis focused on regions that, *a priori*, we anticipated would be sensitive to semantic retrieval and integration demands—specifically left ventrolateral, dorsolateral, and frontopolar subregions in PFC. Task-related responses (analogy versus semantic) in these *a priori* predicted regions are reported if they consisted of at least 5 contiguous voxels that exceeded an uncorrected threshold of $P < 0.001$ (see Table 1). The Associative Strength effect (low versus high) that was *a priori* predicted in aLIPC did not meet the $P < 0.001$ threshold, but is reported at $P < 0.005$ with a 5-voxel extent threshold (Table 1). In addition to voxel-based characterization of these regions, subsequent region-of-interest (ROI) analyses were conducted, as described below. Finally, exploratory analyses, conducted to examine possible effects beyond the *a priori* predicted regions, adopted a threshold of $P < 0.05$, corrected for multiple comparisons (random field theory correction; Worsley *et al*, 1992).

Theoretical interest was primarily focused on regions demonstrating above-baseline differential responses for the analogy and semantic conditions. Accordingly, voxel-based contrasts comparing analogy and semantic conditions were masked to exclude voxels that were deactivated, relative to fixation, during performance of the condition associated with lower activation (using an uncorrected threshold of $P < 0.05$ for the contrast with fixation). Contrasts examining the effects of Associative Strength were masked to exclude voxels that were deactivated, relative to fixation, across conditions ($P < 0.05$, uncorrected).

The ROI analyses were performed using a toolbox for use with SPM (written by Russell Poldrack; http://sourceforge.net/projects/spm-toolbox/). The purpose of these ROI analyses was to further characterize the sensitivity of targeted brain regions to Associative Strength (high/medium/low) and analogical or semantic Relatedness (related/unrelated). Unless otherwise noted, ROIs were defined from the contrast of all conditions relative to the fixation baseline. ROIs included all significant voxels (at $P < 0.001$) within an 8 mm radius of each maximum; no two ROIs contained the same voxel. Signal within an ROI was calculated for each subject by selectively averaging the data with respect to peristimulus time for trials in each condition. Statistics

were performed on the integrated percent signal change, summed over peristimulus times 4–16 s.

Results

Performance Data

Repeated-measures analyses of variance (ANOVA), with factors of Task (analogy/semantic), Associative Strength (high/medium/low) and Relatedness (analogically or semantically related/unrelated), were conducted on the accuracy data and on RTs from correctly performed trials (Fig. 2). Subjects were more accurate and responded more quickly on semantic than on analogy trials [accuracy, 86 versus 72%; $F(1,19) = 39.1$, $P < 0.0001$; RT = 1918 versus 2344 ms; $F(1,19) = 123.1$, $P < 0.0001$]. Associative Strength affected accuracy [$F(2,38) = 12.7$, $P < 0.0001$], such that subjects were more accurate on high than low strength trials [82 versus 76%; $F(1,19) = 24.2$, $P < 0.0001$], and on medium than low strength trials [80 versus 76%; $F(1,19) = 11.5$, $P < 0.002$]. Associative Strength also affected response latencies [$F(2,38) = 6.4$, $P < 0.005$], such that subjects were faster on high than low strength trials [2066 versus 2178 ms; $F(1,19) = 11.8$, $P < 0.002$] and high than medium strength trials [2066 versus 2149; $F(1,19) = 6.5$, $P < 0.02$]. Thus, high and low strength trials reliably differed in terms of both accuracy and RTs, and high versus medium and medium versus low strength trials differed in terms of one but not both behavioral measures. Thus, in subsequent behavioral and fMRI analyses, the Associative Strength effect was measured by a comparison of High and Low strength trials.

Associative Strength differentially affected accuracy on analogy and semantic trials [Task × Associative Strength: $F(1,19) = 5.2$, $P < 0.05$]. Subjects were more accurate on high than low strength trials for both tasks, but this Associative Strength effect was stronger for analogy than semantic trials [analogy: 77 versus 69%, $F(1,19) = 33.6$, $P < 0.0001$; semantic: 86 versus 82%, $F(1,19) = 6.7$, $P < 0.02$]. A trend towards a Task × Associative Strength interaction was also observed for RTs [$F(1,19) = 3.9$, $P = 0.06$]. Subjects were reliably faster on high than low strength trials in the analogy condition, but not in the semantic condition [analogy: 2253 versus 2418 ms, $F(1,19) = 18.8$, $P < 0.0004$; semantic: 1880 versus 1938 ms, $F(1,19) = 2.3$, $P > 0.10$].

Thus, the Associative Strength manipulation affected performance more for analogy than semantic trials. This result was to be expected, because we manipulated Associative Strength only for pair 1 words. On semantic trials, unlike the analogy trials, subjects need only consider the pair 2 words in order to respond. Thus, the fact that subjects were more accurate on High than Low strength semantic trials was unexpected. However, this finding could be explained by subjects taking longer to process and/or disengage from lower associative strength pair 1 words prior to attending to pair 2 words. According to this account, on trials for which accessing the association between pair 1 words demanded greater controlled retrieval, there was subsequent slowing and less accurate performance during the processing of pair 2. Critically, the finding that Associative Strength affected performance on both tasks — albeit in different ways — strongly supports the claim that subjects retrieved the semantic relation between pair 1 words on the analogy and the semantic tasks. This conclusion was further supported by the outcomes of the fMRI analysis (see below).

'Relatedness' was operationalized differently in the semantic and the analogy tasks, referring to global Relatedness of two

Table 1
A priori predicted regions exhibiting an effect of Task, Associative Strength or Relatedness

| Region of activation	~BA	MNI coordinates			Z-score
		x	y	z	
Effects of Task					
Analogy > semantic					
Frontopolar	L10/11	−42	48	−15	3.84
aLIPC	L45	−48	36	0	4.02
	L45	−36	27	3	3.75
	L47	−51	42	−6	3.59
pLIPC	L44	−48	15	15	3.70
Analogy > semantic — related trials only					
aLIPC	L45	−36	27	3	3.27
	L45/46	−54	36	9	3.59
pLIPC	L44	−54	6	24	3.44
Semantic > analogy					
None					
Effects of Associative Strength ($P < 0.005$)					
Low > high					
aLIPC	L45	−57	24	6	2.89
High > low					
None					
Effects of Relatedness					
Unrelated-analogy > related-analogy					
DLPFC (middle frontal cortex)	R9	51	18	39	4.32
ALIPC	L47	−45	24	0	4.14
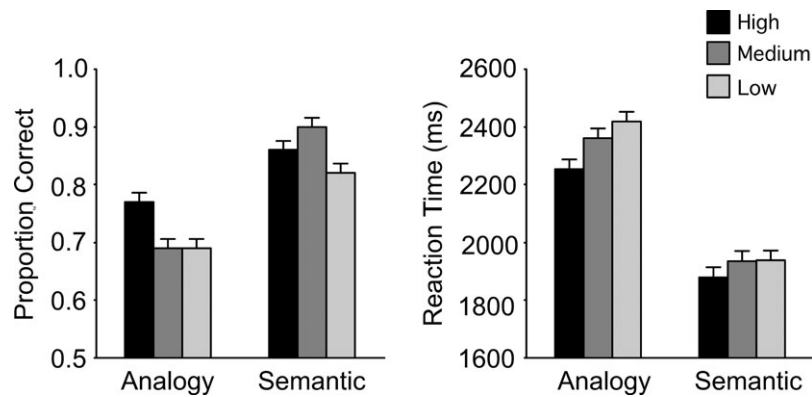
Figure 2. Group-averaged behavioral performance is plotted separately for Task and Associative Strength manipulations. Error bars depict within-subject SE.

words in the semantic task and to the validity of an analogy between word pairs in the analogy task. Performance did not reliably differ between related-semantic and unrelated-semantic trials [accuracy, 83 versus 89%; $F(1,19) = 3.0$, $P > 0.10$; RT = 1874 versus 1962 ms; $F(1,19) = 2.3$, $P > 0.10$]. By contrast, and of central interest, subjects performed related-analogy trials more accurately [87 versus 57%; $F(1,19) = 60.3$, $P < 0.0001$] and more quickly [2057 versus 2630 ms; $F(1,19) = 99.1$, $P < 0.0001$] relative to unrelated-analogy trials. This effect suggests that it was more difficult to reject an invalid analogy than to endorse a valid one. An analysis of RTs for incorrectly performed trials extends this finding by revealing that subjects were consistently slower to reject analogies than to accept them, regardless of whether their answer was correct [endorse versus reject, correct trials: 2015 versus 2648 ms; $F(1,19) = 74.0$, $P < 0.0001$; incorrect trials: 2454 versus 2748 ms; $F(1,19) = 16.0$, $P < 0.0009$]. To minimize the effects of differential accuracy across conditions, all fMRI analyses were restricted to trials on which performance was correct.

fMRI Data

Voxel-based and ROI analyses focused on the effects of Task, Associative Strength and Relatedness in the *a priori* predicted prefrontal regions. Exploratory analyses, conducted to determine whether any additional regions warranted consideration, failed to reveal additional activations.

Task Effects: Analogy versus Semantic Decisions

Voxel-based analyses revealed a substantial overlap in the regions activated by the analogy and semantic tasks relative to baseline, although some regions demonstrated above baseline activation restricted to one of the two tasks (Fig. 3A). Direct comparisons between tasks revealed that anterior and posterior left inferior PFC [aLIPC: ~BA 47, 45; pLIPC: ~BA 44, 45 (~BA = approximate Brodmann area)] and left frontopolar cortex (FPC) (~BA 10) were more active during analogy than during semantic trials (Fig. 3B, Table 1). When the task contrast was restricted to the related trials, greater activation was again observed during analogy than during semantic trials in aLIPC and pLIPC (Table 1). Left FPC (–42, 48, –12) activation was additionally observed for this limited dataset at a liberal statistical threshold ($P < 0.01$ uncorrected).

Associative Strength Manipulation

Consistent with our predictions, activation in aLIPC (~BA 45) was greater during Low than High associative strength trials

($P < 0.005$ uncorrected; Table 1, Fig. 3B). As noted below, this conclusion was further strengthened by subsequent ROI analyses. Thus, as semantic retrieval demands increased with decreasing associative strength between the words in pair 1, a region thought to mediate controlled semantic retrieval — i.e. aLIPC — was differentially engaged (Wagner *et al.*, 2001b).

Relatedness Effects on Analogy Trials

On the basis of the finding that subjects were less accurate and took longer to reject analogies than to endorse them, we hypothesized that the demands placed on processes required for analogical reasoning were likely to be greatest for trials on which there was no valid relation between the word pairs. Specifically, when subjects initially fail to establish an analogical mapping, they are likely to attempt to refine the relation between the first word pair and then re-evaluate the mapping between word pairs. Thus, further semantic retrieval and integration processing is likely to be required during unrelated-analogy trials. Accordingly, we predicted greater activation in PFC regions associated with retrieval or integration during performance of unrelated-analogy relative to related-analogy trials. A mapwise comparison of unrelated-analogy versus related-analogy trials revealed activation in two *a priori* predicted regions: right DLPFC (middle frontal gyrus; ~BA 9) and aLIPC (~BA 47; Table 1). The pattern of activation in right DLPFC, and its relation to the patterns observed in FPC and aLIPC, was further examined through ROI analyses (see below).

Prefrontal ROIs: aLIPC and left FPC

The mapwise comparisons suggest that aLIPC was particularly modulated by the Associative Strength manipulation, whereas FPC was specifically sensitive to the task manipulation. Additional analyses were performed to further characterize the activation of these prefrontal ROIs for the purpose of directly contrasting the relative involvement of PFC subregions in semantic retrieval and/or integration. Unbiased ROIs in aLIPC and left FPC were functionally defined from the contrast of all conditions relative to the fixation baseline. ANOVAs were performed on measures of integrated percent signal change in each ROI, with factors of Task, Associative Strength (high/medium/low) and Relatedness.

Consistent with the mapwise comparisons, ROI analyses showed that (i) left FPC and aLIPC were engaged more strongly by analogy than by semantic trials [FPC: 1.7 versus 0.6;
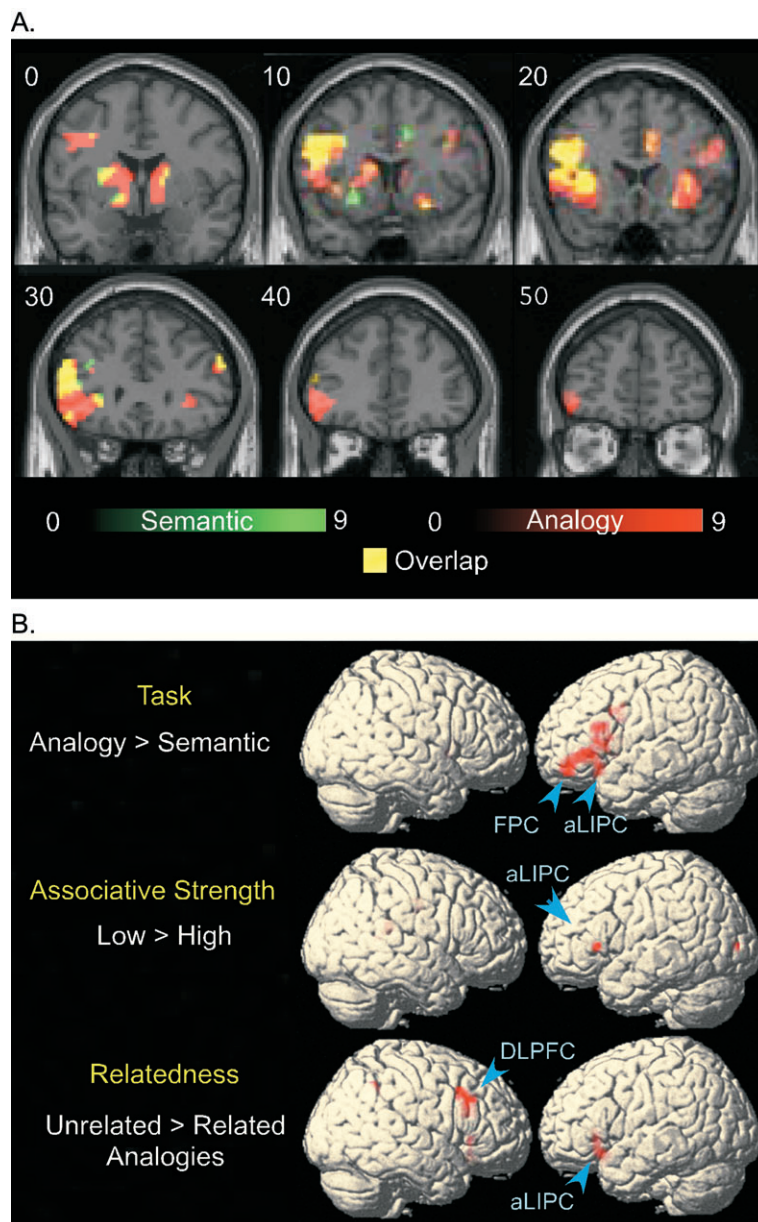
A.

B.

Figure 3. Group-averaged activations for contrasts of interest are displayed. (*A*) Coronal slices through a canonical brain display regions activated by analogy and semantic trials relative to fixation. Areas of overlap between the two contrast maps appear yellow. (*B*) Shown here on a rendered canonical brain are regions activated to a greater extent by analogy relative to semantic trials, by low relative to high Associative Strength trials, and by unrelated- relative to related-analogy trials.

$F(1,19) = 22.5$, $P < 0.0001$; aLIPC: 1.4 versus 0.8; $F(1,19) = 16.9$, $P < 0.0006$]; and (ii) aLIPC, but not FPC, was modulated by Associative Strength [aLIPC: $F(2,38) = 6.5$, $P < 0.004$; FPC: $F(2,38) = 1.6$, $P > 0.20$]. Planned comparisons revealed that aLIPC was engaged more strongly by low than high trials [1.3 versus 0.7; $F(1,19) = 10.2$, $P < 0.003$] and by medium than high trials [1.3 versus 0.7; $F(1,19) = 9.2$, $P < 0.005$]. In contrast, FPC activation did not reliably differ between the three levels of Associative Strength (all $P > 0.05$).

These outcomes suggest that FPC and aLIPC demonstrate dissociable patterns of activation, raising the possibility that they make differential contributions to analogical reasoning. Consistent with this impression, an ANOVA with factors of ROI (aLIPC/FPC), Task, Associative Strength (high/low) and Relatedness revealed a functional double-dissociation between

these two regions. FPC was more sensitive to the Task manipulation than was aLIPC [ROI × Task: $F(1,19) = 5.6$, $P < 0.029$; see also Fig. 4]. In contrast, aLIPC was more sensitive to varying Associative Strength than was FPC [ROI × Associative Strength: $F(1,19) = 4.2$, $P = .05$; see also Fig. 4]. These results are consistent with our hypothesis that aLIPC is particularly important for the controlled retrieval of semantic relations, whereas FPC is particularly important for integrating between retrieved relations.

As noted above, we predicted that PFC subregions would be sensitive to Relatedness on analogy but not semantic trials. Indeed, the profile of activation in FPC was consistent with this prediction [Task × Relatedness: $F(1,19) = 11.6$, $P < 0.003$]. FPC was more active on unrelated than related-analogy trials [2.1 versus 1.3; $F(1,19) = 31.3$, $P < 0.001$], but did not differ

between unrelated and related-semantic trials (0.7 versus 0.6; $F < 1$; see Fig. 4). Anterior LIPC (~BA 45) was also more active on unrelated than related-analogy trials [1.7 versus 1.1; $F(1,19) = 11.4$, $P < 0.004$; see Fig. 4], but the Task × Relatedness interaction was not significant [$F(1,19) = 1.9$, $P > 0.15$]. These results show that both FPC and aLIPC were engaged most strongly on analogy trials for which there was no obvious relationship between the word pairs. For FPC, this enhanced activation was specific to analogy trials, rather than being related more generally to the requirement to reject an incorrect response on both analogy and semantic trials.

Prefrontal ROIs: DLPFC
The preceding analyses provide strong evidence for functionally distinct roles of aLIPC and left FPC in analogical reasoning. In a final set of ROI analyses focusing on PFC subregions, we assessed the activation pattern in right DLPFC and its relation to that in aLIPC and FPC. As observed in the whole-brain contrasts, right DLPFC was more strongly activated on unrelated- than related-analogy trials. An ROI analysis revealed that activation in this region did not differ between unrelated- and related-semantic trials ($F < 1$). Moreover, activation did not differ between related-analogy and related-semantic trials ($F < 1$), and thus — unlike FPC and aLIPC — the main effect of Task was not significant [0.6 versus 0.2; $F(1,19) = 3.3$, $P > 0.05$]. Additionally, unlike aLIPC, right DLPFC was not modulated by Associative Strength ($F < 1$).

Cross-region analyses revealed that right DLPFC was functionally dissociable from both aLIPC and FPC. An ANOVA with factors of ROI (DLPFC/aLIPC), Task, Associative Strength (high/low) and Relatedness demonstrated an ROI × Associative Strength interaction [$F(2,38) = 8.2$, $P < 0.01$], such that aLIPC was engaged more strongly by low than high trials [$F(1,19) = 13.8$, $P < 0.002$], whereas DLPFC was not modulated by Associative Strength ($F < 1$). A similar ANOVA comparing DLPFC and FPC revealed an ROI × Task interaction [$F(1,19) = 15.9$, $P < 0.001$], such that FPC was more strongly modulated by Task (analogy > semantic) than was DLPFC [FPC: $F(1,19) = 69.1$, $P < 0.0001$; DLPFC: $F(1,19) = 7.8$, $P < 0.02$]. As seen previously, DLPFC was not consistently modulated by Task, in that it did not differentiate between analogy-related and semantic-related trials. Thus, right DLPFC differed from aLIPC in that it was insensitive to Associative Strength, and differed from FPC in that it was not consistently sensitive to integration demands.

Consideration of Response Latency Differences between Conditions
As noted above, differences in RTs were observed between conditions in the present experiment (e.g. analogy versus semantic trials, unrelated-analogy versus related-analogy trials). We believe that such RT differences are often meaningful, in that they can reflect differential engagement of specific cognitive processes across conditions. However, one potential concern is the possibility that RT differences are process-general,
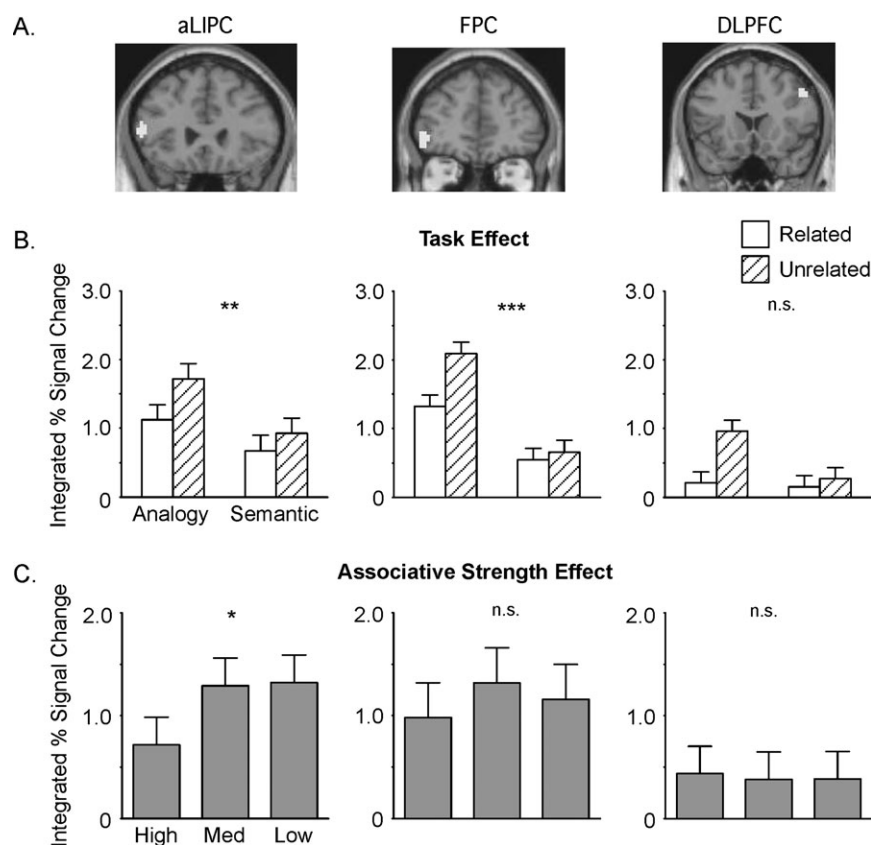

Figure 4. Shown here is the activation profile of three ROIs in PFC. (*A*) The ROIs in aLIPC (centered on coordinates of −57, 27, 12), left FPC (−45, 45, −6) and right DLPFC (51, 18, 39) are plotted here on a canonical brain. (*B*) These bar graphs display the Task effects for the three ROIs. The effect of task was greater in FPC than in aLIPC, and was not significant in DLPFC. (*C*) These bar graphs depict the Associative Strength effects for the three ROIs. Only aLIPC was significantly modulated by Associative Strength. *$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$.

reflecting global time on task rather than the engagement of specific processes. To address this concern, we reanalyzed the individual subjects' fMRI data, including RT for each trial as a nuisance variable. Importantly, the results reported above for aLIPC, FPC and DLPFC were replicated in this additional analysis. Thus, the differential engagement of FPC and aLIPC for analogy than semantic trials was not simply related to an increase in time on task. Similarly, the differential recruitment of DLPFC for unrelated-analogy than other trial types was not simply accounted for by the fact that this condition was associated with the longest RTs.

Discussion

The objectives of the present study were to (i) extend prior neuroimaging studies of visuospatial reasoning by considering the neural correlates of reasoning in the semantic domain; and (ii) specify the role of PFC subregions in analogical reasoning, directly testing the hypothesis that distinct subregions subserve retrieval and integration computations. By varying retrieval and integration demands in an event-related design, the present results revealed that aLIPC, left FPC and right DLPFC were correlated with distinct aspects of reasoning demands and thus appear to make unique contributions to the ability to reason analogically. Anterior LIPC was differentially sensitive to semantic retrieval demands, consistent with a role in retrieving relevant semantic knowledge about and associations between stimuli. In contrast, left FPC was insensitive to semantic retrieval demands, but was differentially sensitive to integration demands. This profile suggests that FPC operates subsequent to semantic retrieval for the purpose of integrating across multiple retrieved relations. Finally, right DLPFC was insensitive to retrieval and integration demands, instead exhibiting a pattern consistent with a role in response selection.

Left FPC and Representational Integration

In the present study, left FPC was engaged by the need to integrate across two semantic relations. Unlike aLIPC, however, FPC was insensitive to the associative strength manipulation, suggesting that this region is not important for semantic retrieval *per se*. This finding is consistent with our prior suggestion that FPC is involved in the subsequent processing of information retrieved from long-term stores via ventrolateral PFC retrieval mechanisms (Bunge *et al.*, 2004). Taken together with the finding that FPC is sensitive to the number of visuospatial relations that must be considered simultaneously (Wharton *et al.*, 2000; Christoff *et al.*, 2001; Kroger *et al.*, 2002), the present results suggest that FPC plays a domain-general role in integrating across multiple relations in the service of analogical reasoning.

Although the present findings support a role for FPC in relational integration, the involvement of FPC across a variety of task demands suggests that FPC function may be more general (Braver and Bongiolatti, 2002; Christoff and Gabrieli, 2002). FPC is engaged not only during performance of problem-solving or reasoning tasks, but also episodic memory retrieval tasks in which subjects must evaluate the products of retrieval in order to make a response (for reviews, see Tulving *et al.*, 1994; Cabeza and Nyberg, 2000; Fletcher and Henson, 2001). On this basis, FPC has been hypothesized to be in-

volved in the active processing of self-generated information — i.e. information that must be inferred rather than perceived (Christoff and Gabrieli, 2002). Such active computations might include the manipulation or evaluation of retrieved information and the integration of this knowledge with decision criteria. An alternative, but related, hypothesis is that FPC is engaged when 'cognitive branching' is required — i.e. when subjects must maintain a primary task goal while simultaneously attending to a subgoal (Koechlin *et al.*, 1999; see also Badre and Wagner, 2004). Support for this hypothesis comes from a continuous performance task (CPT) that included a condition that bears interesting similarities to the analogy task in the present study (Braver and Bongiolatti, 2002). To test this hypothesis, Braver and Bongiolatti elegantly manipulated both semantic retrieval demands and subgoal processing demands in a blocked-design continuous performance task (AX-CPT). In the subgoal task, subjects had to press a button to indicate when any abstract word was presented on the screen directly following any concrete word. This condition was compared with (i) a control condition in which a specific abstract word (FATE) was presented after a specific concrete word (LIME); and (ii) a semantic classification task in which subjects judged each word as abstract or concrete. Bilateral FPC (but more strongly on the right) was selectively engaged in the subgoal task, in which — as in the analogy condition of the present study — subjects had to retrieve two pieces of semantic information and then integrate them. On the basis of findings from the CPT task, it was proposed that FPC might be engaged when the results of subgoal processing must be integrated with information stored in working memory (Braver and Bongiolatti, 2002). This perspective elaborates on the hypothesis that FPC mediates the processing of self-generated information (i.e. working with the products of subgoal processing).

The present observation of greater FPC activation during analogical reasoning relative to semantic retrieval is consistent with the hypothesis that FPC mediates integration of the products of a cognitive operation, such as semantic retrieval, in the context of information currently held in mind. That is, during the analogy condition, subjects had to evaluate whether newly retrieved or synthesized information could be integrated with previously retrieved representations currently being maintained in working memory. Moreover, FPC was most strongly recruited when subjects had to reject an invalid analogy, the condition under which demands on integration should be highest.

Laterality of FPC Activation

In the present study, as in the few preceding imaging studies of reasoning, activation was observed in left but not right FPC (Goel *et al.*, 1997; Wharton *et al.*, 2000; Kroger *et al.*, 2002). By contrast, episodic retrieval tasks sometimes engage right FPC more so than left FPC (Tulving *et al.*, 1994; Nyberg *et al.*, 1996; Cabeza and Nyberg, 2000). This observation — together with the finding that left FPC was more strongly implicated in relational integration in a RPM-like task — led to the suggestion that right FPC may be preferentially involved in the evaluation of self-generated information, whereas left FPC may be involved in manipulating self-generated information for the purpose of further abstracting new information (Christoff and Gabrieli, 2002). We suggest, instead, that the observed laterality effects

can be reconciled by considering the type of memory processes invoked by subjects during performance of episodic memory tasks. Memory judgements that require attempts to recollect specific details about an episode tend to engage left FPC (Nolde *et al.*, 1998; Henson *et al.*, 1999; Ranganath *et al.*, 2000; Dobbins *et al.*, 2002, 2003; Kahn et al., 2004), and this is the case irrespective of whether the to-be-retrieved episodic details are conceptual or perceptual (I.G. Dobbins and A.D. Wagner, in preparation). By contrast, judgements that can be based on assessments of stimulus familiarity tend to engage right or bilateral FPC (Wagner *et al.*, 1998; Henson *et al.*, 1999, 2000; Dobbins *et al.*, 2003). Taken together with the present findings, these data raise the possibility that left FPC is engaged when subjects must attempt to integrate the products of a retrieval attempt for specific detailed information — be it from semantic or episodic memory — with the current contents of working memory.

ALIPC and Controlled Semantic Retrieval

The present results revealed that the anterior extent of left inferior prefrontal cortex (~BA 47, 45), unlike other PFC subregions, was reliably sensitive to the Associative Strength between the words in pair 1 during both analogy and semantic decision trials. Specifically, aLIPC exhibited greater activation for weakly than for strongly associated word pairs, consistent with prior studies (Fletcher *et al.*, 2000; Wagner *et al.*, 2001b). This finding provides further evidence that aLIPC computations are engaged during semantic processing conditions to the extent that controlled retrieval of semantic knowledge is required (Fiez, 1997; Gabrieli *et al.*, 1998; Poldrack *et al.*, 1999; Wagner *et al.*, 2001b). When pre-existing associative relations are sufficiently strong that target knowledge may readily come to mind via bottom-up, automatic retrieval mechanisms, demands on aLIPC processes are minimized relative to when these associations are weak and thus require a top-down control signal to further guide knowledge recovery (Raichle *et al.*, 1994; Badre and Wagner, 2002).

In addition to demonstrating a main effect of Associative Strength, aLIPC was also differentially engaged by analogy relative to semantic trials, although the effect of Task was not as strong as in FPC. This pattern can be accommodated by the controlled retrieval perspective, as semantic retrieval demands likely varied across analogy and semantic trials. On semantic trials, subjects had to make a global Relatedness judgement about pair 2 (i.e. are the words in pair 2 related along any dimension?). In contrast, on analogy trials, subjects had to engage in controlled retrieval to determine whether the words in pair 2 were related along the same dimension as those in pair 1. This latter task demand likely required retrieval of more specific semantic knowledge, and was less amendable to solution through bottom-up, automatically retrieved knowledge. Thus, aLIPC appears to be important for semantic analogical reasoning because it contributes to retrieving the conceptual relations between stimuli.

Right DLPFC and Response Selection

Several theorists (e.g. Holyoak and Kroger, 1995; Waltz *et al.*, 1999) have hypothesized that analogical mapping relies on DLPFC. Interestingly, DLPFC was not globally modulated by integration demands in the present study. DLPFC activation has been observed together with FPC activation in other analogical

reasoning studies (Prabhakaran *et al.*, 1997; Wharton *et al.*, 2000; Christoff *et al.*, 2001), but it has been argued that activation in this region is not related specifically to relational integration (Christoff and Gabrieli, 2002).

Our results revealed that right DLPFC was differentially engaged during the condition that required rejection of an invalid analogy (i.e. unrelated-analogy). Given the behavioral finding that subjects tended to endorse invalid analogies more often (and more quickly) than they rejected valid ones, this pattern of results is consistent with the possibility that DLPFC is recruited — at a stage subsequent to semantic retrieval and relational integration — for the purpose of overriding a bias to endorse invalid analogies. This interpretation, although admittedly *post hoc*, is consistent with a posited role for DLPFC in response selection (e.g. Rowe *et al.*, 2000; Bunge *et al.*, 2002b; Hazeltine *et al.*, 2003). It has been previously shown that DLPFC is recruited when there is a need to override prepotent responses or to resolve response competition (e.g. Casey *et al.*, 1997; Garavan *et al.*, 1999; MacDonald *et al.*, 2000; Liddle *et al.*, 2001; Bunge *et al.*, 2002a,b), with right DLPFC in particular appearing to play a general role in response selection across different stimulus materials (Hazeltine *et al.*, 2003; for review, see Jonides *et al.*, 2002). Moreover, mid-DLPFC response selection mechanisms have been reported to dissociate from FPC subgoaling/integration mechanisms (Badre and Wagner, 2004), a pattern that is consistent with the present dissociative outcome. Thus, the present findings complement prior reports in suggesting the DLPFC does not mediate integration *per se*, but rather may be engaged during reasoning under situations that require overcoming a prepotent response bias.

Conclusion

Representational integration — which can be described as the process of jointly considering, comparing, or linking separate mental representations — is likely to be a fundamental building-block for high-level cognitive function, enabling one to (i) evaluate whether the products of long-term memory retrieval are consistent with previously retrieved information or with a specific goal (e.g. during analogical reasoning or episodic memory retrieval); (ii) consider whether multiple constraints are simultaneously satisfied (e.g. during deductive reasoning; Goel *et al.*, 1998; Waltz *et al.*, 1999); or (iii) predict the consequence of a series of future actions (e.g. while performing a prospective task like the Tower of London; Owen *et al.*, 1996a; Rowe *et al.*, 2001; see Kroger *et al.*, 2002). The present findings suggest that the most rostral portion of PFC contributes to high-level cognition by enabling domain-general integration of newly retrieved information with other representations currently held in mind.

Beyond integration, a number of other cognitive operations are required for successful analogical reasoning, including the retrieval of relations between representations and the selection of a contextually appropriate response. These processes differentially tax distinct subregions of PFC, lending credence to the suggestion that interaction between multiple PFC regions is central to high-level cognition. Moreover, the present findings suggest that the cognitive consequences of damage to PFC should at least partially depend on the specific locus of the deficit, with distinct deficits in high-level cognition likely to follow insult to frontopolar, dorsolateral, and ventrolateral PFC

structures. Future research with targeted transcranial magnetic stimulation (e.g. Mottaghy *et al.*, 2002) or consideration of select lesion populations (e.g. Thompson-Schill *et al.*, 1998) may provide further evidence for the multi-component nature of analogical reasoning.

Notes

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