Common and Dissociable Prefrontal Loci Associated with Component Mechanisms of Analogical Reasoning

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The ability to draw analogies requires 2 key cognitive processes, relational integration and resolution of interference. The present study aimed to identify the neural correlates of both component processes of analogical reasoning within a single, nonverbal analogy task using event-related functional magnetic resonance imaging. Participants verified whether a visual analogy was true by considering either 1 or 3 relational dimensions. On half of the trials, there was an additional need to resolve interference in order to make a correct judgment. Increase in the number of dimensions to integrate was associated with increased activation in the lateral prefrontal cortex as well as lateral frontal pole in both hemispheres. When there was a need to resolve interference during reasoning, activation increased in the lateral prefrontal cortex but not in the frontal pole. We identified regions in the middle and inferior frontal gyri which were exclusively sensitive to demands on each component process, in addition to a partial overlap between these neural correlates of each component process. These results indicate that analogical reasoning is mediated by the coordination of multiple regions of the prefrontal cortex, of which some are sensitive to demands on only one of these 2 component processes, whereas others are sensitive to both.

Keywords: analogy, executive control, inhibition, interference resolution, relational integration, working memory

Introduction

Analogical reasoning (Holyoak 2005) is a core component of fluid intelligence (Duncan et al. 2000), and may reflect a general ability to reason with abstract relations that is unique to humans (Penn et al. 2008). The cognitive mechanisms underlying analogical reasoning are closely related to the functions of the prefrontal cortex (Knowlton and Holyoak, 2009; Robin and Holyoak 1995). Populations showing impaired frontal lobe function, either due to lesion or aging (as well as children, in whom the frontal lobe has not yet fully developed), are impaired in their ability to solve analogies and similar problems that involve reasoning about relations (Waltz et al. 1999; Morrison et al. 2004; Viskontas et al. 2004; Richland et al. 2006; Krawczyk et al. 2008).

A major cognitive component of complex analogical reasoning is the integration of multiple relations (Robin and Holyoak 1995; Halford et al. 1998). Neuroimaging studies of reasoning have consistently shown that problems requiring relational integration activate prefrontal regions. In several studies using problems modeled after the Raven's Progressive Matrices (RPM; Raven 1938), the most widely used measure of fluid reasoning, bilateral middle (MFG) and inferior frontal gyri (IFG) as well as parietal and occipital regions were found to increase activity when multiple relations had to be integrated

in order to arrive at a solution, compared with problems that required processing of only a single relation (Prabhakaran et al. 1997; Christoff et al. 2001; Kroger et al. 2002). Among these regions, which constitute a network commonly activated in visuospatial working memory tasks, the activation pattern of the most anterior part of the prefrontal cortex (PFC) has been particularly noteworthy. Christoff et al. (2001) found that the left lateral frontopolar region remained preferentially activated even after controlling for the influence of increased problem-solving time. Kroger et al. (2002) confirmed and extended these results, providing evidence that the left anterior lateral prefrontal region becomes increasingly activated as more relations need to be integrated, yet is not affected by sheer perceptual difficulty (an increasing number of visuospatial distractors). Thus, the lateral frontopolar region seems to be uniquely associated with the specific requirement of integrating multiple relations, above and beyond general cognitive difficulty or visuospatial working-memory demands inherent in nonverbal relational reasoning.

Similarly, studies of verbal analogical reasoning have distinguished neural substrates of reasoning from semantic processing demands within working memory (Luo et al. 2003; Bunge et al. 2005; Green et al. 2006). Activation in the left lateral frontopolar region has been shown to increase selectively when making judgments of analogical similarity compared with processing of semantic associations or categories in working memory (Bunge et al. 2005; Green et al. 2006; Wendelken et al. 2008); moreover, 4-term verbal analogy problems in which the 2 pairs of concepts are more distant in semantic space yield greater lateral frontopolar activation (Green et al. 2009). Thus, based on a substantial body of findings involving solution of analogy problems, the lateral frontopolar region seems to play a special role in the process of integrating relational representations to arrive at a solution.

But in contrast to the extensive set of neuroimaging studies that have examined the neural basis of relational integration, the neural substrates of other possible cognitive processes that may be critical to analogical reasoning have received little or no attention. In particular, findings from behavioral studies suggest that control of interference from salient but misleading information may also be a key component process in analogical reasoning (Morrison et al. 2004; Richland et al. 2006; Cho et al. 2007; Krawczyk et al. 2008). However, it remains unclear whether relational integration, and interference resolution are in fact distinct cognitive and neural processes, or whether one subsumes the other. Halford et al. (1998) proposed a computational model in which distraction can be viewed as a special case of higher relational complexity (the number of relations that need to be simultaneously considered). Under this hypothesis,

resolving interference during analogical reasoning would activate lateral frontopolar regions involved in relational integration. At present, neither behavioral studies nor computational modeling have succeeded in answering the basic question of whether integrating relations and coping with interference are distinct or separable processes in analogical reasoning.

Given this unresolved question, it is natural to consider neuroimaging evidence, which can potentially reveal whether manipulations of relational complexity and of interference activate distinct, overlapping, or identical brain regions. But in contrast to the extensive research on the neural correlates of relational integration, no study has specifically probed the neural basis for the mechanism of interference resolution in the context of analogical reasoning. Indeed, no study has manipulated any additional source of reasoning difficulty in conjunction with a manipulation of relational complexity. The goal of the present study is to fill this gap in our knowledge about the neural basis of analogical reasoning.

Although it has not been investigated in the context of analogical reasoning, interference resolution (often referred to as "inhibition" or "selection") has been extensively studied in other cognitive processes, including other forms of reasoning. Previous studies have identified the lateral PFC as an important substrate for interference resolution across diverse tasks including inhibition of a motor response, proactive interference resolution in working memory, selection among competing alternatives, controlled semantic retrieval, inhibiting belief-bias during deductive reasoning and avoiding heuristic bias during decision making (Thompson-Schill et al. 1997, 2002; Jonides et al. 1998; D'Esposito et al. 1999; Goel et al. 2000; Wagner et al. 2001; Aron et al. 2003; Goel and Dolan 2003; Zhang et al. 2004; Badre et al. 2005; De Neys et al. 2008).

As noted above, no previous imaging study of analogical reasoning has examined interference resolution, nor has any previous study systematically manipulated multiple component processes within a single analogical reasoning task. Accordingly, the present study aimed to simultaneously examine the neural correlates of 2 processes, relational integration and interference resolution, that are hypothesized to be key components of analogical reasoning. Prior work indicates that the lateral frontal pole is closely associated with integration of multiple relational representations in both verbal and nonverbal relational reasoning. However, it remains unclear whether the lateral frontal pole is specialized for relational integration per se or may be sensitive to other processing demands that determine the cognitive difficulty of relational reasoning, such as interference resolution. By varying demands on both relational integration and interference resolution in a single task, we aimed to determine whether the lateral frontopolar region is specialized for relational integration or exhibits sensitivity to demands on interference resolution as well. With respect to the neural correlates of interference resolution, we were especially interested in examining activations in lateral prefrontal regions—bilateral MFG and IFG, respectively, that have been associated with inhibition/selection in previous studies. In addition, given that the lateral PFC has also been associated with relational integration in previous studies, we aimed to explore whether the neural correlates of interference resolution coincides with or are separable from those of relational integration in lateral PFC.

Thus, the main goals of the present study were to 1) examine whether the lateral frontal pole is specifically sensitive to demands on integration of relations or additionally responds to demands on interference resolution, 2) determine whether the lateral PFC regions found to be important for cognitive control in previous studies coincide with regions that show sensitivity to demands on interference resolution during analogical reasoning, and 3) explore the spatial overlap or separability of neural correlates of relational integration and interference resolution in the prefrontal cortex. In order to test these hypotheses, we used a nonverbal, 4-term analogy task (A:B::C:D) called the People Pieces Analogy (PPA) task (Sternberg 1977; Morrison et al. 2001; Viskontas et al. 2004; Cho et al. 2007) which allows independent and simultaneous variation in demands on the 2 key component processes of analogical reasoning.

The present study is the first neuroimaging study to jointly examine neural correlates of relational integration and interference resolution using a single paradigm. In the PPA task, subjects are asked to verify whether the relationship between the A:B pair corresponds to the relationship between the C:D pair with respect to selected dimension(s). The greatest advantage of using the PPA task compared with other reasoning tasks (such as the RPM or verbal analogy) is that it enables independent variation of demands on 2 component processes of reasoning at once, by varying the number of relations to be considered (relational complexity, RC; Halford et al. 1998) and need for interference (IN) resolution, without any concomitant variation in visuospatial complexity (see Supplementary Fig. 1 for the complete set of PPA stimuli).

Materials and Methods

Subjects

Seventeen healthy adults (9 females, 16 right-handed, 1 ambidextrous) were recruited following procedures approved by the Office for the Protection of Research Subjects at the University of California, Los Angeles (UCLA). All participants provided informed consent and received payment for their participation. Participants had a mean age of 23 years, SD = 3.8, and had no reported history of neurological illness or drug abuse.

Behavioral Task and Experimental Design

Each problem of the PPA task consists of 2 pairs of human cartoon characters described by 4 binary traits: clothing color, gender, height, and width (Fig. 1). There were 16 different possible characters, presented horizontally as 2 pairs. The task was to determine whether the analogy
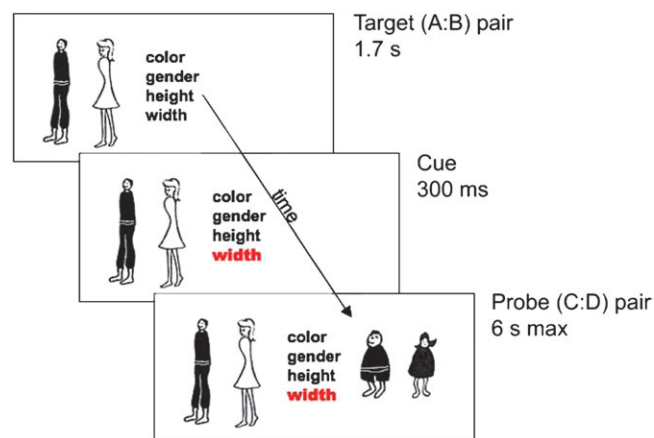

Figure 1. Example of a PPA problem and the sequence of stimuli presentation. (Fixation periods not shown; for complete depiction of trial, see Supplementary Fig. 3.)

between the 2 pairs was valid, based on a subset of trait(s) randomly selected for each trial. Participants were instructed to solve each problem based on traits that were cued to be relevant on a given trial ("to-be-attended" traits) only, to ignore traits that were not cued to be relevant ("to-be-ignored" traits), and to decide as quickly and accurately as possible. The trait list consisted of 4 words naming each trait, displayed in black font in the center of the screen, between the 2 pairs of cartoon characters. The to-be-attended trait name was shown in red font at a certain point during the trial until the subject made a response.

In the example trial shown in Figure 1, the to-be-attended dimension is "width." The within-pair relation of the target pair (A:B) is "SAME" because both A and B characters are thin ("thin" = "thin"). The within-pair relation of the probe pair (C:D) is also "SAME" because both C and D characters are wide ("wide" = "wide"). Thus, the relations match across pairs ("SAME" matches "SAME"), resulting in a valid analogy. However, if subjects mistakenly considered the color dimension, which was to be ignored, they could be misled into concluding that the analogy is invalid because the color relation for the target pair is "DIFFERENT" ("black" ≠ "white") and does not match the "SAME" relation ("black" = "black") of the probe pair ("DIFFERENT" does not match "SAME"). Note that in this example, the other to-be-ignored dimensions, "gender" and "height," are benign, because across-pair comparisons regarding either "gender" or "height" will lead to a response compatible with that of the to-be-attended "width" dimension. This example trial is classified as relational complexity (RC) level 1, interference (IN) level 1, because there is one to-be-attended dimension (width), and one to-be-ignored dimension (color) that had a potential to cause interference in making a correct response. Examples of trials in the 3 remaining experimental conditions are depicted in Supplementary Figure 2A-C.

The design of the PPA stimuli and task thus allowed RC and IN to be varied without introducing changes in visuospatial complexity. Visuospatial complexity was controlled by having all PPA problems consist of 4 cartoon figures selected from a set of sixteen characters with equivalent visual complexity, each cartoon placed at one of 4 fixed locations (Viskontas et al. 2004; Cho et al. 2007). Levels of RC and IN were jointly and independently manipulated for valid trials in a 2 by 2 factorial design, with 24 trials for each of the 4 conditions. The level of RC was defined by the number of to-be-attended traits (1 or 3), whereas the level of IN was defined by the number of to-be-ignored traits that supported an incorrect response (0 or 1). Thus, the design included 4 experimental conditions: RC level 1/IN level 0; RC level 1/IN level 1; RC level 3/IN level 0; and RC level 3/IN level 1. We elected to use RC level 3 (rather than level 2) in order to maximize the impact of RC while still allowing variation in IN. A total of 96 valid analogy problems were presented (24 in each condition) across 3 functional magnetic resonance imaging (fMRI) scans.

Invalid trials (a total of 36) were created by introducing an across-pair relational mismatch on exactly one of the to-be-attended dimension(s), whereas the across-pair relation regarding the to-be-ignored dimension(s) always matched. IN levels in invalid analogy trials were not manipulated because it is not clear whether the presence of information supporting the validity of an analogy interferes with the process of rejecting an analogy. Also, invalid analogy trials at RC level 3 were likely to vary in the extent to which subjects engaged in relational integration, as subjects could reject the analogy based on a nonexhaustive search for the nonmatching relation. Therefore, the present study mainly focused on valid analogy trials and thus included a greater number of valid trials compared with invalid trials to increase statistical power of the 2 × 2 factorial design crossing RC and IN among valid trials. However, we included enough invalid trials to prevent participants from adopting a strategy of blindly endorsing the validity of an analogy, by using a valid:invalid trial ratio similar to those used in previous behavioral studies (Viskontas et al. 2004; Cho et al. 2007). Invalid trials were equally divided into RC levels 1 and 3.

Each trial began with a variable duration of fixation randomly jittered between 2 and 8 s (Fig. 1, fixation period not shown). For a complete depiction of stimulus presentation including fixation see Supplementary Fig. 3). In each 8-s trial, the target pair (A:B) first appeared on the left side of the screen (target phase). The trait names were all shown in black font during the target phase. After 1.7 s, the to-be-attended trait cue(s) turned red (cue phase) and remained on the screen. After 0.3 s, the probe pair (C:D) appeared on the right side of the screen (probe

phase). Subjects were allowed a maximum of 6 s to respond with a key press for valid (index finger) or invalid (middle finger) analogy problems. The presentation of the A:B pair prior to indicating which trait(s) was to-be-attended ("delayed cueing" of to-be-attended traits) ensured that subjects had to actively pay attention to all visual information about the A:B pair, and that potential sources of interference would therefore be encoded into working memory. This delayed cueing procedure is an effective method of manipulating IN and of examining the interaction between RC and IN, as subjects will have to actively suppress sources of interference that had been attended to and maintained in working memory while processing relations. A previous study (Cho et al. 2007) showed that when to-be-attended traits were known from the beginning, subjects were able to withdraw attention from and filter out possible sources of interference, so that interference resolution did not impose a reliable burden on executive resources in WM.

In addition to these standard trials, 30 "catch" trials in which the A:B pair disappeared after the target phase were randomly intermixed with the standard trials. The catch trials were included to encourage participants to fully attend to the A:B pair from the beginning of all trials, further ensuring that sources of interference could not simply be ignored during initial encoding (target phase). The structure and timing of catch trials were otherwise identical to standard trials (see Supplementary Fig. 4).

Stimulus presentation and behavioral data acquisition were accomplished using E-prime (Psychological Software Tools, Inc., Pittsburgh, PA) on a PC laptop. Trials of all 4 conditions were presented in a pseudo-randomized order that maximized efficiency for our contrasts of interest, and were administered in 3 counterbalanced lists in counterbalanced order. In addition to main effects of RC and IN, we examined regions exhibiting either an overadditive or underadditive interaction (modulatory influence of one factor over the effect of the other factor) between RC and IN by using a regression model contrasting the difference between RC1/IN0 and RC1/IN1 (i.e., the simple main effect of IN at RC level 1) with the difference between RC3/IN0 and RC3/IN1 (i.e., the simple main effect of IN at RC level 3). (An overadditive interaction will manifest as the simple main effect of IN at RC level 3 being greater than the simple main effect of IN at RC level 1, whereas an underadditive interaction will be found when the simple main effect of IN at RC level 3 is smaller than the simple main effect if IN at RC level 1.) Catch trials, and trials in which subjects made an error, were excluded from the statistical analyses due to insufficient number of trials. For invalid analogy trials, the RC level of a problem does not directly relate to relational integration, because the search for a nonmatching relation will terminate at varying times for items at RC level 3, depending on whether the nonmatch is the first, second, or third relation considered. However, to allow a comparison between the RC main effects among valid and invalid trials, we analyzed the RC main effect among invalid trials and report the results in Supplementary Table 1 and Supplementary Figure 7.

Prior to fMRI acquisition, participants were given instruction on the task, and practice trials outside the scanner, so that they would be able to correctly identify traits in each human cartoon and to solve the analogies as instructed. When debriefed after the experiment was finished, subjects reported that they were not aware of the interference manipulation.

MRI Data Acquisition

Images were acquired using a Siemens Allegra 3T whole-brain MRI scanner at the Ahmanson-Lovelace Brain Mapping Center at UCLA. We collected blood-oxygenation level–dependent (BOLD) functional echo-planar images (EPIs) using a pulse sequence with the following parameters: repetition time (TR), 2 s; echo time (TE), 30 ms; flip angle, 90°; 33 slices; voxel dimensions; 3.1 × 3.1 × 3.5 mm; field of view (FOV), 200 mm; and matrix, 64 × 64. Slices were acquired with interleaved order. The data collected during the first 2 TRs were discarded to allow for T_1 equilibration and the first trial of each scan was not included in the contrasts of interest. Two anatomical scans were acquired for each subject: a T_2-weighted matched-bandwidth high-resolution scan co-planar to the EPIs with TR, 5 s; TE, 33 ms; flip angle, 90°; 33 slices; voxel dimensions, 1.6 × 1.6 × 3.5 mm, FOV, 200 mm; and matrix, 128 × 128, and a T_1-weighted magnetization-prepared rapid-acquisition gradient echo

(MPRAGE) image with TR, 2.3 s; TE, 2.1 ms; flip angle, 8°; 160 slices; voxel dimensions, 1.3 × 1.3 × 1.0 mm, FOV, 256 mm; and matrix, 192 × 192.

Image Processing and Analysis

Image preprocessing and analysis were carried out using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)'s Software Library (FSL, Smith et al. 2004). Spatial smoothing was applied using a full-width half-maximum Gaussian kernel of 5 mm. Preprocessing and analysis were run using fMRI Expert Analysis Tool version 5.63 (FMRIB Centre, Oxford, UK). To remove low-frequency artifacts, each functional run was temporally filtered using a high-pass cutoff of 66 s. For each EPI run, motion correction was applied using 3-dimensional coregistration of each image to the middle image of the time series with Motion Correction using FMRIB's Linear Image Registration Tool (Jenkinson et al. 2002).

For functional runs in which the subjects had moved more than 3 mm throughout the scan, an independent components analysis was carried out using the FMRIB's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) tool (Beckmann and Smith 2004). The spatial and temporal characteristics of each isolated component were examined and components that were clearly related to motion or other sources of low- or high-frequency noise were removed. Only 3 among 51 runs were subject to this analysis. All statistical analyses were carried out both before and after denoising. The group statistical results including the denoised data set did not differ qualitatively from those before denoising with MELODIC. One functional run from one subject was excluded from the image analysis due to technical errors caused by the MR scanner.

Registration of the functional data followed a 3-stage process using linear registration with FMRIB's Linear Registration Tool: each functional run was first registered to a higher resolution T_2-weighted matched-bandwidth anatomical image of each subject (7° of freedom affine transforms), then to an even higher resolution T_1-weighted MPRAGE image (7° of freedom affine transforms), and finally to the Montreal Neurological Institute (MNI) 152 standard template anatomical image (12 degrees of freedom affine transforms).

The BOLD signal was modeled using a variable-length boxcar function convolved with a canonical double-gamma hemodynamic response function. The boxcar for each trial spanned from the time of target pair presentation to the time of each button press, in order to account for trial-to-trial variation in problem-solving time (Christoff et al. 2001). Specific comparisons of interest were tested using linear contrasts. (The regressors of the general linear model [GLM] model as well as contrasts used for hypothesis testing are listed in Supplementary Methods.) Statistical analysis was first performed on each subject's individual functional run using FMRIB's Improved Linear Model. The second step analysis combined the 3 functional runs for each subject using a fixed effects model; then, at the third step, a cross-subjects group analysis was carried out for each contrast using a mixed effects model by FMRIB's Local Analysis of Mixed Effects (Beckmann et al. 2003; Woolrich et al. 2004). Resulting Z statistic images were thresholded using a cluster-forming threshold of $Z > 2.3$ (uncorrected) and a corrected cluster extent threshold of $P = 0.05$ based on the theory of Gaussian Random Fields (Worsley et al. 1992).

Two a priori defined anatomical regions of interest (ROIs) were derived from the Harvard-Oxford probabilistic atlas (Flitney et al. 2007) for small volume correction. The first ROI mask was created by combining the entire lateral PFC comprising bilateral MFG, and IFG pars opercularis and pars triangularis (Fig. 3A). The second ROI mask comprised bilateral frontal pole (Fig. 3B). For small volume correction, we used the FSL Randomize tool, which implements a Monte Carlo permutation test using the maximum statistic (Nichols and Holmes 2002). Familywise error within these a priori anatomical ROI masks was controlled with a cluster-based correction at $P < 0.05$ using a cluster-forming threshold of $t = 2.3$.

Results

Behavioral Data

RT and proportion of correct answers (accuracy) were analyzed as dependent variables. Only data from valid analogy

trials on which a correct response was collected were included in the analysis. Geometric means of RTs and accuracy for each condition are reported in Table 1. RT increased significantly with the need to integrate more complex relations (mean ± SEM = 1472 ± 100 ms for RC level 1, 3358 ± 132 ms for RC level 3, $F_{1,16} = 309.6$, MSe = 0.2, $P < 0.001$, $\eta^2 = 0.95$). Conversely, accuracy decreased for more complex analogy conditions (0.91 ± 0.02 for RC level 1, 0.87 ± 0.02 for RC level 3, $F_{1,16} = 5.15$, MSe = 0.005, $P < 0.04$, $\eta^2 = 0.24$). The overall effect of IN was not reliable for RT ($P > 0.1$), but yielded a reliable decrease in accuracy (0.93 ± 0.02 for level 0, 0.85 ± 0.02 for level 1, $F_{1,16} = 13.7$, MSe = 0.01, $P < 0.002$, $\eta^2 = 0.46$). Moreover, simultaneous increase in the load of relational integration and interference resolution resulted in an overadditive increase in processing time ($F_{1,16} = 6.07$, MSe = 0.01, $P < 0.03$, $\eta^2 = 0.28$.). No interaction was found for accuracy ($P > 0.1$). This behavioral pattern, including the interactive impact of RC and IN, has also been observed in similar experiments with young adults that did not involve brain imaging (Cho et al. 2007), as well as in studies of changes in analogical reasoning over the course of aging (Viskontas et al. 2004).

Whole-Brain Analysis

Regions that showed increased activation during solution of problems with more relations to integrate from a whole-brain analysis (Table 2, Fig. 2) were found in the lateral frontal pole, MFG and IFG, medial superior frontal gyri (SFG), precuneus, cerebellum and thalamus in both hemispheres, left superior parietal cortex continuing to the lateral occipital lobe, and left occipital pole (whole-brain corrected, uncorrected cluster-forming threshold, $Z > 2.3$; corrected cluster extent threshold, $P < 0.05$). These regions of activations are consistent with results of previous studies of relational reasoning using

Table 1

Geometric means of RTs (correct trials only) and proportion correct (accuracy) across experimental conditions (mean ± SEM)

RC	RC level 1		RC level 3	
IN	IN level 0	IN level 1	IN level 0	IN level 1
RT (ms)	1470 ± 105	1473 ± 101	3291 ± 141	3426 ± 131
Accuracy	0.96 ± 0.02	0.86 ± 0.02	0.90 ± 0.03	0.84 ± 0.03

Table 2

Summary of clusters for the main effect of RC from a whole-brain analysis

Region	Hem.	Voxels	Loci of maxima			Z of max.	BA[a] of max.
			x	y	z		
Frontal pole	L	502	−50	42	−10	3.81	10, 47
MFG	R	1771	58	28	34	3.96	9
	L	1305	−50	22	26	4.29	9, 46
SFG	R	992	4	22	52	4.38	6, 8
Superior parietal lobe	L	433	−26	−58	42	3.32	7
	R	673	4	−66	46	4.26	7
Thalamus	Bilateral	1709	0	−6	6	3.81	N/A
Cerebellum	Bilateral	1812	0	−90	−28	3.97	N/A
	L	533	−28	−70	−38	3.65	N/A

Note: Loci of maxima are in MNI coordinates in mm. Hem, hemisphere; Max, maxima; BA, Brodmann's area.

[a]BAs are based on the Talairach atlas (Talairach and Tournoux 1988); thus the precision of localization should be interpreted with caution. Putative BAs are reported in Tables 2 and 3 to aid communication given current practice; however, we believe that labeling activations with informal estimates of BAs should be discouraged throughout the neuroimaging community in order to improve standards for anatomical localization (Devlin and Poldrack 2007).
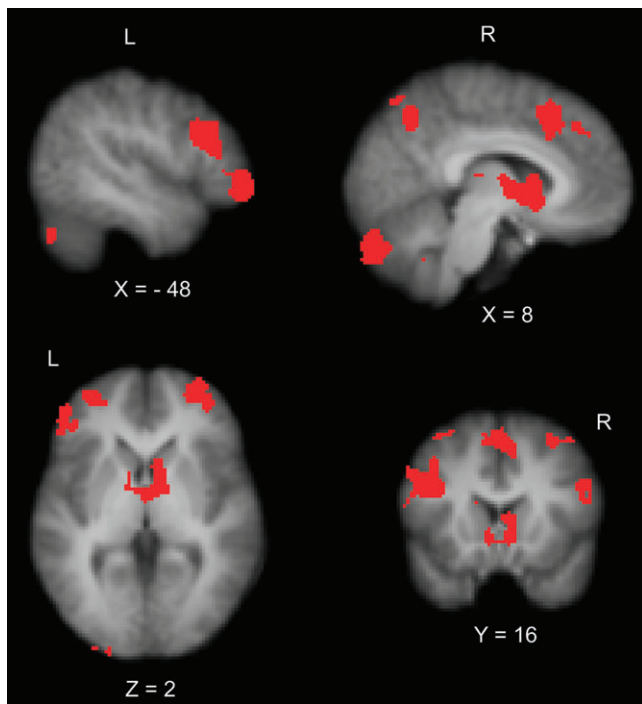
Figure 2. Cortical clusters showing a significant main effect of RC from the whole-brain analysis (uncorrected cluster-forming threshold, $Z > 2.3$, corrected cluster extent threshold, $P < 0.05$). R, right hemisphere; L, left hemisphere. Coordinates are in MNI space (mm).

Figure 3. A priori defined ROIs. (*A*) Lateral prefrontal cortices combining MFG and IFG pars opercularis and pars triangularis in both hemispheres; (*B*) bilateral frontal pole.

RPM-type tasks (Prabhakaran et al. 1997; Christoff et al. 2001; Kroger et al. 2002; Lee et al. 2006). In order to confirm that our activations for the main effect of RC could not be explained solely by increased processing time, we reanalyzed this effect with a covariate reflecting the increase in RT from RC level 1 to RC level 3 for each subject. Even with the effects of RT increase regressed out, the regions showing the main effect of RC remained essentially the same. The region correlated with increase in processing time was identified as one cluster in the occipital lobe (number of voxels, 1842; locus of max Z, $x = -6$, $y = -84$, $z = -2$, MNI coordinates, mm; $P < 0.00001$). Activation increases related to demands on interference resolution were not significant in the whole-brain analysis ($Z > 2.3$, $P > 0.05$). We did not conduct a similar analysis using RT increase as a regressor for the main effect of IN, given the lack of significant increase in RT for the main effect of IN.

Small Volume Correction within A Priori Defined Anatomical ROIs

In order to identify regions sensitive to demands on interference resolution, we tested for the main effect of IN by a permutation-based nonparametric test within 2 a priori defined anatomical ROIs, one consisting of the lateral PFC (MFG and IFG) in both hemispheres (Fig. 3*A*), and the other comprising bilateral frontal pole (Fig. 3*B*). These ROIs were selected to test specific hypotheses based on previous neuropsychological and neuro-imaging data indicating the importance of these prefrontal regions to cognitive control, as reviewed in the introduction.

Within the bilateral frontal pole ROI, there was no cluster of activation showing a significant main effect of IN ($P > 0.1$), demonstrating that the frontal pole was sensitive only to
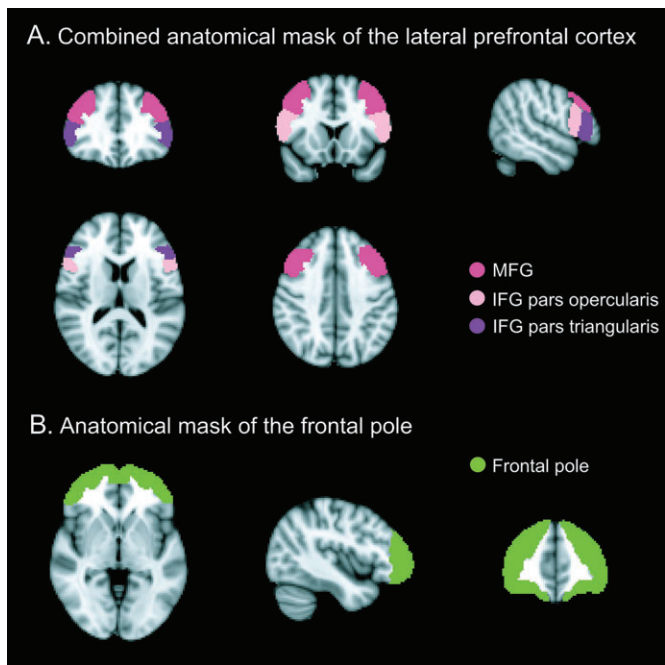
demands on relational integration and not to interference resolution. Furthermore, there were no significant main effects of IN within functionally defined ROIs showing RC main effects from the whole-brain analysis within the left and right lateral frontal poles, tested separately (P's > 0.1), providing further evidence of the lateral frontal pole's insensitivity to variation in IN. In contrast, nonparametric tests of RC main effects within the frontal pole ROI overlapped in location and size with the whole-brain RC main effects in the lateral frontal pole ($P = 0.01$ for the right hemisphere cluster; left hemisphere clusters were marginally significant, $P = 0.12$).

Within the lateral PFC ROI, regions that showed greater activation with increased demands on interference resolution were found in bilateral MFG and IFG pars opercularis and IFG pars triangularis in the right hemisphere (Fig. 4, main effect of IN shown in yellow; small volume corrected, cluster-forming threshold, $t > 2.3$; cluster extent threshold, $P < 0.05$, Table 3). In order to compare activations between IN and RC within the lateral PFC, the whole-brain statistical map of the main effect of RC was masked with the same ROI mask of the lateral PFC and used as a colored overlay in Figure 4 along with the main effect of IN (main effect of RC shown in red). These neural correlates of interference resolution partially overlapped with those of relational integration in bilateral MFG and IFG pars opercularis and IFG pars triangularis in the right hemisphere (Fig. 4, overlap of main effects shown in blue).

To assess the possibility that there may also be separable neural correlates of relational integration and interference resolution within MFG and IFG, we conducted exclusivity analyses to identify regions showing a main effect of RC (or IN) excluding all voxels that evidenced above-chance association with the other variable (defined by $P > 0.5$, a liberal criterion for association). We identified prefrontal regions that could be deemed exclusive for relational integration in bilateral MFG,
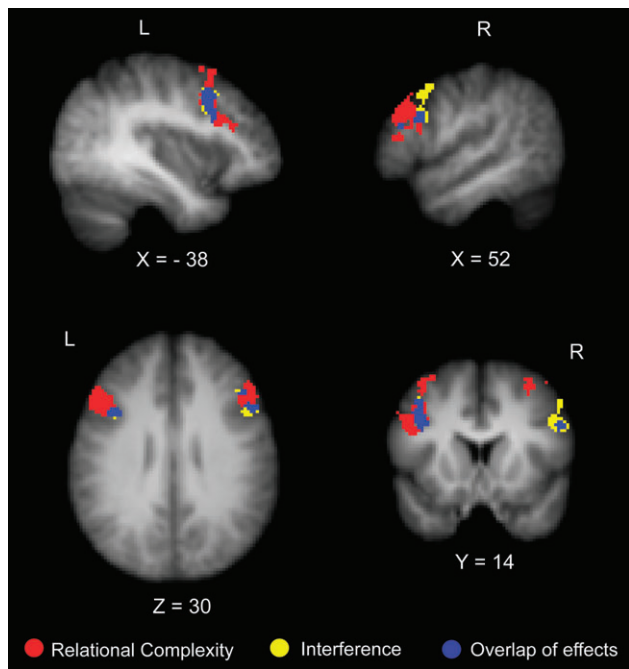
Figure 4. Regions showing the main effects of RC (shown in red), IN (shown in yellow; small volume corrected, cluster-forming threshold $t > 2.3$, cluster extent threshold, $P < 0.05$), and regions where main effects overlapped (blue) within an a priori defined anatomical ROI mask of the bilateral MFG and IFG pars opercularis and pars triangularis. R, right; L, left. Coordinates are in MNI space (mm).

Table 3

Summary of clusters for effects tested within an a priori defined anatomical mask combining bilateral MFG and IFG pars opercularis and pars triangularis (IFG tri)

	Hem	Region of Max	Voxels	Loci of Max			Max T	P	BA of Max
				x	y	z			
IN main	R	MFG	374	34	0	66	4.81	0.023	6
	L	MFG	209	−40	10	36	3.39	0.049	9
RC exclusive	L	IFG tri	654	−52	24	24	5.88	0.01	6
	R	MFG	349	56	24	32	4.22	0.02	9
IN exclusive	R	MFG	220	34	0	66	4.81	0.03	6
Underadditive interaction	L	IFG tri	278	−44	28	14	4.26	0.03	46
SME of RC at IN 0	L	IFG tri	1066	−52	24	24	6.54	0.001	46
	R	IFG tri	704	56	28	20	3.7	0.004	46
SME of IN at RC 1	L	IFG tri	425	−44	28	14	4.32	0.02	46
	R	IFG tri	419	44	28	20	4.13	0.02	46

Note: Loci of maxima are in MNI coordinates in mm. Hem, hemisphere; Max, maxima; BA, Brodmann's area.

IFG pars triangularis and pars opercularis and for interference resolution in the right MFG and IFG pars opercularis (small volume corrected, cluster-forming threshold, $t > 2.3$; cluster extent threshold, P's < 0.05, Table 3, Supplementary Fig. 5). The IN-exclusive region was lateralized to the right and more posterior compared with the RC-exclusive cluster. These results support the possibility that, in addition to overlapping neural mechanisms that are sensitive to processes common to relational integration and interference resolution, there may also be separable mechanisms corresponding to cognitive demands that are dissociable between the 2 components of analogical reasoning.

Analyses of interactive effects of RC and IN in the 2 a priori defined ROI masks revealed no significant overadditive interaction in either region (P's >0.05). However, 2 regions

yielded underadditive interactions between RC and IN (i.e., less activity was observed than would be expected from the sum of the main effects of the 2 factors). Within the lateral PFC ROI mask, a region encompassing the left MFG, IFG pars triangularis and pars opercularis was identified as exhibiting a significant underadditive increase in activation when multiple relational integration and interference resolution were required at the same time (small volume corrected, cluster-forming threshold, $t > 2.3$; cluster extent threshold, $P < 0.05$) (see Table 3, Supplementary Fig. 6A; for percent signal change of each condition compared with baseline, see Supplementary Fig. 6B). A second cluster in the right IFG was marginally significant (number of voxels, 170; locus of max Z, $x = 46$, $y = 28$, $z = 18$, MNI coordinates, mm; $P = 0.07$). The left IFG region showing underadditivity was part of larger clusters showing a simple main effect of RC at IN level 0 and a simple main effect of IN at RC level 1 (small volume corrected, cluster-forming threshold, $t > 2.3$; cluster extent threshold, P's < 0.05, Table 3). This region exhibiting underadditive interactive modulation partially overlapped with regions showing the main effect of RC and where the main effect of RC and IN overlapped. Within the bilateral frontal pole ROI mask, there was no significant underadditive interaction between RC and IN (P's > 0.05).

Discussion

The present neuroimaging study is the first to vary demands on multiple component processes of analogical reasoning within a single task. The PPA task allowed us to hold visuospatial complexity constant while manipulating both relational complexity and need for interference resolution. Using an event-related fMRI design, we identified cortical regions sensitive to increase in demands on relational integration, interference resolution, or both component processes of reasoning, as well as regions showing interactive modulation by RC and IN. These results support computational models of analogical reasoning in which both the integration of relations and the selection of critical relations among distractors are fundamental processes (Hummel and Holyoak 1997, 2003).

The main goals of the present study were 1) to test whether the lateral frontal pole is sensitive to demands on relational integration per se or to demands on interference resolution as well, 2) to test whether the lateral prefrontal regions known to be important for cognitive control in a diverse range of other cognitive tasks are also recruited for interference resolution during analogical reasoning, and 3) to examine the spatial overlap or separability between the neural correlates of relational integration and interference resolution.

To achieve the first goal, we used a whole-brain analysis to identify regions sensitive to RC variation. Clusters activated by an increase in RC were identified in lateral frontal pole, as well as in MFG, IFG, medial SFG, precuneus, thalamus, cerebellum in both hemispheres, and left superior parietal and visual cortex. To achieve our second goal, we used an ROI analysis of PFC regions to assess whether activity was modulated by level of IN during analogical reasoning. Regions sensitive to increase in demands on interference resolution were found in bilateral MFG and IFG pars opercularis and the IFG pars triangularis in the right hemisphere. In regards to our third goal, we found that regions showing sensitivity to IN partially overlapped with those that responded to increases in RC at the border of IFG and MFG, located in bilateral MFG and IFG pars opercularis and the right

IFG pars triangularis. In addition, we identified regions in the a priori defined ROI of the lateral PFC showing exclusive sensitivity to either RC or IN. In the a priori defined ROI of bilateral frontal pole, signal changes associated with RC were observed, consistent with findings in previous studies. In contrast, sensitivity to demands on interference resolution was not found, even when the statistical test was limited to functionally defined ROIs manifesting RC main effects from the whole-brain analysis within the left or right lateral frontal pole separately. These results suggest that there are common as well as distinct neural circuits within the prefrontal cortex that support cognitive control required for relational integration and interference resolution. The present findings lend support to computational models of the neural basis of analogical reasoning that include mechanisms corresponding to both relational integration and interference control (Morrison et al. 2004).

Relational Integration and the Lateral Frontal Pole

A number of previous fMRI studies support the importance of the most anterior portion of the lateral PFC in tasks requiring relational integration (Kroger et al. 2002; Christoff et al. 2001; Bunge et al. 2005; Green et al. 2006). Consistent with proposals that the lateral frontopolar region will be engaged when the outcomes of 2 or more relational comparisons must be integrated to arrive at a solution (Waltz et al. 1999; Christoff et al. 2001; Kroger et al. 2002), we found signal increases in the lateral frontal pole in both hemispheres related to increases in RC but not IN. By eliminating alternative explanations based on visual complexity or general cognitive difficulty, our results provide strong evidence supporting the hypothesis that the lateral frontal pole may play a distinct role in reasoning tasks that require the integration of multiple relations.

Other neuroimaging studies have found bilateral or right lateral frontopolar activation during complex cognitive paradigms involving a requirement to keep in mind a primary cognitive goal while performing concurrent subgoal(s) (Koechlin et al. 1999; Braver and Bongiolatti 2002). These and several other studies of the anterior lateral PFC, considered along with the anatomy of the anterior PFC, led Ramnani and Owen (2004) to suggest that the function of the anterior lateral PFC is to integrate the results of 2 or more separate cognitive operations. The present findings add to previous evidence that lateral frontopolar activation is selectively engaged by the need to integrate multiple relations to reason (Christoff et al. 2001; Kroger et al. 2002), whereas also showing that this region is not engaged by the need to resolve interference.

Interference Resolution and the Lateral PFC

The neural substrate for interference resolution has received much less attention in previous neuroimaging studies of analogical reasoning. However, interference resolution has been extensively studied in a wide range of cognitive tasks under the name of "inhibition," "selection," or "cognitive control." These studies include inhibition of a motor response (Konishi et al. 1998, 1999; Garavan et al. 1999; Aron et al. 2003), proactive interference resolution in working memory (Jonides et al. 1998; D'Esposito et al. 1999; Thompson-Schill et al. 2002), selection among competing alternatives (Thompson-Schill et al. 1997; Zhang et al. 2004), controlled semantic retrieval (Wagner et al. 2001; Badre et al. 2005) and inhibition of cognitive set

(Konishi et al. 2003). Reasoning tasks involving interference include inhibition of belief bias during deductive reasoning (Goel et al. 2000; Goel and Dolan 2003), overcoming perceptual mismatches in a truth table task (Prado and Noveck 2007), and avoiding heuristic bias during decision making (De Neys et al. 2008). Although the precise loci of reported anatomical regions vary across tasks and studies, lateral PFC has been consistently reported to be involved in resolving conflict or interference between representations.

In agreement with prior work on interference resolution, we found that interference resolution during reasoning led to increased activation in bilateral MFG and IFG, but not in the frontal pole in either hemisphere. These activations in the lateral PFC included a cluster in the left MFG and IFG in the vicinity of loci reported in previous studies focusing on interference resolution (Jonides et al. 1998; D'Esposito et al. 1999; Milham et al. 2001; Nelson et al. 2003; Zhang et al. 2004; Badre et al. 2005). Another cluster of activation sensitive to demands on interference was found in the right MFG and IFG, similar to regions identified in previous studies of both logical reasoning (Goel et al. 2000; Goel and Dolan 2003; Prado and Noveck 2007; De Neys et al. 2008) and response inhibition (Konishi et al. 1998; Garavan et al. 1999; Chevrier et al. 2007). In addition, a cluster in the right lateral PFC showed exclusive sensitivity to demands on interference resolution. Considered together with previous studies, our findings thus indicate that areas of the lateral PFC that have been identified as important in executive control in a variety of tasks are also activated by the need to resolve interference during analogical reasoning.

Recent studies of patients with PFC damage have also indicated the importance of inhibitory control in analogical reasoning, These patients perform poorly on analogy problems when semantically-related distracting information was present, even when the problems were relatively low in relational complexity (Morrison et al. 2004; Krawczyk et al. 2008). Morrison et al. (2004) applied a neural-network model of analogical reasoning, LISA (Learning and Inference with Schemas and Analogies; Hummel and Holyoak 1997, 2003) to account for selective reasoning deficits observed with the patients with PFC damage. Two parameters of the model proved to be essential in fitting the patient data. First, the rate of learning for analogical mappings based on multiple mappings was reduced, a computational process that can be identified with relational integration. Second, a parameter for inhibitory control was reduced, a computational process hypothesized to underlie control of interference. Due to the limited capacity of working memory inherent to the model, an inability to effectively limit intrusions from superficial distractors will impair learning of correct relational mappings, making incorrect analogical responses more frequent. Based on the framework suggested by the LISA model, brain regions activated when interference was present may serve to select relevant representations for processing in working memory. A similar mechanism has been described for the role of IFG in various cognitive functions (Badre and Wagner 2007).

The prefrontal regions that showed sensitivity to demands on interference resolution partially overlapped with those that were associated with demands on relational integration in the lateral PFC near the border of MFG and IFG. Because solving a PPA problem involving multiple relations requires assessing and comparing relations for each dimension sequentially (rather

than holistically), it is likely that relational integration and interference resolution both demand cognitive control for selectively activating representations in working memory and for rapid, flexible switching between inhibition and disinhibition (for sequential processing and integration of multiple relational representations). Regions showing sensitivity to both RC and IN may subserve this common component of cognitive control required for both relational integration and interference resolution.

Interactive Impact of Relational Complexity and Interference on Lateral PFC

By manipulating both relational complexity and need for interference resolution using a factorial design, we examined the interactive impact of increasing cognitive demands on both processes at once. We observed an underadditive modulation of activation due to joint requirements of multiple relational integration and interference resolution in the lateral PFC (bilaterally, but marginally significant in the right hemisphere), partially coinciding with regions where the main effects of RC and IN overlapped, and where the main effect of RC was found. This region showing an underadditive interaction was identified as being part of larger prefrontal clusters showing a simple main effect of IN at RC level 1 (but not at RC level 3) and simple main effect of RC at IN level 0 (but not at IN level 1), indicating that these regions exhibited significantly greater signal increase for interference resolution only at the lower level of RC, and for relational integration only at the lower level of IN (for percent signal change for each condition compared with intertrial interval baseline, see Supplementary Fig. 6B).

The underadditive pattern of interaction is consistent with findings in the dual-task literature. When component tasks that do not depend on the prefrontal cortex by themselves are combined into a dual task, activation in the prefrontal cortex increased during dual-task coordination (Corbetta et al. 1991; D'Esposito et al. 1995; Johannsen et al. 1997; Iidaka et al. 2000). On the other hand, when component tasks that themselves depend on the prefrontal cortex are combined into a dual task, activation in the prefrontal cortex is commonly found to be reduced or unchanged when both tasks are performed concurrently (Goldberg et al. 1998; Fletcher et al. 1998; Klingberg 1998). Kane and Engle (2002) argue that these results may reflect depletion of PFC-dependent executive resources when multiple tasks demanding prefrontal resources are performed simultaneously. Our results are consistent with these observations in that these 2 PFC-dependent components of analogical reasoning, relational integration and interference resolution, produce an underadditive level of activation of prefrontal cortex when engaged simultaneously. The observed underadditive interaction in the present study may reflect the depletion of a common pool of executive resources required for cognitive control when the brain has to integrate multiple relations while resolving interference. The overadditive behavioral interaction between RC and IN may result from overloading of limited-capacity executive mechanisms required for coordination of relational integration and interference resolution, and is manifested as prefrontal clusters showing an underadditive interaction. These results extend and generalize the observations from dual-task paradigms to the case of coordinating multiple, executive component processes in a single reasoning task. It should be noted, however, that we cannot exclude an alternative possibility that the underadditive interaction may be due to a physiological limit or saturation of BOLD signal increase in response to overloading cognitive demand. The hemodynamic response property of the BOLD signal as a function of cognitive load is an important question that should be addressed in future research.

Conclusion

By manipulating multiple cognitive demands simultaneously in a single reasoning task, the present study was able to provide new insights into the neural architecture of the component mechanisms underlying analogical reasoning. Our findings show that analogical reasoning, which requires integration of multiple relations in the face of interference, is associated with the coordination of activity in multiple, functionally dissociable regions of the prefrontal cortex. These subregions include those that are sensitive to demands on one component process, as well as regions that are jointly taxed by both relational integration and interference resolution. Our results strongly support the hypothesis associating the lateral frontal pole with relational integration, whereas demonstrating its insensitivity to interference resolution. We also observed further functional segregation in the lateral PFC, mapping onto common and dissociable components of cognitive control required for relational integration and interference resolution during analogical reasoning.

Supplementary Material

Supplementary material can be found at: http://www.cercor. oxfordjournals.org/.

Notes

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