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Localizing the rostrolateral prefrontal cortex at the individual level

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The functions of the rostrolateral prefrontal cortex (RLPFC) have recently become the target of multiple theories and empirical investigations. This region can be loosely defined as the lateral portion of Brodmann area (BA) 10. One of the challenges in testing theories about RLPFC functions is the difficulty in defining its boundaries when formulating predictions for its recruitment. Here we present a procedure that goes beyond the currently available anatomical definitions to attempt a functional localization of RLPFC. A combination of functional and anatomical criteria was employed, consistent with other localizer procedures. Functional localization was performed by comparing a relational condition involving relational matching to a control condition involving feature matching. It was expected that within an anatomically defined BA10 region, this procedure would produce functional activations in the lateral but not the medial subregions. The task was administered in the course of a single 13-min fMRI session. Results showed remarkable consistency, with all subjects activating RLPFC and activations consistently localized in the lateral part of BA10. These results demonstrate the practical feasibility of localizing RLPFC using a short procedure and a combination of functional and anatomical criteria. Such localization presents with a number of potential advantages for testing theories of RLPFC functions, including improved anatomical precision of experimental predictions, as well as the possibility of reduction in the rate of false-negative findings across studies. In addition, the results provide further support for the previously proposed functional dissociation between lateral and medial BA10.

Introduction

The rostrolateral prefrontal cortex (RLPFC) has recently become the centre of a minor explosion of investigations in the field of cognitive neuroscience, from both empirical and theoretical points of view. This region, which can be loosely defined as the lateral portion of Brodmann area (BA) 10, appears to be involved in some of the most complex and uniquely human cognitive functions (Christoff and Gabrieli, 2000; Gilbert et al., 2006b; Koechlin et al., 1999; Ramnani and Owen, 2004). RLPFC recruitment occurs across a wide range of domains (Christoff and Owen, 2006), from highly structured reasoning (e.g., Bunge et al., 2005; Christoff et al., 2001; Kroger et al., 2002), working memory (e.g., Braver and Bongiolatti, 2002; Koechlin et al., 1999) and episodic memory (e.g., Buckner et al., 1996; Rugg et al., 1998; Tulving et al., 1996) tasks, to the relatively unstructured state of rest (Andreasen et al., 1995; Christoff et al., 2004; Shulman et al., 1997; Smith et al., 2006). Therefore, achieving a better understanding of the functions of RLPFC can enhance our knowledge of neural mechanisms in many domains of human cognition.

Several theories about the function of RLPFC co-exist at present. One theory holds that the RLPFC is involved in metacognitive, introspective thought processes such as the evaluation of self-generated information (Christoff et al., 2001; Christoff et al., 2003). Another theory links the RLPFC to the processing of a hierarchy of goals, a process referred to as cognitive branching or sub-goal processing (Braver and Bongiolatti, 2002; Koechlin et al., 1999; Ramnani and Owen, 2004). Yet other theories emphasize mental processes such as establishing an "episodic retrieval mode" (Lepage et al., 2000; Rugg and Wilding, 2000), maintaining an abstract mental set (Christoff and Keramatian, 2007; Sakai and Passingham, 2003), or the goal-directed co-ordination of stimulus-independent and stimulus-oriented thought (Burgess et al., 2005).

Testing these theories and advancing our knowledge of RLPFC functions is a challenging endeavor marked by a number of difficulties. One of the biggest difficulties that investigators face is the question of how to define the boundaries of this region in formulating predictions for its recruitment. Current definitions rely exclusively on anatomical criteria, which presents with a number of disadvantages. At one extreme, predictions for RLPFC recruitment could be formulated as "any activations that occur within BA10." This definition, however, would include not only the lateral but also the medial portions of BA10, which are known to have distinct cytoarchitectonic (Ongur et al., 2003) and functional (Burgess et al., 2005; Gilbert et al., 2006a,b; Lane et al., 1997; Ochsner et al., 2004) properties. Indeed, a recent meta-analysis by Gilbert and colleagues (2006b) identified the RLPFC

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as a separate functional subdivision within BA10, having different functions than the rostromedial and ventromedial portions of BA10. Clearly, a definition of RLPFC that includes any activations within BA10 is too broad to be useful in testing theories of RLPFC functions.

At the other extreme, RLPFC could be defined as "the intersection between BA10 and the middle frontal gyrus," a definition which we have previously used (Christoff et al., 2001, 2003) to narrow the predicted anatomical boundaries of RLPFC so that it includes only the lateral portion of BA10. This definition, however, is too conservative in that it excludes the portions of superior and inferior frontal gyri that lie on the lateral surface of BA10.

Furthermore, both of these definitions are problematic because they can only be implemented within the standard stereotaxic space of Talairach and Tournoux (1988), which has only an indirect relation to individual anatomical space (Brett et al., 2001, 2002; Saxe et al., 2006) and does not take into account individual variability in cytoarchitectonic boundaries. The recent emergence of probabilistic cytoarchitectonic maps (Eickhoff et al., 2006; Eickhoff et al., 2005) presents a strong alternative to reliance on the Talairach stereotaxic reference system. Such probabilistic maps can be used to define *a priori* regions of interest and to identify the location of functional activations**.** However, while probabilistic cytoarchitectonic maps have been developed for a number of cortical areas, including BA44, 45, 6, 4a, 3b, 17 and 18, this method is not yet available for application to studies focusing on BA10, since a cytoarchitectonic probabilistic map does not yet exist for this cortical region.

Another possible approach towards alleviating difficulties in RLPFC definition may be to move beyond the use of strictly anatomical criteria towards developing a procedure for the functional localization of this region. Such a procedure could allow us to identify the relevant portion of BA10 with improved precision, and to formulate predictions of RLPFC recruitment with greater clarity. Furthermore, if it proves reliable at activating RLPFC at the individual level, a functional localizer procedure could allow us to test hypotheses not only at the standard group-analysis level, but for individual subjects too. This would allow for a test against group-level false negative findings that may result from unaccounted anatomical variability across subjects (Brett et al., 2002). In addition, the ability to functionally define RLPFC within each subject may improve the sensitivity of group-level analyses — an effect which has been reported for other brain regions (Saxe et al., 2006; Swallow et al., 2003).

Although well-established functional localizer tasks exist for a number of regions such as the motor cortex (Kim et al., 1993), visual cortex (Sereno et al., 1995), the parahippocampal place area (PPA) and the fusiform face area (FFA) (e.g., Epstein and Kanwisher, 1998; Kanwisher et al., 1997), there is at present no available equivalent procedure for the RLPFC. Here we aimed to develop such a procedure based on a combination of a functional localizer task and anatomical landmarks, in line with existing localizers. We also sought a task that can be administered in the course of a single scanning session, as is standard for localizer tasks (Saxe et al., 2006).

To this end, we chose a relatively simple task (Fig. 1) that has been shown to activate the RLPFC at the group level (Christoff et al., 2003). This task, which can be described as a relational matching-to-sample task (Thompson et al., 1997), involves a second-order comparison between the relations formed by two

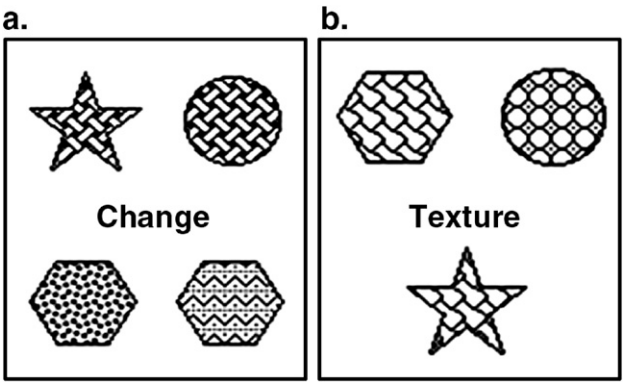

Fig. 1. Examples of stimuli for the RLPFC localizer task. (a) The relational condition required a second-order (relational) comparison: subjects had to infer the dimension of change between the top pair of objects (texture or shape) and then determine whether the bottom pair of objects changed along the same dimension. (b) The control condition required a first-order (feature) comparison: subjects had to determine whether the bottom object matched either one of the top two objects along the specified dimension (texture or shape). The correct answers to the examples shown here are (a) "no" and (b) "yes".

pairs of objects. This process, also known as "relational matching", represents one of the basic cognitive processes associated with RLPFC activation (Christoff et al., 2003). It recruits RLPFC with remarkable consistency during paradigms such as the Raven's Progressive Matrices (Christoff et al., 2001; Kroger et al., 2002) and analogical reasoning (Bunge et al., 2005; Green et al., 2006). The task employed here, however, requires relational matching in the absence of complex reasoning processes, which presents a strong advantage for developing an easy to administer and relatively short localizer task. Finally, while this task has previously been used in a relatively long event-related study designed to examine different processing stages (Christoff et al., 2003), here the task was employed in a blocked design fashion in order to reduce the total experimental time while improving the efficiency of design (Mechelli et al., 2003). We hypothesized that within a defined search space consisting of both lateral and medial BA10, this procedure would consistently activate only lateral BA10 and that this lateral activation would be consistently observed at the individual subject level.

Whenever BA10 functions are under investigation, special consideration needs to be given to the commonly observed blood oxygenation level-dependent (BOLD) signal attenuations and distortions due to susceptibility artifacts in this region. Such artifacts arise due to susceptibility differences between ethmoidal air cells and brain tissue, which result in signal attenuation in regions adjacent to bone and air sinuses (Ojemann et al., 1997). These artifacts may result in partial or complete signal loss from the ventromedial and frontopolar regions. Whereas distortions can be corrected (Jezzard and Balaban, 1995), signal loss cannot be compensated for. Therefore, it is necessary to ensure that the absence of activation in these regions is not simply due to signal loss. While the quality of signal in susceptibility regions can be enhanced through region-specific shimming (Guo and Song, 2003), this usually leads to decreased signal quality in other brain regions. Since the present study is the first to investigate an RLPFC localizer procedure, it was important to examine the overall pattern of brain activation, and not just activations in BA10. Therefore, a

whole-brain shimming approach was employed, optimizing the quality of signal throughout the brain. However, the quality of signal in BA10 and the ability to detect activations throughout its extent was assessed through separate analyses. This was important in order to ensure that the hypothesized lack of activation in medial BA10 in the relational versus control task comparison was not due to signal loss.

Materials and methods

Participants

Ten right-handed University of British Columbia (UBC) students (mean age 19; age range 18–23; 4 female) gave their written consent to participate and received either course credit or $20/h as compensation. All participants had normal or corrected vision and were screened for MRI compatibility. Procedures were approved by the UBC Clinical Research Ethics Board and by the UBC High Field Magnetic Imaging Centre.

Experimental task

The task was administered in the course of a single 13-min session. The stimuli consisted of 6 different geometric shapes (triangle, square, star, circle, hexagon, cross) filled with one of 6 different textures (Fig. 1). In the relational condition (Fig. 1a), subjects were presented with 2 pairs of objects (top and bottom). They had to infer the dimension of difference between the top two objects (objects differed either in terms of their shape or their texture), and then determine whether the bottom two objects differed along the same dimension. For example, in Fig. 1a, the top two objects differ only in their shape, while the bottom two objects differ in terms of their texture, but not their shape. The correct response, therefore, would be "no". In the control condition (Fig. 1b), subjects were presented with 3 objects, and had to determine if the bottom object matched either one of the top two objects along the specified dimension (either shape or texture). For example, in Fig. 1b, the star (the bottom object) matches the hexagon (one of the top objects) along the specified dimension (texture). The correct response, therefore, would be "yes".

The relational and control conditions were presented in 24 alternating blocks (12 blocks per condition). Each block was 32 s long and was preceded by 1 s of instructions. In the relational condition, the instructions stated "Match Change". In the control condition, they were either "Match Shape" or "Match Texture". The stimuli were displayed on the screen until the subject's response, but no longer than 3500 and 2800 ms for the relational and control conditions respectively. Following the subject's response or the end of the maximum stimulus duration, a blank was displayed for the remaining trial duration. There were 8 trials per block in the relational condition and 10 trials per block in the control condition. During scanning, stimuli were presented on a screen located above the participant's head, using a magnet-compatible back projection method. Subjects responded with their right hand, pressing one of two buttons on a handheld button box, to indicate their response ("yes" or "no").

fMRI data acquisition

Data acquisition was performed using a 3.0 Tesla Intera MRI scanner (Best, Netherlands). An eight element, six channel phased array head coil with parallel imaging capability (SENSE) (Pruessman et al., 1999) was positioned around the participant's head to obtain the MRI signal. Head movement was restricted using foam padding around the head. The functional volumes contained BOLD contrast intensity values and were acquired using a T2*-weighted single shot echo-planar imaging (EPI) gradient echo sequence sensitive to BOLD contrast [time of repetition (TR)=1000 ms; echo time (TE)=30 ms; flip angle (FA)=90°; field of view (FOV) =24×24 cm^2; matrix size 80×80, reconstructed to 128×128, SENSE factor=2.0]. The volumes covered the whole brain and consisted of 19 slices (each 6 mm thick, separated by a 1 mm inter-slice gap) acquired parallel to the anterior commissure/posterior commissure (AC/PC) line. A total of 796 functional volumes were acquire for each participant over 13 min (1 session).

Prior to functional imaging, an inversion recovery prepared T1-weighted fast spin-echo anatomic volume was obtained for each participant (TR=2000 ms; TE=10 ms; spin echo turbo factor=8, FA=90°; FOV=24×24 cm^2; 256×256 voxels, inversion delay IR=800 ms), containing 19 slices (6 mm thick, separated by 1 mm skip) acquired in the same slice locations used for functional images.

fMRI data analysis

Preprocessing

Data were preprocessed and analyzed using SPM5 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Prior to analysis, all images underwent a series of preprocessing steps. Slice-timing correction to correct for the different sampling times of the slices was performed by interpolating the voxel time series using sinc interpolation and resampling with the middle (tenth) slice as a reference point. All functional volumes were realigned to the first one in the time series to correct for between-scan motion. The structural T1-weighted volume was segmented to extract a gray matter image for each subject, which was spatially normalized (Ashburner and Friston, 1999) to a gray matter image of the MNI template. The derived spatial transformations for each subject were applied to the realigned functional volumes, in order to bring them into standardized MNI space. After normalization, all volumes were resampled in 2×2×4 mm voxels using sinc interpolation in space. Finally, the T2*-weighted volumes were then smoothed using a Gaussian kernel with 8 mm full-width at half-maximum (FWHM), in order to account for any residual between-subject variation and allow application of Gaussian random field theory to provide for corrected statistical inference (Friston et al., 1994).

Whole-brain analysis

Whole-brain voxel-wise analyses were performed to assess the magnitude of difference between the relational and control condition at each voxel. To remove low-frequency drifts in the BOLD signal, the data was high-pass filtered using an upper cut-off period of 128 s. Condition effects at each voxel were estimated according to the general linear model (Friston et al., 1995), using a single regressor of interest (a boxcar convolved with the canonical HRF), modeling the relational task. A regressor modeling the control task was not necessary to include in the model as it would have simply consisted of the inverse of the relational task regressor. Regionally specific effects were estimated by positively or negatively weighting the parameter estimate for the relational task regressor in linear contrasts. A positive weight was used to form

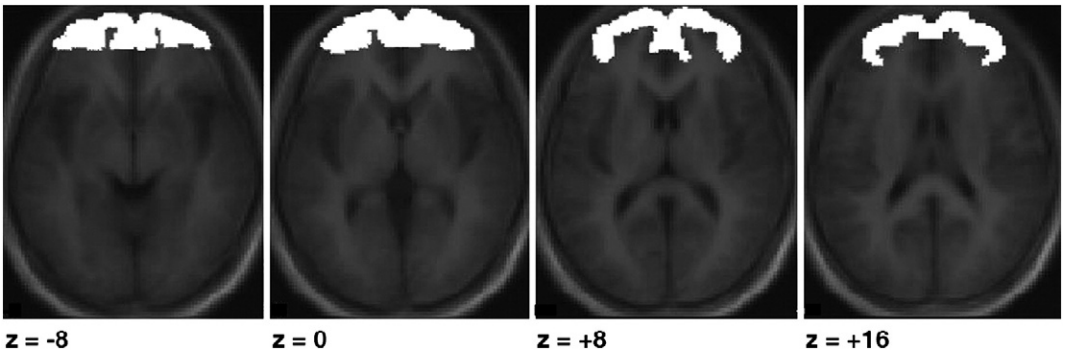

Fig. 2. Anatomical BA10 mask used to define the search space, overlaid on the averaged anatomical image across participants.

the relational versus control task comparison, while a negative weight was used to estimate the opposite control versus relational task comparison. To ensure that statistical analysis was performed in all brain regions, including those where signal may have been low as a result of susceptibility artifacts, an anatomically defined gray matter mask was created and explicitly specified during analysis.

RLPFC localization

Localization was performed using a combination of anatomical and functional criteria for each individual subject. An anatomically-defined BA10 mask in MNI space (Fig. 2) was used to define the search space for voxel-wise SPM analysis. The mask was constructed using labels from the Talairach Daemon database (http://ric.uthscsa.edu/RIC_WWW.data/Components/talairach/talairachdaemon.html). The mask consisted of all voxels labelled as BA10 and was transformed from Talairach into MNI space by applying transformation parameters derived from normalizing the Talairach gray matter image to the SPM5 gray matter template (Brett et al., 2001). It was then smoothed with an 8 mm isotopic Gaussian kernel thresholded at 0.2 intensity value. The areas reported below consist of voxels that survived a threshold of $P<0.05$ corrected for multiple comparisons across BA10, corresponding to an average $Z>3.69$ (range $Z>3.44$ to $Z>3.88$ across participants).

Whole-brain probabilistic activation map

In order to examine activations occurring outside of BA10, a probabilistic map of activations for the relational versus control contrast was created. First, a binary image was created for each subject using the individual level of analysis. These images contained all voxels surviving a threshold of $P<0.05$ ($Z>4.80$) corrected for multiple comparisons across the entire gray matter volume and voxels surviving $P<0.05$ ($Z>3.69$) corrected for multiple comparisons within BA10. Voxels surviving this threshold were assigned a value of 1, while the remaining voxels were assigned a value of 0. The resulting binary images were summed to create a probabilistic map containing values ranging from 0 (voxels that no subject activated) to 10 (voxels activated by all 10 subjects).

Activation differences in medial prefrontal cortex

Since the main hypothesis of this experiment stated that the relational versus control condition would activate the lateral but not the medial prefrontal cortex, it was necessary to verify that any lack of activations in medial prefrontal cortex was not simply due to the inability to detect activations in medial BA10. In order to assess this, deactivations across BA10 were examined by comparing the control condition to the relational condition. If such deactivations are present, it can be argued with greater confidence that the absence of activations in medial BA10 in the relational versus control condition comparison is not simply due to artifacts.

To examine such deactivations, regionally specific effects were first estimated at the individual level. Group analysis was performed using a random effects model by entering the estimated individual contrast images into a voxel-specific regression across participants. The search volume was restricted to all voxels within BA10 using the previously described mask. Since the reverse contrast was not specifically designed to activate medial BA10, the threshold for significance was set at a relatively lenient threshold, $P<0.05$ ($Z>1.64$) uncorrected. The foci of maximum activation were displayed on an anatomical image created by averaging the normalized individual T1-weighted images.

Results

Behavioral results

Subjects maintained a high level of performance throughout the task. Mean accuracy was 92.31%, and was lower during the relational condition ($M=88.85\%$, range = 79.17–95.83%) compared to the control condition ($M=95.08\%$, range = 90–99.17%), as indicated by a repeated-measures ANOVA ($F_{1,9}=32.05$, $P<0.001$). Mean reaction time for correct responses was 1719.6 ms. Reaction times were on the average slower during the relational condition ($M=2042.3$ ms, range = 1540.4–2424.0 ms) than during the control condition ($M=1396.9$ ms, range = 1177.4–1551.1 ms) ($F_{1,9}=134.84$, $P<0.001$).

fMRI results

The activation maxima for the relational versus control comparison for each subject are shown in Fig. 3 and a representative list of foci is given in Table 1. Every subject activated BA10 significantly at the $P<0.05$ corrected level. The volume of activated area ranged from 5.65 cm^3 (353 voxels;[1]

[1] The voxel numbers reported here concern the resampled voxels, each of which was 16 mm^3, or 2×2×4 mm.

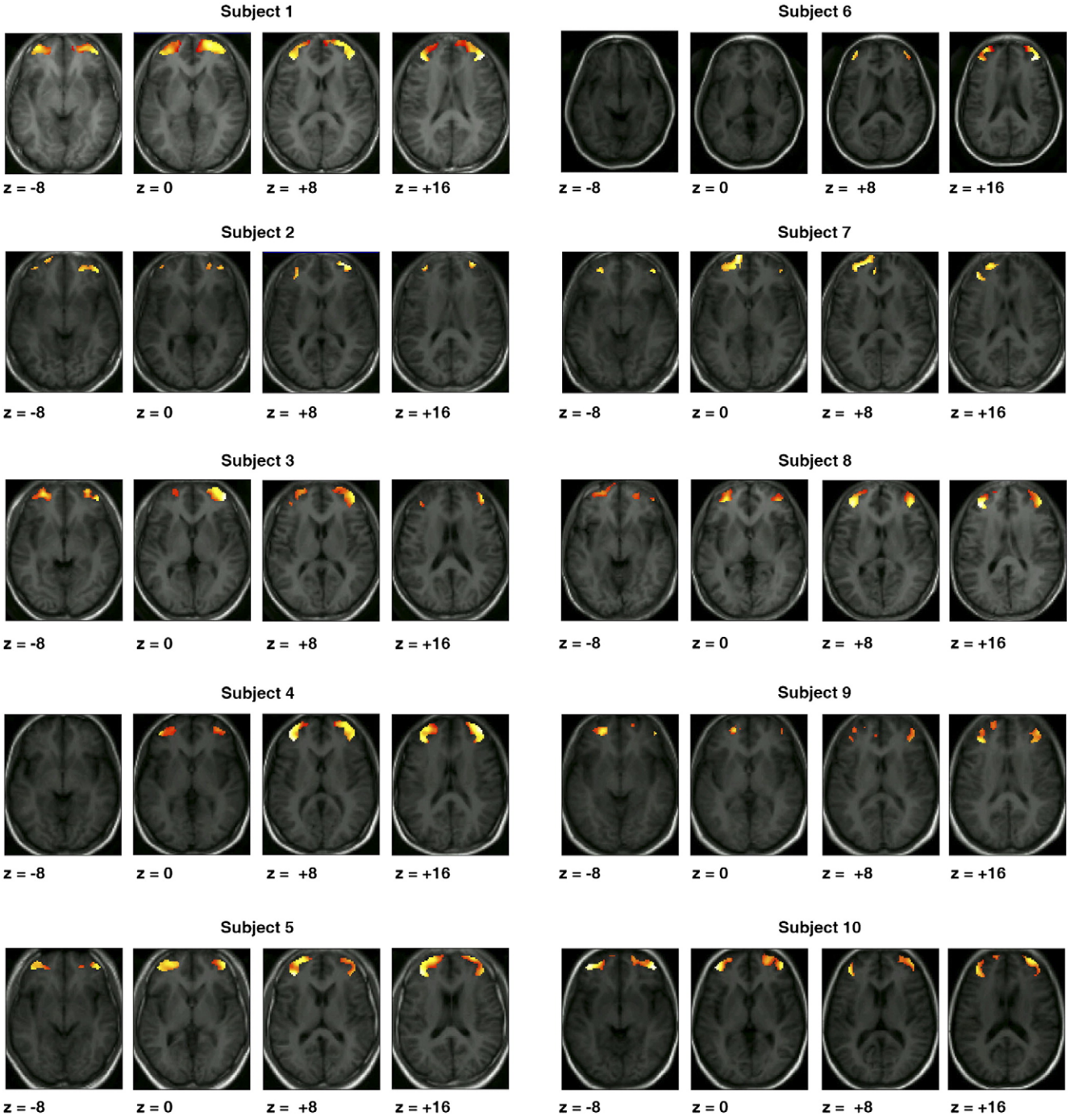

Fig. 3. Regions of activations for each individual subject in the relational versus control condition comparison ($P<0.05$ corrected), displayed on the individual subject's normalized structural image. Search space for individual voxel-based analysis was defined by a structurally defined BA 10 mask, including both the lateral and medial aspects of this region.

Subject 2) to 23.34 cm^3 (1459 voxels; Subject 1), with a mean of 12.89 cm^3 (806 voxels) across subjects. Activation was observed bilaterally in all subjects. The mean number of activated voxels was 392 (S.E.=64.18) in the left hemisphere and 413 (S.E.=70.17) in the right hemisphere, and did not differ significantly between the two hemispheres ($T_9=0.31$, $P=0.77$).

In all 10 subjects, activations were localized in the lateral part of BA10. No medial BA10 activations were observed, with the exception of one subject (Subject 9), for whom a small cluster of activation (20 voxels) was observed in the ventromedial part of BA10. This cluster, however, represented only 2.8% of the activations observed for this subject; the remaining 690 activated voxels were localized within lateral BA10.

Activations outside of BA10 were examined using a wholebrain probabilistic activation map. Fig. 4 shows this activation map for voxels that were activated by 6 or more subjects. A number of

Table 1
Activation foci within BA10 for the relational versus control task comparison

Subject	Left hemisphere (BA10)						Right hemisphere (BA10)					
	No. of voxels	Gyrus	Co-ordinates			*T*-value	No. of voxels	Gyrus	Co-ordinates			*T*-value
			x	*y*	*z*				*x*	*y*	*z*	
1	613	MFG	−38	42	16	20.93	846	MFG	42	44	16	22.6
		MFG	−34	58	−8	15.88		MFG	42	52	−8	17.96
2	54	SFG	−36	54	16	7.36	256	MFG	30	62	12	9.21
	25	MFG	−42	56	−4	5.37		MFG	44	50	−8	6.85
3	212	SFG	−30	62	−12	12.18	467	IFG	44	52	0	13.93
		MFG	−28	64	12	7.22		MFG	42	58	12	10.96
4	494	MFG	−42	50	12	15.38	493	MFG	38	58	20	16.03
		MFG	−34	60	12	12.73		SFG	40	56	16	15.28
5	796	MFG	−38	44	12	13.05	472	MFG	46	56	−4	10.82
		MFG	−40	50	20	11.88		SFG	32	64	16	8.72
6	199	SFG	−30	54	12	23.92	200	MFG	38	42	20	29.8
		MFG	−32	42	24	19.31						
7	377	SFG	−14	70	0	8.41	25	MFG	44	50	−8	6.3
		SFG	−24	60	8	7.44						
	43	MFG	−42	46	20	7.65						
8	446	MFG	−38	42	16	14.66	334	MFG	42	46	12	13.05
		SFG	−28	60	−4	7.37		SFG	20	56	−12	5.97
9	188	MFG	−36	44	24	11.62	271	MFG	34	40	20	8.35
	151	MFG	−26	54	−12	9.18	20	MedFG	2	60	−12	5.03
	80	SFG	−16	58	20	5.79		MedFG	8	58	−12	4.64
10	358	IFG	−46	52	0	13.33	496	MFG	46	54	−8	13.96
		SFG	−38	48	24	11.27		SFG	36	62	16	9.99

Activation maxima for voxels surviving $P<0.05$ corrected for multiple comparisons within BA10 are reported. Where the cluster encompassed more than one gyrus, more than one activation foci are reported for representativeness. Gyral distinctions are based on standard Talairach space. Abbreviations: BA, Brodmann Area; MFG, middle frontal gyrus; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; MedFG, medial frontal gyrus.

regions emerged as being consistently activated by at least 9 out of 10 subjects. In the right hemisphere, lateral BA10 and the borderline region of 10/46 were the only prefrontal cortex regions of activation. The only other right hemisphere regions of activation observed were in the visual cortex (BA 17 and 18) and the parietal cortex (BA 40). In the left hemisphere, the observed anterior prefrontal cortex activation extended from BA10 into the adjacent BA 9 and BA 46. Outside of the prefrontal cortex, the regions of activation were similar to those observed in the right hemisphere, including left visual cortex (BA 17, 18) and parietal cortex (BA 40/7).

Whereas medial prefrontal cortex was not activated in the relational versus control condition comparison, medial BA10 activations were observed in the reverse comparison, i.e., when the control condition was compared to the relational condition. A group level analysis of BA10 activations in the control versus relational comparison is displayed in Fig. 5. A cluster of activation within medial BA10 emerged from this analysis, with activation maximum at *x*, *y*, *z*=0, 62, 8 ($P<0.001$ uncorrected, $Z=3.22$).

Discussion

The localizer procedure described here activated the lateral portion of BA10 at the individual level with remarkable consistency, demonstrating the practical feasibility of localizing RLPFC using a short procedure and a combination of functional and anatomical criteria. Across subjects, activations were consistently localized in the lateral portion of BA10, supporting the

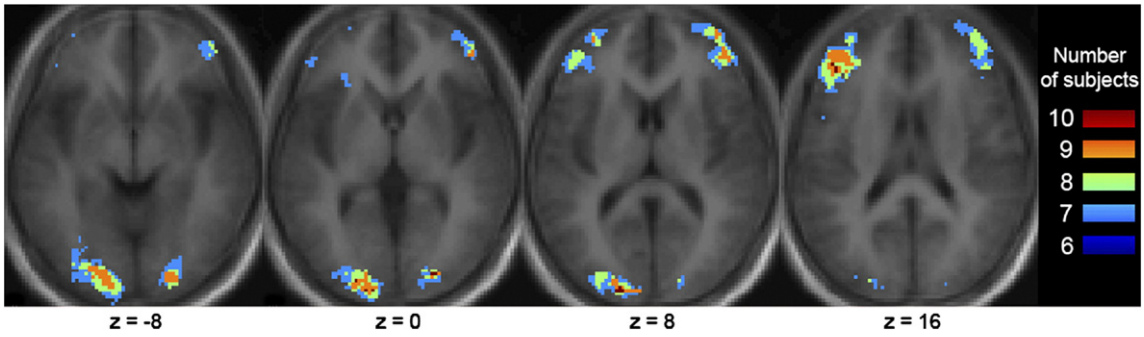

Fig. 4. Whole-brain probabilistic activation map for the relational versus control task comparison. The figure shows voxels that were activated by 6 or more subjects, thresholded at $P<0.05$ corrected at the individual level of analysis, overlaid on the average anatomical image.

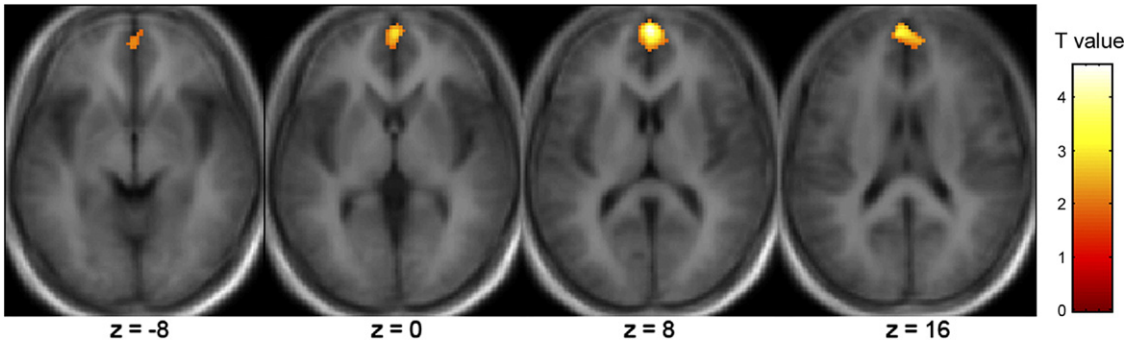

Fig. 5. Regions of activation at the group level of analysis in the control versus relation condition ($P<0.05$ uncorrected) overlaid on the average anatomical image. Search space was defined at the group level by a structurally defined BA10 mask, including both the lateral and medial aspects of this region.

notion that the RLPFC is a distinct functional subregion of BA10 (Christoff et al., 2003; Gilbert et al., 2006a; Koechlin et al., 2000). The reliability of RLPFC activation across individuals is particularly striking, especially in the context of the high variability of activations typically observed in fMRI studies of higher cortical regions (e.g., Braver et al., 1997; Brett et al., 2002).

The observed lateral BA10 activation in the context of no medial BA10 activation for the relational versus control condition comparison is in line with previously proposed functional dissociations between the lateral and medial rostral prefrontal regions. Such dissociations have been reported in multiple tasks, including those involving expected versus unexpected sequences of events (Koechlin et al., 2000), prospective memory (Burgess et al., 2003), and low versus high cognitive demand (Gilbert et al., 2006a). The results reported here provide additional support for this distinction, by demonstrating that lateral BA10 can be functionally separated from medial BA10 at the individual subject level. Furthermore, the findings of activation in medial BA10 for the reverse (control versus relational task) comparison demonstrate that the absence of activation in medial BA10 for the main (relational versus control task) comparison was not simply due to subthreshold differences or lack of statistical power; rather, activations in this region tended to occur in the opposite direction. The present results, however, are only possible to interpret with confidence in respect to the more dorsal aspects of medial prefrontal cortex. A potential caveat should be noted in regards to the most ventral regions of the medial prefrontal cortex, which are subject to the strongest susceptibility artifacts. Since the present study optimized the signal from the whole brain rather than specifically from the medial prefrontal cortex, lower statistical power in these ventral prefrontal regions remains a possibility.

While the RLPFC was activated in all subjects, a whole-brain analysis also revealed a number of activation areas outside of BA10, which were observed consistently across subjects (Fig. 4). Within the prefrontal cortex, the only area of activation outside of BA10 was the left anterior mid-dorsal PFC, bordering left BA10. Outside of prefrontal cortex, consistent activations across subjects were observed in bilateral parietal and occipital cortices. The observation of activations outside of the target anatomical region in functional localizer tasks is not unique to the present procedure. Previously published functional localizers have also reported activations extending beyond the anatomically defined region of interest (e.g., Kourtzi and Kanwisher, 2000). Thus, an approach involving a combination of anatomical and functional landmarks was employed here, similarly to other localizer procedures. In future studies, however, it may be possible to improve the present procedure by matching more closely the two experimental conditions in terms of overall visual and attentional demands, in order to reduce reliance on anatomical markers. Matching visual and attentional demands between conditions has been shown to reduce and sometimes eliminate posterior cortical activations in cognitive contrasts designed to activate prefrontal regions (Christoff et al., 2001; D'Esposito et al., 1997).

The fMRI acquisition parameters utilized in the present study were selected to optimize BOLD signal across the whole brain in order to enable standard whole-brain voxel-wise analysis. However, the sensitivity of this localizer procedure may be further improved by selecting acquisition parameters to optimize BOLD signal from the anterior prefrontal cortex. This may be achieved through region-specific BA10 shimming (Guo and Song, 2003) or by optimizing the amplitude of the slice-select refocus gradient for each individual slice (Wild et al., 2002). Although optimization of signal quality within BA10 may reduce the sensitivity in other parts of the brain, such optimization may better enable the quantification of the variability and extent of RLPFC across subjects. While signal drop-out did not preclude testing the main hypotheses of the present study, variability of signal quality across subjects did occur, precluding us from examining with precision the individual variability of task-related activations within BA10.

The localizer procedure described here could yield a number of potential advantages for testing theories of RLPFC functions. It may allow for improved definition of the hypothesized region of interest (ROI), by helping define the boundaries of RLPFC more precisely than is possible based on anatomical criteria alone. In previous studies (Christoff et al., 2001, 2003), we have used anatomical information in standardized space to define RLPFC as "the intersection between BA10 and the middle frontal gyrus". While the middle frontal gyrus lies exclusively on the lateral surface of BA10, the superior frontal gyrus covers both the lateral and the medial surface. Anatomical definitions of RLPFC based on the intersection between gyri and BA10 would, therefore, be necessarily either too conservative (if the superior frontal gyrus is excluded) or too liberal (if included). The functional localizer procedure employed here, on the other hand, allows for a more precise definition: it reliably distinguishes between the lateral and medial part of the superior frontal gyrus, by activating only the lateral part. Finally, by providing a more precise definition of the boundaries of the hypothesized region of interest, hypotheses as to the lack of RLPFC involvement in particular tasks and mental processes could be tested more precisely. Determining which tasks

do not engage the RLPFC is just as important for understanding its functions, as identifying the tasks that do engage this region.

In addition, the present RLPFC localizer procedure could help improve the sensitivity of tests of RLPFC function, by helping overcome some of the limitations of traditional inter-subject averaging. One such limitation is the potential for false-negative findings due to between-subject variability in functional anatomy; if functional areas are not well aligned between individuals, there might appear to be no location at which there is an average increase in activation, even if all subjects have activated a homologous region (Brett et al., 2002). Higher-order regions, such as the RLPFC, are particularly likely to exhibit a high degree of inter-subject variability in localization (Brett et al., 2002). By performing functional localization at the individual level, and then group-averaging these individually defined ROIs in a subsequent task, a region's selectivity can be improved. Examples of such improved selectivity to a process of interest have been reported for a number of regions, including the FFA (Saxe et al., 2006), which exhibits higher selectivity when its area is defined functionally at the individual level compared to when it is defined in a typical group analysis. Analogous results have been reported for the frontal eye-field (FEF) and the MT+ complex (Swallow et al., 2003). The functional localizer procedure described here may provide a similar advantage of increased sensitivity of group-level analysis in tests of RLPFC function, and may help reduce the number of false negative findings.

Functional localizers can be included in an experiment either as a separate session, in addition to the sessions of the main experiment (Epstein and Kanwisher, 1998; Kanwisher et al., 1997), or as one of the comparisons in a factorial design (Friston et al., 2006). Both of these methods have their own advantages and disadvantages (Friston and Henson, 2006; Friston et al., 2006; Saxe et al., 2006). The procedure presented here can be readily used as a separate session. In addition, the cognitive manipulation it employs (relational versus feature matching) provides clues about how to design factorial experiments that would contain the necessary comparison in order to allow for RLPFC localization.

Having an available functional localizer procedure for the RLPFC also provides a strong advantage for the development of novel methods for studying RLPFC functions, such as those employing real-time fMRI (Christoff et al., 2006) and developmental neuroscience methods for studying the maturation and early development of RLPFC functions (Bunge and Zelazo, 2006). In real-time fMRI, the analysis and display of results occurs simultaneously with signal acquisition, and real-time fMRI information about the level of activation in a particular region can be presented to subjects while they are being scanned (Caria et al., 2007; deCharms et al., 2004, 2005; Posse et al., 2003). This technique allows us to test whether subjects can learn to control the level of activation in a target ROI by engaging in a particular mental process (deCharms et al., 2004, 2005). We have recently suggested that this may provide a valuable additional method for testing RLPFC functions (Christoff et al., 2006), that goes beyond the traditional task-based paradigms by allowing both the subject and the experimenter to observe the moment-to-moment effect that a given mental process has on RLPFC signal. Using a functional RLPFC localizer procedure in order to define the target ROI for real-time fMRI training would provide much more precise and sensitive definitions than possible based on the currently available anatomical definitions used in real-time fMRI (e.g., deCharms et al., 2004).

In addition to the potential increase in sensitivity, such individualized definitions may be of particular use for detecting changes in RLPFC during the course of development (Bunge and Zelazo, 2006; Crone et al., 2006). The limitations of traditional inter-subject averaging on functional localization are of particular relevance to developmental studies; the brains of children differ from the commonly used anatomical templates to a greater extent than adult brains, which increases the error in spatial normalization (Wilke et al., 2002, 2003). Thus, individual functional localization could be particularly advantageous when applied in developmental research.

The present localizer procedure employed a particular cognitive process, relational matching, to activate the RLPFC. This process is present in a variety of reasoning and working memory tasks that have been reported to produce RLPFC activation. However, since a range of other cognitive tasks and mental processes have been shown to activate the RLPFC, the usefulness of the present procedure to serve as a functional localizer for different cognitive tasks, especially those that do not involve relational processing, remains to be determined by further empirical investigations. At present, no functional subdivisions within the RLPFC have been identified and the tasks that have been reported to activate the RLPFC produce largely overlapping activations. Thus, episodic retrieval and working memory – two tasks that together account for more than half of the reported RLPFC activations in the literature (see Gilbert et al., 2006b) – produce overlapping clusters of RLPFC activation, as demonstrated both in meta-analyses such as those published by Gilbert et al. and in individual studies where both tasks have been employed (e.g., Ranganath et al., 2003). A Hotelling's *T*-test conducted on the lateral activation maxima of the episodic and working memory studies included in the meta-analysis by Gilbert and colleagues indicates that the activation maxima for these two tasks do not differ significantly ($F_{2,39}=1.84$, $P=0.16$). Thus, the relational matching task used in the present localizer procedure could prove helpful as a functional localizer for working memory, episodic memory, as well as reasoning tasks, but the extent of this usefulness remains to be determined.

Research and discussion about the functional role of the RLPFC in human cognition began more than 10 years ago, with the publication of the first paper to specifically identify the RLPFC as a separate functional region of the prefrontal cortex (Baker et al., 1996). Although debates about the specific functional role of the RLPFC continue to this day, the results of the present study demonstrate that in the course of the last 10 years, sufficient knowledge has been accumulated to allow for the design of a task that reliably activates RLPFC at the individual subject level in a single scanning session. It is our hope that this functional localizer procedure will prove a useful addition to the available tools for investigating the functions of this nebulous and yet highly intriguing cortical region.

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References

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1995. Remembering the past: two

facets of episodic memory explored with positron emission tomography. Am. J. Psychiatry 152, 1576–1585.
Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7, 254–266.
Baker, S.C., Rogers, R.D., Owen, A.M., Frith, C.D., Dolan, R.J., Frackowiak, R.S.J., Robbins, T.W., 1996. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 34, 515–526.
Braver, T.S., Bongiolatti, S.R., 2002. The role of frontopolar cortex in subgoal processing during working memory. NeuroImage 15, 523–536.
Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. NeuroImage 5, 49–62.
Brett, M., Christoff, K., Cusak, R., Lancaster, J., 2001. Using the Talairach atlas with the MNI template. NeuroImage 13, S85.
Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. Nat. Rev., Neurosci. 3, 243–249.
Buckner, R.L., Raichle, M.E., Miezin, F.M., Petersen, S.E., 1996. Functional anatomic studies of memory retrieval for auditory words and visual pictures. J. Neurosci. 16, 6219–6235.
Bunge, S.A., Zelazo, P.D., 2006. A brain-based account of the development of rule use in childhood. Curr. Dir. Psychol. Sci. 15, 118–121.
Bunge, S.A., Wendelken, C., Badre, D., Wagner, A.D., 2005. Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. Cereb. Cortex 15, 239–249.
Burgess, P.W., Scott, S.K., Frith, C.D., 2003. The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. Neuropsychologia 41, 906–918.
Burgess, P.W., Simons, J.S., Dumontheil, I., Gilbert, S.J., 2005. The gateway hypothesis of rostral prefrontal cortex (area 10) function. In: Duncan, J., Phillips, L., McLeod, P. (Eds.), Measuring the Mind: Speed, Control, and Age. Oxford Univ. Press, Oxford, pp. 217–248.
Caria, A., Veit, R., Sitaram, R., Lotze, M., Weiskopf, N., Grodd, W., Birbaumer, N., 2007. Regulation of anterior insular cortex activity using real-time fMRI. NeuroImage 35, 1238–1246.
Christoff, K., Gabrieli, J.D.E., 2000. The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. Psychobiology 28, 168–186.
Christoff, K., Owen, A.M., 2006. Improving reverse neuroimaging inference: cognitive domain versus cognitive complexity. Trends. Cogn. Sci. 10, 352–353.
Christoff, K., Keramatian, K., 2007. Abstraction of mental representations: theoretical considerations and neuroscientific evidence. In: Bunge, S.A., Wallis, J.D. (Eds.), The Neuroscience of Rule-Guided Behavior. Oxford Univ. Press.
Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J.K., Holyoak, K.J., Gabrieli, J.D.E., 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. NeuroImage 14, 1136–1149.
Christoff, K., Ream, J.M., Geddes, L.P.T., Gabrieli, J.D.E., 2003. Evaluating self-generated information: anterior prefrontal contributions to human cognition. Behav. Neurosci. 117, 1161–1168.
Christoff, K., Ream, J.M., Gabrieli, J.D., 2004. Neural basis of spontaneous thought processes. Cortex 40, 623–630.
Christoff, K., Keramatian, K., Smith, R., Maedler, B., 2006. Going in and out of metacognitive awareness: improved anterior prefrontal cortex modulation using real-time fMRI feedback training. NeuroImage 31, S18.
Crone, E.A., Donohue, S.E., Honomichl, R., Wendelken, C., Bunge, S.A., 2006. Brain regions mediating flexible rule use during development. J. Neurosci. 26, 11239–11247.
deCharms, R.C., Christoff, K., Glover, G.H., Pauly, J.M., Whitfield, S., Gabrieli, J.D., 2004. Learned regulation of spatially localized brain activation using real-time fMRI. NeuroImage 21, 436–443.
deCharms, R.C., Maeda, F., Glover, G.H., Ludlow, D., Pauly, J.M., Soneji, D., Gabrieli, J.D., Mackey, S.C., 2005. Control over brain activation and pain learned by using real-time functional, MRI. Proc. Natl. Acad. Sci. 102, 18626–18631.
D'Esposito, M., Zarahn, E., Aguirre, G.K., Shin, R.K., Auerbach, P., Detre, J.A., 1997. The effect of pacing of experimental stimuli on observed functional MRI activity. NeuroImage 6, 113–121.
Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25, 1325–1335.
Eickhoff, S.B., Heim, S., Zilles, K., Amunts, K., 2006. Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. NeuroImage 32, 570–582.
Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392, 598–601.
Friston, K.J., Henson, R.N., 2006. Commentary on: divide and conquer; a defence of functional localisers. NeuroImage 30, 1097–1099.
Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.
Friston, K.J., Worsley, K.J., Frackowiak, R.S.J., Mazziotta, J.C., Evans, A.C., 1994. Assessing the significance of focal activations using their spatial extent. Hum. Brain Mapp. 1, 210–220.
Friston, K.J., Rotshtein, P., Geng, J.J., Sterzer, P., Henson, R.N., 2006. A critique of functional localisers. NeuroImage 30, 1077–1087.
Gilbert, S.J., Spengler, S., Simons, J.S., Frith, C.D., Burgess, P.W., 2006a. Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain–behavior associations. Cereb. Cortex 16, 1783–1789.
Gilbert, S.J., Spengler, S., Simons, J.S., Steele, J.D., Lawrie, S.M., Frith, C.D., Burgess, P.W., 2006b. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J. Cogn. Neurosci. 18, 932–948.
Green, A.E., Fugelsang, J.A., Kraemer, D.J., Shamosh, N.A., Dunbar, K.N., 2006. Frontopolar cortex mediates abstract integration in analogy. Brain Res. 1096, 125–137.
Guo, H., Song, A.W., 2003. Single-shot spiral image acquisition with embedded z-shimming for susceptibility signal recovery. J. Magn. Reson. Imaging 18, 389–395.
Jezzard, P., Balaban, R.S., 1995. Correction for geometric distortion in echo planar images from B0 field variations. Magn. Reson. Med. 34, 65–73.
Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. 17, 4302–4311.
Kim, S.G., Ashe, J., Georgopoulos, A.P., Merkle, H., Ellermann, J.M., Menon, R.S., Ogawa, S., Ugurbil, K., 1993. Functional imaging of human motor cortex at high magnetic field. J. Neurophysiol. 69, 297–302.
Koechlin, E., Basso, G., Pietrini, P., Panzer, S., Grafman, J., 1999. The role of the anterior prefrontal cortex in human cognition. Nature 399, 148–151.
Koechlin, E., Corrado, G., Pietrini, P., Grafman, J., 2000. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proc. Natl. Acad. Sci. 97, 7651–7656.
Kourtzi, Z., Kanwisher, N., 2000. Cortical regions involved in perceiving object shape. J. Neurosci. 20, 3310–3318.
Kroger, J.K., Sabb, F.W., Fales, C.L., Bookheimer, S.Y., Cohen, M.S., Holyoak, K.J., 2002. Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. Cereb. Cortex 12, 477–485.
Lane, R.D., Fink, G.R., Chau, P.M., Dolan, R.J., 1997. Neural activation during selective attention to subjective emotional responses. NeuroReport 8, 3969–3972.
Lepage, M., Ghaffar, O., Nyberg, L., Tulving, E., 2000. Prefrontal cortex and episodic memory retrieval mode. Proc. Natl. Acad. Sci. U. S. A. 97, 506–511.
Mechelli, A., Price, C.J., Henson, R.N., Friston, K.J., 2003. Estimating efficiency a priori: a comparison of blocked and randomized designs. NeuroImage 18, 798–805.
Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S.,

Gabrieli, J.D., Gross, J.J., 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23, 483–499.

Ojemann, J.G., Akbudak, E., Snyder, A.Z., McKinstry, R.C., Raichle, M.E., Conturo, T.E., 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. NeuroImage 6, 156–167.

Ongur, D., Ferry, A.T., Price, J.L., 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. J. Comput. Neurol. 460, 425–449.

Posse, S., Fitzgerald, D., Gao, K., Habel, U., Rosenberg, D., Moore, G.J., Schneider, F., 2003. Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. NeuroImage 18, 760–768.

Pruessman, K., Weiger, M., Scheidegger, M., Boesiger, P., 1999. SENSE—Sensitivity encoding for fast MRI. Magn. Reson. Med. 42, 952–962.

Ramnani, N., Owen, A.M., 2004. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat. Rev., Neurosci. 5, 184–194.

Ranganath, C., Johnson, M.K., D'Esposito, M., 2003. Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia 41, 378–389.

Rugg, M.D., Wilding, E.L., 2000. Retrieval processing and episodic memory. Trends Cogn. Sci. 4, 108–115.

Rugg, M.D., Fletcher, P.C., Allan, K., Frith, C.D., Frackowiak, R.S., Dolan, R.J., 1998. Neural correlates of memory retrieval during recognition memory and cued recall. NeuroImage 8, 262–273.

Sakai, K., Passingham, R.E., 2003. Prefrontal interactions reflect future task operations. Nat. Neurosci. 6, 75–81.

Saxe, R., Brett, M., Kanwisher, N., 2006. Divide and conquer: a defense of functional localizers. NeuroImage 30, 1088–1096.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., Tootell, R.B., 1995. Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science 268, 889–893.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E., 1997. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J. Cogn. Neurosci. 9, 648–663.

Smith, R., Keramatian, K., Smallwood, J., Schooler, J., Luus, B., Christoff, K., 2006. Mind-wandering with and without awareness: an fMRI study of spontaneous thought processes. Proceedings of the 28th Annual Conference of the Cognitive Science Society (Ed. R. Sun): 804–809. Vancouver: Erlbaum.

Swallow, K.M., Braver, T.S., Snyder, A.Z., Speer, N.K., Zacks, J.M., 2003. Reliability of functional localization using fMRI. NeuroImage 20, 1561–1577.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers, Stuttgart.

Thompson, R.K.R., Oden, D.L., Boysen, S.T., 1997. Language-naive chimpanzees (Pan troglodytes) judge relations between relations in a conceptual matching-to-sample task. J. Exp. Psychol., Anim. Behav. Processes 23, 31–43.

Tulving, E., Markowitch, H.J., Craik, F.I.M., Habib, R., Houle, S., 1996. Novelty and familiarity activations in pet studies of memory encoding and retrieval. Cereb. Cortex 6, 71–79.

Wild, J.M., Martin, W.R., Allen, P.S., 2002. Multiple gradient echo sequence optimized for rapid, single-scan mapping of R^{*2} at high B_0. Magn. Reson. Med. 48, 867–876.

Wilke, M., Schmithorst, V.J., Holland, S.K., 2002. Assessment of spatial normalization of whole-brain magnetic resonance images in children. Hum. Brain Mapp. 17, 48–60.

Wilke, M., Schmithorst, V.J., Holland, S.K., 2003. Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. Magn. Reson. Med. 50, 749–757.