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Distinct functional connectivity associated with lateral versus medial rostral prefrontal cortex: A meta-analysis

Sam J. Gilbert *, Gil Gonen-Yaacovi, Roland G. Benoit, Emmanuelle Volle, Paul W. Burgess

Institute of Cognitive Neuroscience and Division of Psychology and Language Sciences, University College London, London, UK

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ABSTRACT

Recent studies have shown that functional connectivity in the human brain may be detected by analyzing the likelihood with which different brain regions are simultaneously activated, or "co-activated", across multiple neuroimaging experiments. We applied this technique to investigate whether distinct subregions within rostral prefrontal cortex (RoPFC) tend to co-activate with distinct sets of brain regions outside RoPFC, in a meta-analysis of 200 activation peaks within RoPFC (approximating Brodmann Area 10) and 1712 co-activations outside this region, drawn from 162 studies. There was little evidence for distinct connectivity between hemispheres or along rostral/caudal or superior/inferior axes. However, there was a clear difference between lateral and medial RoPFC: activation in lateral RoPFC was particularly associated with co-activation in dorsal anterior cingulate, dorsolateral PFC, anterior insula and lateral parietal cortex; medial RoPFC activation was particularly associated with co-activation in posterior cingulate, posterior superior temporal sulcus and temporal pole. These findings are consistent with anatomical studies of connectivity in non-human primates, despite strong cross-species differences in RoPFC. Furthermore, associations between brain regions inside and outside RoPFC were in some cases strongly influenced by the type of task being performed. For example, dorsolateral PFC, anterior cingulate and lateral parietal cortex tended to co-activate with lateral RoPFC in most tasks but with medial RoPFC in tasks involving mentalizing. These results suggest the importance of changes in effective connectivity in the performance of cognitive tasks.

Two important aims of cognitive neuroscience are to understand the specialized functions of individual brain regions, and the interactions between them that support competent behavior. There are a variety of methods for investigating such interactions, both in terms of the direct anatomical connectivity between distinct brain areas (most commonly studied in the non-human brain) and in terms of functional connectivity (typically studied in the human brain). The term "functional connectivity" refers to the correlation between remote neurophysiological events (Friston et al., 1996), in the sense that the signal in one region predicts the signal in another. This can potentially be detected in moment-by-moment fluctuations in brain activity (e.g. by showing a correlated signal in two regions across the timepoints of an fMRI timecourse), or across entire studies (e.g. by showing that studies that report activations in region 1 also tend to report activations in region 2). Here, we use the term in the latter sense. Functional connectivity between two regions should not be taken to imply the existence of direct anatomical (i.e. monosynaptic) links, although it would be consistent with such links.

Recently, Toro et al. (2008) showed that consistent patterns of functional connectivity may be detected by analyzing peak activations across multiple functional imaging studies that were originally performed for other purposes (see also Kober et al., 2008; Koski and Paus, 2000, and Postuma and Dagher, 2006, for similar approaches). They investigated a database of results from earlier studies and calculated, for each pair of locations in the brain, the likelihood that one region would be activated given that the other was activated. If one region is more likely to be activated if the other is also activated, this was taken as evidence of functional connectivity between the two regions. Toro et al. (2008) showed that this technique can recover patterns of functional connectivity predicted from anatomical studies (e.g. activation in one region is associated with a greater probability of activation in the homologous contralateral region), along with patterns of functional connectivity predicted from frequently associated activation patterns in earlier studies (e.g. co-activations in multiple nodes of the so-called "default mode" network).

In the present study we adopted a similar approach to Toro et al. (2008) in order to investigate associations between activation within particular subparts of rostral prefrontal cortex (RoPFC), approximating Brodmann Area (BA) 10, and activations elsewhere in the brain. Specifically, we investigated whether patterns of activation outside RoPFC are predicted by the precise location of co-activations within RoPFC. Were such results to be found, this would indicate that different subregions of RoPFC are distinguished by distinct patterns of functional connectivity.

* Corresponding author. Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR, UK. Fax: +44 20 7813 2835.
E-mail address: sam.gilbert@ucl.ac.uk (S.J. Gilbert).

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Recent anatomical studies suggest that RoPFC may be divided into distinct architectonic regions. Carmichael and Price (1994) suggested that in monkeys, area 10 should be divided into two distinct areas: medial and orbital (areas 10m and 10o respectively), while in humans, three different subregions: medial, rostral and polar (areas 10m, 10r and 10p, respectively) have been proposed (Ongur et al., 2003).

Furthermore, recent functional neuroimaging studies in humans have provided evidence for considerable functional specialization within RoPFC, at a remarkably fine scale. A meta-analysis by Gilbert et al. (2006c) found that RoPFC may be divided into at least three functionally distinct regions, according to both a lateral/medial and an anterior/posterior axis. An anterior polar region was associated with multitasking, i.e. situations where participants have more than one task to perform within a single block of trials. More posteriorly, a lateral region was associated with episodic memory retrieval whereas a medial region was associated with mentalizing, i.e. explicit reflection on one's own mental states or those of others. These meta-analytic findings have also been corroborated in a within-subjects fashion, in functional neuroimaging studies demonstrating segregation between distinct nearby regions of RoPFC (Gilbert et al., 2007a; Gilbert et al., 2010).

The evidence reviewed above indicates the presence of both anatomical and functional subdivisions within RoPFC. However, it is not clear whether these functional subdivisions reflect differences in functional connectivity between distinct subregions within RoPFC and other brain regions outside this region. We therefore examined a database of neuroimaging studies reporting activation both within and outside RoPFC, to investigate whether activation peaks outside RoPFC differed according to the location of co-activated regions within RoPFC. Furthermore, we additionally asked whether these findings differed as a function of task category. This allowed us to investigate whether activation in particular regions of RoPFC was inevitably associated with increased likelihood of activation in particular regions outside RoPFC (reflecting fixed functional connectivity), or whether patterns of co-activation varied according to task category (potentially reflecting changes in effective connectivity depending on experimental conditions).

Methods

Study selection

The present study required a database of activation peaks within RoPFC from previous functional neuroimaging studies. Additionally, for each contrast producing an activation peak within RoPFC we recorded the set of activation peaks outside RoPFC that were also reported. All studies from the earlier meta-analysis of RoPFC activations by Gilbert et al. (2006c) were included in the present database, so long as they also reported at least one activation peak outside RoPFC (102 studies; 124 independent contrasts). A further 60 studies (76 contrasts) were added to the database on the basis of additional searches in November 2008 of the PubMed database for the terms 'PET' or 'fMRI' along with one of the following: "anterior prefrontal", "rostral prefrontal", "Brodmann's area 10", "BA 10", "frontal pole", "frontopolar". Although this fixed set of search terms may have led us to miss relevant studies that did not include the relevant keywords in the abstract, it also allowed us to avoid experimenter bias in the selection of studies to be included in the meta-analysis.

Inclusion criteria were identical to Gilbert et al. (2006c), with the exception that there was no requirement that studies report response time for all conditions, unlike the earlier meta-analysis. We included studies using PET or fMRI that 1) investigated unmedicated healthy young adults; 2) reported the coordinates of activations in the space of the MNI template brain (Collins et al., 1994) or according to the atlas of Talairach and Tournoux (1988); and 3) reported one or more activations with peak coordinates falling within BA 10, according to the atlas of Talairach and Tournoux or as defined by the Brodmann map in MNI space supplied with MRIcro (Rorden and Brett, 2000). When activations were reported in Talairach and Tournoux coordinates, they were transformed into MNI space using a nonlinear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging; Brett et al., 2001) so that all coordinates were in a common stereotaxic framework. Activations were accepted as significant according to the criteria set by each individual study. The database therefore included any significant difference in signal between a pair of conditions (using the criteria for statistical significance set by each study), regardless of which condition was labeled by the original authors as "experimental" and which as "control".

Where a contrast yielded more than one activation peak falling within BA 10, only the most statistically significant was included in the list of RoPFC activations. Furthermore, only independent contrasts were included in the meta-analysis; for example, if two contrasts involving a shared baseline condition were reported, only the most significant would be included. The final database included 200 activation peaks falling within RoPFC, drawn from 162 studies. Each RoPFC activation peak was associated with between 1 and 46 co-activations (mean: 8.7). We refer to these as "extra-RoPFC" activation peaks, because they could fall anywhere within the brain, although in a few contrasts (where more than one RoPFC activation was reported) additional RoPFC activations were included in this list. In total there were 1712 extra-RoPFC activation peaks. All studies were categorized into one of the following eight task categories, based on the criteria described by Gilbert et al. (2006c): Attention, Perception, Language, Working memory, Episodic retrieval, Other memory, Mentalizing, Multitask. The first six of these were based on categories described by Cabeza and Nyberg (2000); the final two were added by Gilbert et al. (2006c), where Mentalizing refers to any study involving explicit reflection on one's own or others' mental states and Multitask refers to any study in which there was more than one task to perform within a single block of trials. Studies were categorized into task categories by two raters (inter-rater reliability for studies that were not included in Gilbert et al., 2006c: 91%; all disagreements were resolved by discussion).

Activation likelihood estimation analyses

Data were analyzed using an approach based on Activation Likelihood Estimation, a common technique for meta-analyses of neuroimaging results (Laird et al., 2005; Turkeltaub et al., 2002; Wager et al., 2007), modified here to allow statistical comparisons between two sets of results. In all analyses, activation peaks within RoPFC were divided into two categories (e.g. left versus right hemisphere; medial versus lateral etc.). Activation peaks were classified as lateral or medial by calculating whether the x coordinate was closer to the midpoint or lateral edge of the MNI template brain (Collins et al., 1994), given the y and z coordinates (where x defines a left–right axis, y defines a rostral–caudal axis, and z defines a superior–inferior axis). Activation peaks were classified as rostral/caudal and superior/inferior by a median split of y and z coordinates respectively (median y coordinate: 56; median z coordinate: 10); this ensured that the sample size in each category was approximately equal. Extra-RoPFC activation peaks associated with these two categories were then compared, with the aim of finding regions that were significantly more likely to be associated with one category (e.g. lateral RoPFC) than the other (e.g. medial RoPFC). The brain was divided into 5 mm isotropic voxels and results were computed at each voxel. This voxel size was chosen to maximize efficiency given the available computational resources, seeing as the time taken for analyses scales with the cube of the voxel size in each dimension (e.g. 3 mm voxels would increase computation time by a factor of approximately five).

Table 1
Additional contrasts included in the meta-analysis, beyond those reported in Gilbert et al. (2006c).

Study	x	y	z	Medial/lateral	Superior/inferior	Rostral/caudal	Category
Abe, N. et al. (2007). Journal of Cognitive Neuroscience, 19, 287	36	62	−2	L	I	R	Mentalizing
Abraham, A. et al. (2008). Journal of Cognitive Neuroscience, 20, 965	−2	59	−5	M	I	R	Episodic
Addis, D.R and Schacter, D. (2008). Hippocampus, 18, 227	20	64	14	L	S	R	Episodic
Addis, D.R. et al. (2007). Neuropsychologia, 45, 1363	−2	64	8	M	I	R	Multitasking
Arnott, S.R. et al. (2005). Journal of Cognitive Neuroscience, 17, 819	30	51	27	L	S	C	Working
	32	51	3	L	I	C	Working
Antonova, E. et al. (2009) Memory, 17, 125	−12	52	−13	M	I	C	Episodic
Bengtsson, S and Ulle´n, F. (2006). NeuroImage, 30, 272	−36	42	−3	L	I	C	Multitasking
Blondin, F. and Lepage, M. (2008). Human Brain Mapping, 29, 1159	4	42	−10	M	I	C	Episodic
Cunningham, W.A., Raye, C.L. and Johnson, M.K. (2004). Journal of Cognitive Neuroscience, 16, 1717	−8	52	20	M	S	C	Mentalizing
Daselaar, S. et al. (2008). Cerebral Cortex, 18, 217	−42	45	−1	L	I	C	Episodic
De Martino, B. et al. (2009). Cerebral Cortex, 19, 127	30	54	10	L	–	C	Attention
Deeley, Q. et al. (2008). NeuroImage, 40, 389	−18	43	−6	M	I	C	Perception
	14	64	32	L	S	R	Perception
den Ouden, H.E. et al. (2005). Neuroimage, 28, 787	−9	63	12	M	S	R	Mentalizing
	27	63	6	L	I	R	Multitasking
Dobbins, I. and Han, S. (2006). Cerebral Cortex, 16, 1614	33	60	12	L	S	R	Episodic
Dobbins, I., and Han, S. (2006). Journal of Cognitive Neuroscience, 18, 1439	33	63	21	L	S	R	Episodic
Dudukovic, N. and Wagner, A. (2007). Neuropsychologia, 45, 2608	−24	57	9	L	I	R	Episodic
Erk, S. et al. (2006). European Journal of Neuroscience, 1227	12	57	12	M	S	R	Working
Evan Nee, D. et al. (2007). NeuroImage, 38, 740	32	64	16	L	S	R	Working
Flores-Gutiérrez, E.O. et al. (2007). International Journal of Psychophysiology, 65, 69–84.	−34	56	−7	L	I	–	Perception
Gilbert, S.J. et al. (2007). SCAN, 2, 217	0	58	−14	M	I	R	Attention
	−8	54	30	M	S	C	Mentalizing
Goel, V. and Vartanian, O. (2005). Cerebral Cortex, 15, 1170	−16	58	10	M	–	R	Multitasking
Green, A. et al. (2006). Brain Research, 1096, 125	−8	60	31	M	S	R	Multitasking
Harrison, B.J. et al. (2005). Neuroimage, 24, 181	−38	61	−2	L	I	R	Attention
	34	64	−10	L	I	R	Attention
Heatherton, T. et al. (2006). SCAN, 1, 18	9	60	3	M	I	R	Mentalizing
Henson, R.N. et al. (2005). Journal of Cognitive Neuroscience, 17, 1058	24	60	12	L	S	R	Episodic
Kikyo, H. and Miyashita, Y. (2004). Neuroimage, 23, 1348	33	60	21	L	S	R	Episodic
King, J.A. et al. (2005). Neuroimage, 28, 256	−33	54	−6	L	I	C	Episodic
	30	57	−6	L	I	R	Episodic
Koch, K. et al. (2006). Brain Research, 1107, 140	−32	56	−2	L	I	–	Working
Koenig, P. et al. (2005). Neuroimage, 24, 369	−16	57	12	M	S	R	Other
	−24	57	25	L	S	R	Other
Konishi, S. et al. (2005). PNAS, 102, 12584	−30	51	22	L	S	C	Multitasking
Konrad, K. et al. (2005). Neuroimage, 28, 429	3	57	−12	M	I	R	Attention
Kroger, J.K. (2008). Brain Research, 1243, 86	30	61	−4	L	I	R	Attention
Kulkarni, B. (2005). European Journal of Neuroscience, 21, 3133	−32	68	6	L	I	R	Attention
Lee, T.W. (2006). SCAN, 1, 122	−3	58	−5	M	I	R	Perception
Leung, H.C. et al. (2005). Cerebral Cortex, 15, 1742	29	54	13	L	S	C	Working
Lie, C. et al. (2006). NeuroImage, 30, 1038	−32	54	14	L	S	C	Working
Locke, H and Braver, T. (2008). Cognitive, Affective, & Behavioral Neuroscience, 8, 99	−32	61	10	L	–	R	Perception
Luks, L. et al. (2008). Neuroreport, 19, 155	42	51	12	L	S	C	Attention
Marklund, P. et al. (2007). Cortex, 43, 22	38	56	−4	L	I	–	Working
Milham, M.P.and Banich, M.T. (2005). Human Brain Mapping, 25, 328	−30	58	5	L	I	R	Attention
Okuda, J. et al. (2007). International Journal of Psychophysiology, 64, 233	−16	48	24	M	S	C	Multitasking
	−2	66	4	M	I	R	Multitasking
Ramnani, N. et al. (2004). Neuroimage, 23, 777	−10	64	6	M	I	R	Other
	12	58	16	M	S	R	Other
Ranganath, C. et al. (2007). NeuroImage, 35, 1663	7	63	0	M	I	R	Episodic
Reed, C.L. et al. (2005). Neuroimage, 25, 718	0	60	33	M	S	R	Perception
Schnell ,K. et al. (2007). NeuroImage, 34, 332	24	60	9	L	I	R	Attention
Simons, J.S. et al. (2006). NeuroImage, 32, 696	−30	48	18	L	S	C	Episodic
Simons, J.S. et al. (2006). Neuropsychologia, 44, 1388	39	54	15	L	S	C	Multitasking
	0	48	−6	M	I	C	Multitasking
Simons, J.S. et al. (2008). Journal of Cognitive Neuroscience, 20, 447	−33	57	6	L	I	R	Episodic
Sommer, M. et al. (2007). NeuroImage, 35, 1378	34	64	6	L	I	R	Mentalizing
Stelzel, C. et al. (2008). Journal of Cognitive Neuroscience, 20, 613	−50	36	26	L	S	C	Multitasking
Stern, E. et al. (2007). Brain Research, 1176, 92	22	54	20	M	S	C	Attention
Knutson, K. et al. (2007). Human Brain Mapping, 28, 915	20	52	13	M	S	C	Other
Strangman, G. et al. (2005). Neurohabilitation and Neural Repair, 19, 93	16	60	12	M	S	R	Other
Tanabe, J. et al. (2007). Human Brain Mapping, 28, 1276	25	58	−8	L	I	R	Working
Turner, G. and Levine, B. (2006). Neuroscience, 139, 327	−37	38	24	L	S	C	Working
	−37	38	24	L	S	C	Working
	−37	38	24	L	S	C	Working
	−37	38	24	L	S	C	Working
van Eimeren, T. et al. (2006). Neuroimage, 29, 286	−33	57	6	L	I	R	Attention
Vartanian, O., Goel, V. (2005). Neuroimage, 27, 927	4	68	2	M	I	R	Language
Wager, T.D. et al. (2005). Neuroimage, 27, 323	34	41	20	L	S	C	Attention
	−26	49	15	L	S	C	Attention
	30	49	30	L	S	C	Attention

(continued on next page)

Table 1 (*continued*)

Study	x	y	z	Medial/lateral	Superior/inferior	Rostral/caudal	Category
Wolf, R.C. et al. (2006). Neuropsychologia, 44, 2558	−39	54	21	L	S	C	Working
Yarkoni, T. et al. (2005). Cognitive Brain Research, 23, 71	−38	53	3	L	I	C	Working
	−2	62	3	M	I	R	Working

First, all extra-RoPFC activation peaks associated with one category (e.g. lateral RoPFC) were considered. We generated a full three-dimensional map of activations throughout the brain associated with this category, by first smoothing each activation peak with a 8 mm full-width half-maximum Gaussian kernel, then summing together the three-dimensional volumes, each representing a single smoothed activation peak. A second whole-brain three-dimensional map was generated in an analogous fashion from extra-RoPFC activation peaks associated with the other category (e.g. medial RoPFC). These two maps were then subtracted from each other to create, at all voxels outside RoPFC, a new map representing the difference in the likelihood of co-activations associated with the two categories of RoPFC activations. This difference map was compared against a null-distribution as follows. Each RoPFC activation and its associated extra-RoPFC activations were randomly assigned to one of two categories. The number of RoPFC activations in these randomly-generated categories matched the two categories under investigation (e.g. lateral versus medial RoPFC). Difference maps between the two randomly-assigned categories were generated as above. This process was repeated 1000 times. At each voxel, a z score was calculated by comparing the true difference score against the mean and standard deviation obtained by randomly assigning activations to the two categories. This z score indicated whether a particular voxel was significantly more likely to be associated with one or the other RoPFC category than would be expected by chance. Below, we refer to this map of z scores as the "difference z-map".

Predictive validity of extra-RoPFC activations

In order to mitigate the multiple-comparisons problem created by the mass-univariate approach described above, we first performed a test that was sensitive to the entire difference map, rather than investigating results at a voxel-by-voxel level. This allowed us to perform a single test to investigate whether there were differences in extra-RoPFC activations associated with two types of RoPFC activation, looking at the whole brain rather than specific regions. If this test was significant, we then went on to examine which regions outside RoPFC had a different likelihood of co-activation with different categories of RoPFC activations (i.e. performing a test at each voxel). We investigated four binary classifications of RoPFC activation peaks: left versus right hemisphere; lateral versus medial; rostral versus caudal; and superior versus inferior. For each of these classifications, we investigated whether it was possible to predict the category of RoPFC activation peaks, just from knowing the coordinates outside RoPFC that were activated in the same contrast. Because these classifications did not divide RoPFC activation peaks perfectly in half, chance performance for these predictions ranged from 52–59% for the various classifications. Performance significantly above chance would indicate significantly different patterns of functional connectivity associated with the two categories of RoPFC activations, licensing follow-up voxel-by-voxel analyses of the extra-RoPFC regions differentially associated with these two categories. These follow-up analyses investigated clusters of voxels showing differential associations with the two RoPFC regions, using a uncorrected threshold of $p<.001$. This relatively liberal threshold was used to discover specific brain regions that may have contributed to the significant omnibus test.

We performed a separate analysis for each classification of RoPFC activation peaks (e.g. lateral versus medial). For these analyses, we considered each RoPFC activation peak in turn. One by one, we labeled each RoPFC activation peak the "target" and attempted to predict its location from the associated extra-RoPFC activation peaks. For each target RoPFC activation peak, we first created a difference z-map as above, but excluding the target RoPFC activation itself and associated extra-RoPFC activations so that they could not bias the results. We then examined this difference z-map at each of the extra-RoPFC coordinates associated with the target RoPFC activation. We summed the values of the difference z-map at each of these extra-RoPFC coordinates and made a prediction for which category the target RoPFC activation fell into (e.g. lateral versus medial) based on the value of this sum (greater or less than zero). This is a form of leave-one-out cross-validation. We repeated this process for all RoPFC activations and then compared the percentage assigned to the correct category (e.g. lateral versus medial) against chance using a binomial test. Where this figure was significantly greater than chance for a particular categorization, we then went on to analyze clusters of voxels significantly associated with one or the other category of RoPFC activation peaks, using the modified activation likelihood estimation technique described above.

Effect of task category

In a final set of analyses, we examined the effect of task category on the link between extra-RoPFC activations and lateral versus medial RoPFC activations. For each extra-RoPFC region that was differentially associated with lateral versus medial RoPFC, we first gathered all extra-RoPFC activations in the database within a 15 mm radius of this region. The value of 15 mm was chosen to ensure sufficient statistical power (mean activation peaks per region: 29.3; range 6–48); smaller search volumes were associated with relatively few activation peaks across all task categories and both RoPFC regions. These activations were then categorized depending on which task category they came from (Attention, Perception, Language, etc.) and on whether they were associated with an activation peak within lateral or medial RoPFC. This was used to generate a 8 (Task) × 2 (lateral/medial RoPFC) contingency table, which was submitted to a chi-square test. A significant chi-square test would indicate that the association of a particular extra-RoPFC region with lateral versus medial RoPFC activations was influenced by the task category. These tests were implemented in SPSS Exact Tests 7.0 for Windows (Mehta and Patel, 1996) so that results were reliable even when sample sizes were small (e.g., expected counts below 5), as in the present data where there were relatively few activation peaks when split into different task categories.

Table 2
RoPFC and extra-RoPFC activations included in the meta-analysis, divided by task category.

Task category	Activations inside RoPFC		Co-activations outside RoPFC	
	N	%	N	%
Attention	30	15	247	14
Perception	10	5	66	4
Language	7	4	60	4
Working memory	30	15	283	17
Episodic memory	49	25	558	33
Other memory	17	9	104	6
Mentalizing	31	16	197	12
Multitasking	26	13	197	12
Total	200	100	1712	100

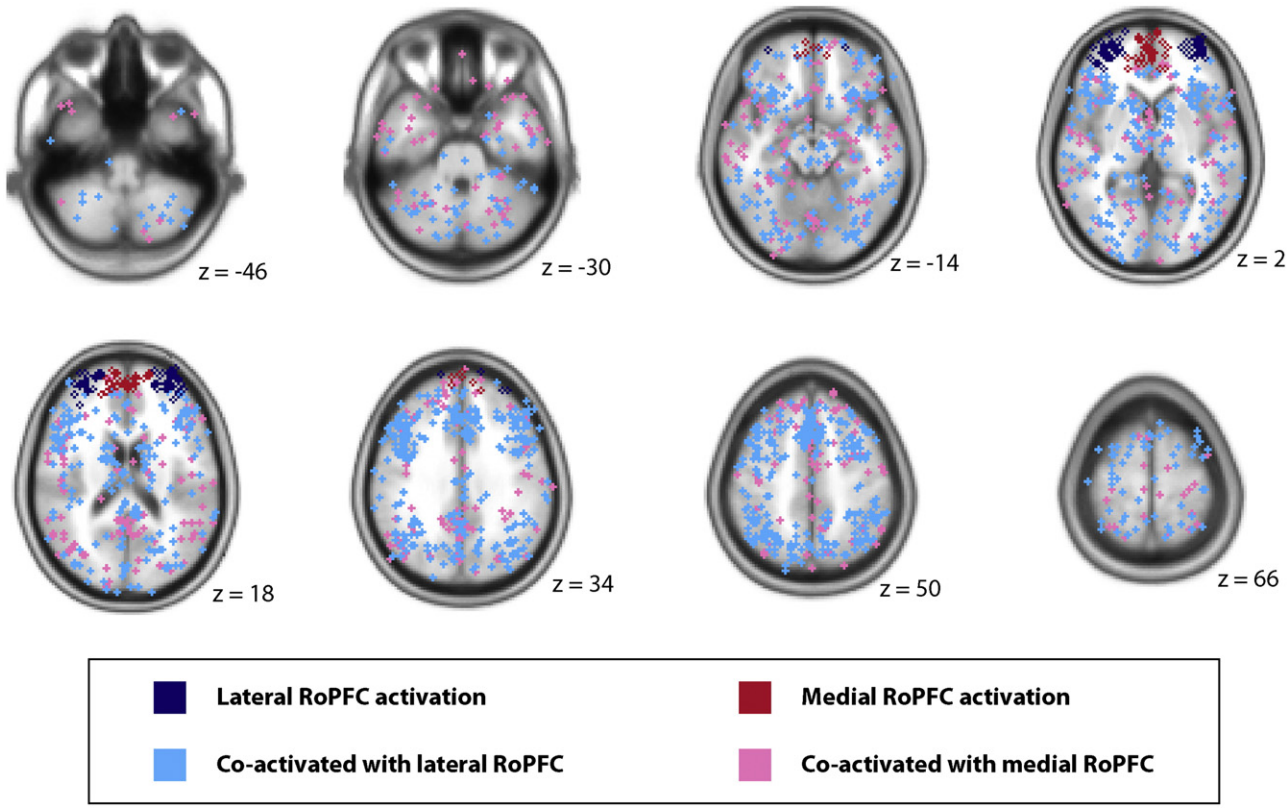

Fig. 1. Activations within lateral RoPFC (dark blue) and medial RoPFC (dark red), along with associated co-activations (light blue and light red). Results are shown on eight axial slices of the MNI 152 template brain; each co-activation is plotted on the nearest slice.

Results

A list of all additional contrasts that were included in the present study but not Gilbert et al. (2006c) is provided in Table 1. In addition, Table 2 provides a breakdown of the full sample of RoPFC and extra-RoPFC activations included in the present study, according to task category.

Predictive validity

Is it possible to predict the location of RoPFC activation peaks just from knowing the location of associated extra-RoPFC activation peaks? Performance was not significantly above chance levels when predicting left versus right hemisphere RoPFC, inferior versus superior RoPFC, or rostral versus caudal RoPFC (55%, 47% and 55% correct respectively versus chance levels of 54%, 52% and 50%; $p > .1$). Thus, we were not able to detect any differences in functional connectivity associated with these classifications of RoPFC. However, performance was well above chance levels when predicting the location of lateral versus medial RoPFC activation peaks from the location of extra-RoPFC activations (76% correct; chance: 59%; $p = .000001$), indicating significantly different functional connectivity associated with these subregions of RoPFC. We therefore went on to examine functional connectivity of lateral versus medial RoPFC. The raw data, indicating all co-activations associated with lateral versus medial RoPFC are illustrated in Fig. 1.

Functional connectivity of lateral versus medial RoPFC

Analysis of predictive validity indicated that lateral and medial RoPFC were associated with significantly different patterns of co-activation outside RoPFC. But which regions outside RoPFC were responsible for this effect? The difference z-map was examined for voxels showing significantly different likelihood of co-activation with lateral versus medial RoPFC; these results are summarized in Table 3. Activation peaks in lateral RoPFC (versus medial RoPFC) were significantly associated with activity in bilateral dorsolateral PFC, anterior cingulate, bilateral lateral parietal cortex, and bilateral anterior insula. Activation peaks in medial RoPFC (versus lateral RoPFC) were significantly associated with posterior cingulate, bilateral temporal pole and posterior superior temporal sulcus. These regions are illustrated in Fig. 2.

Effect of task category

In five of the twelve regions listed in Table 3, differential functional connectivity with lateral versus medial RoPFC was significantly

Table 3
Regions with significantly different probability of co-activation with lateral versus medial rostral prefrontal cortex. PFC = prefrontal cortex.

Region	BA	x	y	z	Zmax	Cluster size/mm^3
Lateral > medial						
Dorsolateral PFC	9/46	−45	15	35	4.89	21,250
	9/46	40	20	35	3.56	625
Anterior cingulate	32	−5	20	45	4.18	8625
Anterior insula	–	40	20	5	3.34	625
	–	−25	20	0	3.22	375
Lateral parietal cortex	40	40	−45	50	3.20	250
	40	−45	−50	40	3.72	2625
	40	35	−65	35	3.71	3875
	7	−15	−70	45	3.22	250
Medial > lateral						
Temporal pole	21	−50	5	−30	3.33	625
Posterior cingulate	23/31	0	−55	20	3.80	1875
Posterior superior temporal sulcus	39	−50	−65	20	3.67	1625

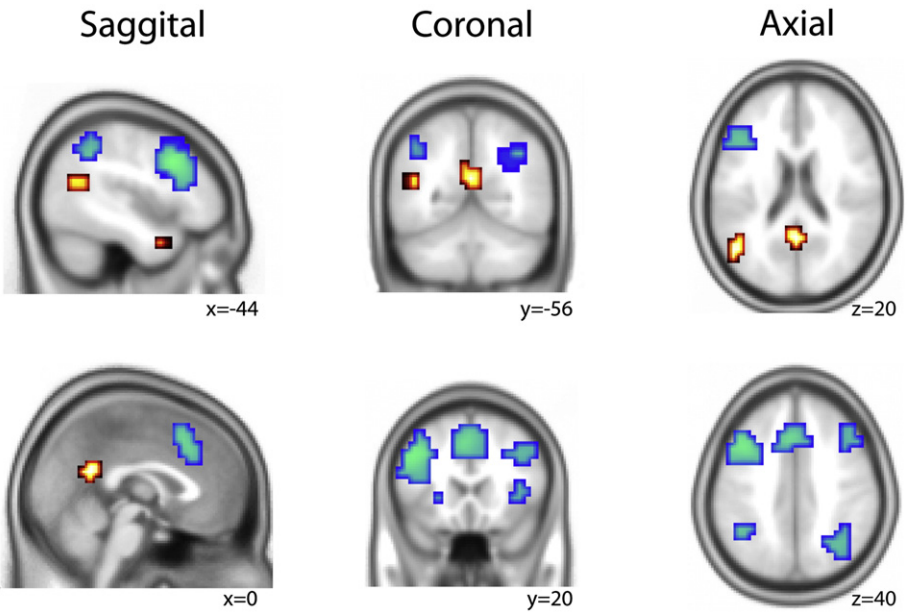

Fig. 2. Regions with significantly different probability of co-activation with lateral versus medial rostral prefrontal cortex. Warm colors indicate greater probability of co-activation with medial rostral prefrontal cortex; cool colors indicate greater probability of co-activation with lateral rostral prefrontal cortex. Results are shown at an uncorrected threshold of $p<.001$.

modulated by task category (chi-square exact test, $p<.05$). Posterior cingulate was generally associated with activations in medial RoPFC, but in the episodic retrieval task category posterior cingulate activations were more commonly associated with lateral RoPFC. Conversely, anterior cingulate, lateral parietal cortex (−45, −50, 40), and bilateral dorsolateral PFC were generally associated with activations in lateral RoPFC, but in the mentalizing task category were associated with medial RoPFC. These results are shown in Table 4 and Fig. 3. Thus, differential functional connectivity with lateral versus medial RoPFC was not always constant across studies, at least assuming that different extra-RoPFC activation peaks within a 15 mm-radius sphere may be considered to correspond with the same region.

Activation versus deactivation

While the majority of the 200 RoPFC activation peaks entered into the meta-analysis resulted from increased signal in an experimental condition versus a control condition, seven resulted from a contrast of a control versus experimental condition (i.e. a "deactivation"). All of these were found in the larger sample of studies described by Gilbert et al. (2006c). In order to assess the possible effect of including both activations and deactivations in our sample, the analysis of co-activations with lateral versus medial RoPFC was rerun with these seven RoPFC activations (and associated co-activations) excluded. Results were similar: all of the 12 activation peaks listed in Table 3 remained significant ($p<.001$) even when deactivations were excluded. Furthermore, the prevalence of deactivations did not differ significantly according to task category ($\chi^2=7.4$, $df=7$, $p=.35$). Thus the present results could not result from the inclusion of both activations and deactivations in the meta-analysis.

Discussion

This study investigated functional connectivity associated with different subregions within RoPFC, by investigating co-activations between particular areas inside and outside RoPFC across a database of neuroimaging studies. There was no evidence for distinct connectivity associated with left versus right RoPFC, superior versus inferior RoPFC, or rostral versus caudal RoPFC. However, there were clear differences between lateral and medial RoPFC, such that knowledge of the extra-RoPFC activation peaks alone was sufficient to predict the location of the co-activated region of RoPFC with 76% accuracy (against 59% expected by chance).

The location of extra-RoPFC regions associated with lateral versus medial subregions of RoPFC accorded well with previous anatomical investigations of RoPFC connectivity in non-human primates. In the rhesus monkey, Barbas et al. (1999) have reported connections between medial prefrontal cortex and posterior superior temporal sulcus. In the macaque monkey, Petrides and Pandya (2007) reported

Table 4
Contingency tables for five regions, describing the number of activations within 15 mm of each region, divided according to task category and whether there was a co-activation in medial or lateral RoPFC. In all five regions, the chi-square test on these data was significant ($p<.05$).

	Left DLPFC (−45, 15, 35)		Right DLPFC (40, 20, 35)		Anterior cingulate (−5, 20, 45)		Lateral parietal cortex (−45, −50, 40)		Posterior cingulate (0, −55, 20)	
	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral
Attention	0	3	0	4	2	9	2	3	2	1
Perception	0	0	2	0	1	1	0	1	1	0
Language	0	2	1	0	0	2	0	0	1	0
Working memory	0	9	0	7	0	10	0	7	1	0
Episodic retrieval	0	19	0	10	0	15	0	16	1	6
Other memory	1	2	1	1	0	0	0	1	1	1
Mentalizing	1	0	2	1	3	1	2	0	15	0
Multitask	0	5	0	7	1	3	2	5	4	0

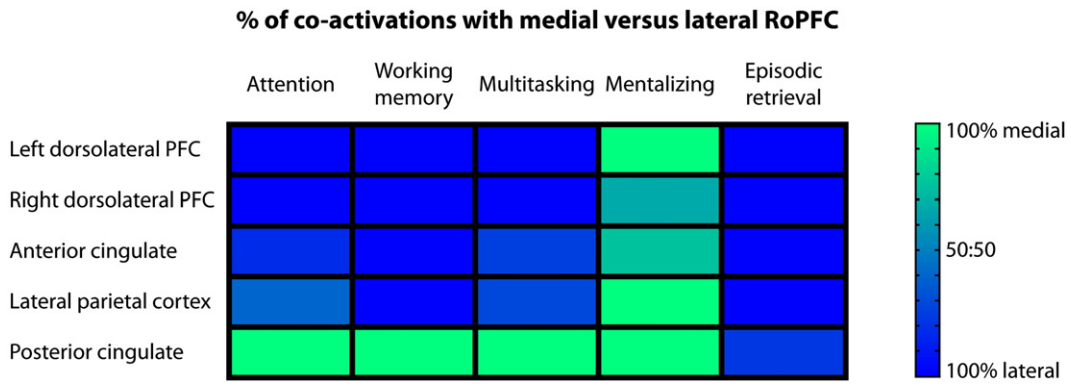

Fig. 3. Percentage of co-activations in medial versus lateral RoPFC, in the five regions whose likelihood of co-activation with medial versus lateral RoPFC was significantly modulated by task category. All RoPFC activation peaks underwent a binary classification into medial or lateral, so a figure of (e.g.) 80% medial indicates 20% lateral. Results are shown separately for the five task categories that were associated with at least one activation in every region. The first four regions tend to co-activate with lateral RoPFC whereas the last region (posterior cingulate) tends to co-activate with medial RoPFC. However, this regularity was significantly affected by task category. In the mentalizing category, regions that typically co-activated with lateral RoPFC instead co-activated with medial RoPFC. In the episodic retrieval category, posterior cingulate, which typically co-activated with medial RoPFC, instead co-activated with lateral RoPFC.

efferent connections from RoPFC to anterior and posterior cingulate, insula, temporal pole, and superior temporal sulcus, all of which were implicated in the present functional neuroimaging results. However, this study did not systematically compare lateral and medial RoPFC. Petrides and Pandya (2007) note the absence of direct connections between RoPFC and occipital and inferotemporal visual areas, and parietal cortex. Consistent with this observation, the present study did not produce any evidence of functional connectivity between RoPFC and occipital or inferotemporal areas. However, there was clear evidence for greater functional connectivity between lateral parietal cortex and lateral rather than medial RoPFC, despite the absence of anatomical evidence for direct RoPFC–parietal pathways. One possibility is that functional connectivity between RoPFC and lateral parietal cortex is mediated via connections of the two regions with caudal DLPFC (BA 9/46). This is supported by studies of the macaque, in which there are dense connections between lateral RoPFC and caudal DLPFC (Petrides and Pandya, 2007), which in turn is strongly connected with parietal cortex (Petrides and Pandya, 1999).

It was not inevitable that the present findings, regarding functional connectivity of medial versus lateral RoPFC, would be congruent with previous anatomical studies in non-human primates. Strong differences in RoPFC anatomy have been reported between humans and other primates, both in relative size (Semendeferi et al., 2001) and cytoarchitecture (Carmichael and Price, 1994; Ongur et al., 2003). Of course, the present results concerning functional connectivity do not necessarily imply anatomical connectivity. However, functional connectivity between a pair of regions suggests the plausibility of anatomical connectivity, which may be then examined in studies of non-human primates, or non-invasively in humans with tractography (Johansen-Berg and Rushworth, 2009). Such studies may help to clarify anatomical subdivisions within RoPFC, which are at present poorly defined.

Our results also fit well with theoretical accounts of large-scale brain networks derived from other functional imaging studies. In particular, lateral PFC, anterior cingulate and superior parietal cortex have been proposed to play a co-ordinated role in a variety of situations involving high cognitive demand (Duncan and Owen, 2000; Duncan, 2005). By contrast, medial PFC, posterior cingulate and temporo-parietal junction have been implicated in low-demand situations, including "rest", and have therefore been proposed to participate in a "default mode" of brain function (Raichle et al., 2001). Some authors refer to the network of regions associated with lateral and medial RoPFC as "task positive" and "task negative" networks respectively (Fox et al., 2005). Although there is clear evidence that these two networks tend to be activated in different experimental paradigms, such as those involving slow versus fast reaction times (Burgess et al., 2007; Gilbert et al., 2006b), their functional role is still a matter of considerable debate. In particular, although it is generally agreed that the "task negative" or "default mode" network supports cognitive processes that are more common in low-demand situations, the precise nature of these processes is not clear (e.g. involvement in task-unrelated mind-wandering, enhanced perceptual attention, or a combination of the two; Gilbert et al., 2007b; Mason et al., 2007).

One advantage of the present technique is that it can reveal the extent to which patterns of functional connectivity depend on task category. There were clear effects of task category on functional connectivity between RoPFC and posterior cingulate, anterior cingulate, lateral parietal cortex and bilateral dorsolateral PFC. These results suggest that participation in large-scale networks such as those described above does not reflect immutable links between sets of brain regions but may instead reflect dynamic shifts in effective connectivity to accomplish particular tasks. Of course, it is possible that a larger sample size and/or a different taxonomy of tasks might have revealed additional effects of task category on functional connectivity between RoPFC extra-RoPFC regions. Furthermore, the studies included in the meta-analysis are probably not exhaustive of all the different states into which the brain can organize itself. Future studies may therefore reveal additional exceptions to the general patterns of functional connectivity reported here.

The effects of task category on functional connectivity suggest that pairs of regions such as medial RoPFC and posterior cingulate have functionally dissociable roles, seeing as they tend to co-activate in some task categories but not others. It is therefore clear that even though it may be helpful to conceive of particular sets of brain regions as part of a functionally connected network (e.g. the "default mode network"), the component regions will have distinct roles. In order to understand these roles it will be necessary to contrast their responses in well-controlled experimental paradigms. It seems less likely that unconstrained, multi-componential cognitive states such as "rest", over which there is little or no experimental control, will yield insights that demarcate the precise roles of individual brain regions that tend to be co-activated in low-demand conditions (see Christoff et al., 2009a; Gilbert et al., 2006a, 2007b for further discussion).

Inspection of Fig. 2 suggests that the effect of task category on functional connectivity of RoPFC was largely driven by studies involving mentalizing. For these studies, four brain regions that typically co-activate with lateral RoPFC (bilateral dorsolateral PFC, anterior cingulate and lateral parietal cortex) instead tended to co-activate with medial RoPFC. Previous studies have suggested that, within RoPFC, mentalizing is specifically associated with a posterior

medial region (Gilbert et al., 2006c, 2007a; Simons et al., 2008). The present results suggest that mentalizing studies may promote interactions between medial RoPFC and a variety of other brain regions, even those that typically co-activate with lateral rather than medial RoPFC. This would be consistent with the idea that mentalizing is not supported by a strictly modular system (Fodor, 1983) but instead involves gathering information from a variety of domains; in other words mentalizing is not "informationally encapsulated" (Goldman, 2006, pp. 104–106).

It should be noted that the relationship between functional connectivity and task category was tested in analyses in which extra-RoPFC activations within a 15 mm sphere were denoted as a single region. This was important to ensure sufficient statistical power for these analyses. However, it is possible that at a finer level of analysis the extra-RoPFC co-activations associated with different categories of task might be spatially distinct. Indeed, studies of functional specialization within RoPFC indicate considerable fine-grained segregation of function (Gilbert et al., 2006c, 2010). Thus, although the present results are valid at a relatively coarse level of analysis, it remains to be seen whether they would also hold at a more detailed level. In order to address this question, a larger database of studies would be required, or additional neuroimaging experiments crossing multiple task demands within the same study. For further discussion of the question of functional specialization at multiple levels of analysis, see Henson (2005) and Gilbert et al. (2010).

Although the present study revealed clear differences in functional connectivity between lateral and medial RoPFC, there were no significant hemispheric effects, or effects of rostral versus caudal or inferior versus superior RoPFC. This is perhaps surprising because functional differences have been reported both between rostral and caudal RoPFC (Gilbert et al., 2006c, 2007a; Simons et al., 2008) and between inferior and superior RoPFC (Mitchell et al., 2006; Van Overwalle, 2009). One possibility is that the present database (containing 200 activations in RoPFC and 1712 co-activations) was too small, or the voxel size of 5 mm^3 too coarse, for sufficient statistical power to detect differences in connectivity along these axes. There may be less variance in connectivity along these axes than the medial/lateral axis, or the types of study that would reveal this variance may have been under-represented in the literature to date. For example, recent studies have suggested a relationship between activation along the rostro-caudal axis of the RoPFC and the level of abstraction of task materials and/or complexity of task demands (Christoff et al., 2009b). However, many studies do not systematically manipulate (or control for) the abstractness of task materials and therefore may potentially yield activations in both rostral and caudal sections of RoPFC, obscuring the ability to discern unique connectivity patterns. In addition, the present approach, using a database simply indicating the presence or absence of a significant signal change based on a single RoPFC activation peak from each contrast, may have missed differences in functional connectivity expressed as differences in the strength of co-activations (e.g. bilateral activation in a particular region, more significant in the hemisphere ipsilateral to the activated area of RoPFC). Alternatively, it may be the case that functional differences between RoPFC subregions along these axes exist in the absence of systematic differences in functional connectivity, i.e. that different RoPFC subregions perform distinct intrinsic computations with equivalent input and output representations.

In summary, the present study established clear evidence for differences in functional connectivity between lateral and medial RoPFC. Furthermore, we found that these differences in connectivity were in some cases modulated by task category. These results underline the importance of delineating 1) particular subregions within RoPFC, and 2) the specific roles of brain regions that tend to co-activate, rather than treating them as functionally homogenous. In addition, the relationship between functional and anatomical connectivity of RoPFC remains to be explored. The present results may provide a starting point for investigations of anatomical connectivity of RoPFC in the human brain using tractography.

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References

Barbas, H., Ghashghaei, H., Dombrowski, S.M., Rempel-Clower, N.L., 1999. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. J. Comp. Neurol. 410, 343–367.
Brett, M., Christoff, K., Cusack, R., Lancaster, J., 2001. Using the Talairach atlas with the MNI template. Neuroimage 13, 85.
Burgess, P.W., Dumontheil, I., Gilbert, S.J., 2007. The gateway hypothesis of rostral prefrontal cortex (area 10) function. Trends Cogn. Sci. 11, 290–298.
Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12, 1–47.
Carmichael, S.T., Price, J.L., 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J. Comp. Neurol. 346, 366–402.
Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., Schooler, J.W., 2009a. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proc. Natl Acad. Sci. USA 106, 8719–8724.
Christoff, K., Keramatian, K., Gordon, A.M., Smith, R., Madler, B., 2009b. Prefrontal organization of cognitive control according to levels of abstraction. Brain Res. 1286, 94–105.
Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.
Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 23, 475–483.
Duncan, J., 2005. Prefrontal cortex and Spearman's g. In: Duncan, J., Phillips, L., McLeod, P. (Eds.), Measuring the Mind: Speed, Control, and Age. Oxford University Press, Oxford, pp. 249–272.
Fodor, J., 1983. The Modularity of Mind. MIT Press, Cambridge, MA.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl Acad. Sci. USA 102, 9673–9678.
Friston, K.J., Frith, C.D., Fletcher, P., Liddle, P.F., Frackowiak, R.S.J., 1996. Functional topography: multidimensional scaling and functional connectivity in the brain. Cerebral Cortex 6, 156–164.
Gilbert, S.J., Simons, J.S., Frith, C.D., Burgess, P.W., 2006a. Performance-related activity in medial rostral prefrontal cortex (area 10) during low-demand tasks. J. Exp. Psychol. Hum. Percept. Perform. 32, 45–58.
Gilbert, S.J., Spengler, S., Simons, J.S., Frith, C.D., Burgess, P.W., 2006b. 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., 2006c. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J. Cogn. Neurosci. 18, 932–948.
Gilbert, S.J., Dumontheil, I., Simons, J.S., Frith, C.D., Burgess, P.W., 2007a. Comment on "Wandering minds: the default network and stimulus-independent thought". Science 317, 43 author reply 43.
Gilbert, S.J., Williamson, I.D., Dumontheil, I., Simons, J.S., Frith, C.D., Burgess, P.W., 2007b. Distinct regions of medial rostral prefrontal cortex supporting social and nonsocial functions. Soc. Cogn. Affect. Neurosci. 2, 217–226.
Gilbert, S.J., Henson, R.N., Simons, J.S., 2010. The scale of functional specialization within human prefrontal cortex. J. Neurosci. 30, 1233–1237.
Goldman, A.I., 2006. Simulating Minds: The Philosophy. Oxford University Press, New York, Psychology and Neuroscience of Mindreading.
Henson, R.N., 2005. What can functional imaging tell the experimental psychologist? Q. J. Exp. Psychol. A 58, 193–233.
Johansen-Berg, H., Rushworth, M.F., 2009. Using diffusion imaging to study human connectional anatomy. Annu. Rev. Neurosci. 32, 75–94.
Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D., 2008. Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. Neuroimage 42, 998–1031.
Koski, L., Paus, T., 2000. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. Exp. Brain Res. 133, 55–65.
Laird, A.R., Fox, P.M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L., Turkeltaub, P.E., Kochunov, P., Fox, P.T., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum. Brain Mapp. 25, 155–164.
Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315, 393–395.
Mehta, C.R., Patel, N.R., 1996. SPSS Exact Tests 7.0 for Windows. SPSS Inc, Chicago, IL.
Mitchell, J.P., Macrae, C.N., Banaji, M.R., 2006. Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. Neuron 50, 655–663.
Ongur, D., Ferry, A.T., Price, J.L., 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. J. Comp. Neurol. 460, 425–449.

Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur. J. Neurosci. 11, 1011–1036.
Petrides, M., Pandya, D.N., 2007. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J. Neurosci. 27, 11573–11586.
Postuma, R.B., Dagher, A., 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cereb. Cortex 16, 1508–1521.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl Acad. Sci. USA 98, 676–682.
Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. Behav. Neurol. 12, 191–200.
Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K., Van Hoesen, G.W., 2001. Prefrontal cortex in humans and apes: a comparative study of area 10. Am. J. Phys. Anthropol. 114, 224–241.
Simons, J.S., Henson, R.N., Gilbert, S.J., Fletcher, P.C., 2008. Separable forms of reality monitoring supported by anterior prefrontal cortex. J. Cogn. Neurosci. 20, 447–457.
Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain. Thieme, Stussgart.
Toro, R., Fox, P.T., Paus, T., 2008. Functional coactivation map of the human brain. Cereb. Cortex 18, 2553–2559.
Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16, 765–780.
Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. 30, 829–858.
Wager, T.D., Lindquist, M., Kaplan, L., 2007. Meta-analysis of functional neuroimaging data: current and future directions. Soc. Cogn. Affect. Neurosci. 2, 150–158.