We analyzed the behavioral data from 104 neuroimaging studies using positron emission tomography or functional magnetic resonance imaging that reported activation peaks in rostral prefrontal cortex (PFC), approximating Brodmann’s area 10. The distribution of absolute x coordinates of activation peaks (i.e., x coordinate regardless of hemisphere) differed significantly from a unimodal normal distribution, reflecting distinct clusters of activation in lateral and medial subregions. These 2 clusters were associated with different patterns of behavioral data. Lateral activations were associated with contrasts between experimental and control conditions where response times (RTs) were slower in the experimental condition. Medial activations were associated with contrasts where RTs were, if anything, faster in experimental than control conditions. These findings place important constraints on theories of rostral PFC functions.

Keywords: Brodmann’s area 10, fMRI, frontal pole, meta-analysis, PET, response time

Introduction

Studies of functional specialization within the primate prefrontal cortex (PFC) have emphasized the distinction between lateral and medial areas. For example, theoretical accounts have been put forward for distinctions between the roles of medial and lateral aspects of the supplementary motor area (Goldberg 1985) as well as between medial and lateral aspects of more rostral prefrontal regions (e.g., dorsolateral PFC vs. anterior cingulate; MacDonald and others 2000) and orbitofrontal cortex (Elliott and others 2000; Kringelbach and Rolls 2004). However, less attention has been paid to the nature of functional subdivisions between lateral and medial regions of the most rostral part of the PFC, approximating Brodmann’s area (BA) 10 (although see Koehl and others 2000; Weidner and others 2002). This is perhaps surprising because BA 10 is probably the single largest cytoarchitectonic region of the human PFC (Ongur and others 2003; Ramnani and Owen 2004), and a growing body of neuroimaging studies point to functional dissociations between its lateral and medial aspects (e.g., Burgess and others 2003; Gilbert and others 2005; Simons, Gilbert, and others 2005; Simons, Owen, and others 2005; Simons, and others 2005, 2006). This is perhaps surprising because BA 10 is probably the single largest cytoarchitectonic region of the human PFC (Ongur and others 2003; Ramnani and Owen 2004), and a growing body of neuroimaging studies point to functional dissociations between its lateral and medial aspects (e.g., Burgess and others 2003; Gilbert and others 2005; Simons, Gilbert, and others 2005; Simons, Owen, and others 2005, 2006).

In a recent meta-analysis of functional neuroimaging studies, Gilbert, Spengler, and others (2006) found that rostral PFC activations have been reported in studies investigating a wide variety of cognitive tasks, but the likelihood of observing activation in medial versus lateral regions of BA 10 differed significantly according to the type of task under investigation. Studies involving working memory or episodic memory retrieval were disproportionately associated with activations in lateral BA 10, whereas studies involving mentalizing (i.e., reflecting on one’s own emotions and mental states or those of other agents) were disproportionately associated with medial BA 10 activations (see also Frith U and Frith CD 2003). Thus, it seems clear that functional differences exist between lateral and medial regions of BA 10. However, despite this highly significant variation in the proportion of lateral versus medial BA 10 activations in different cognitive domains, none of the 8 domains investigated were associated exclusively with activations in either medial or lateral BA 10. In the present study, we therefore investigate whether any commonality may be drawn between the types of contrast associated with medial versus lateral BA 10 activations, regardless of the cognitive domain. Because activations in BA 10 have been reported in studies employing a wide variety of tasks (see Burgess and others 2005, 2006), such cross-domain analyses provide important additional constraints for theorizing about the functions of this brain region.

In earlier studies (e.g., Burgess and others 2003; Gilbert and others 2005; Simons, Gilbert, and others 2005; Simons, Owen, and others 2005; Gilbert, Simons, and others 2006), we have suggested that rostral PFC plays a role in attentional selection between self-generated and perceptually derived information, with dissociable roles of lateral and medial subregions. Here, we examine whether this proposal is supported by a meta-analysis of neuroimaging studies reporting activation in rostral PFC.

One potential means of distinguishing contrasts associated with medial versus lateral BA 10 activations is to consider the accompanying behavioral data. Of course, experimental psychology has a long history of investigating response times (RTs) as a source of insight into the organization of cognitive processes (e.g., Donders 1868/1969; Sternberg 1969; Posner 1978; Luce 1986). Typically, behavioral investigations of RT examine the difference in RT between 2 or more conditions hypothesized to differ according to some variable of experimental interest. In an analogous fashion, neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) typically investigate the difference in regional cerebral blood flow (rCBF) or blood oxygen level-dependent (BOLD) signal between 2 or more conditions hypothesized to differ in some experimentally interesting way. In the present study, the database established by Gilbert, Spengler, and others (2006) was examined in order to investigate the relationship between these 2 forms of data. More specifically, we investigated differences in RT accompanying hemodynamic changes in 1) lateral BA 10 and 2) medial BA 10.

As well as investigating the time from each stimulus until the subsequent response (i.e., RT), we also investigated the time from each response until the subsequent stimulus (i.e., response–stimulus interval [RSI]). Some neuroimaging studies present stimuli at regular intervals (e.g., a new stimulus
every 3 s) or according to a fixed distribution, regardless of RT (e.g., according to an exponential distribution with a mean of 3 s). In this case, 2 conditions that differ in mean RT will also differ in mean RSI. However, the relationship between mean RT and mean RSI need not be perfect because other studies use a fixed interval between each response and the next stimulus (e.g., self-paced tasks). Thus, in the present meta-analysis, we attempted to disentangle the factors of RT and RSI by assessing the unique variance explained by both. The relationship between RT and RSI is particularly important with respect to activations in medial rostral PFC because some authors have suggested that activations in this region are associated with situations where subjects have no instructed task or minimal task demands (e.g., Shulman and others 1997; Raichle and others 2001). One possible explanation of this finding is that medial rostral PFC activity reflects the occurrence of self-initiated mental activity in the absence of an external task (e.g., McKiernan and others 2003; Wicker and others 2003). In this case, one would expect medial rostral PFC activity to be associated with situations where there is a relatively long RSI, even after controlling for RT, because this interval represents the period of time for which there is no instructed task. Alternatively, medial rostral PFC activity may play a functional role in situations requiring fast responses to external stimuli in low-demand tasks (Gilbert, Simons, and others 2006). According to this hypothesis, medial rostral PFC activity should be associated with fast RTs, even after controlling for RSI.

Materials and Methods

In the present study, we analyze data from 104 functional neuroimaging studies using PET or fMRI, reporting 133 independent contrasts associated with hemodynamic change in rostral PFC (approximating BA 10). For full search and inclusion criteria, see Gilbert, Spengler, and others (2006). All contrasts involved a comparison between 2 behavioral tasks, where RTs were available for both. Furthermore, for each contrast, we recorded the mean RSI (i.e., mean time from each response until the presentation of the next stimulus) in the “experimental” and “control” conditions. Where articles did not report RTs, we attempted to obtain these data from authors. Because error rates were not always available, only RTs are considered in this study.

Studies were included only if 1) they investigated unmedicated healthy young adults, 2) they reported the coordinates of the activations in the space of the Montreal Neurological Institute (radiological) template brain (Collins and others 1994) or according to the atlas of Talairach and Tournoux (1988), and 3) they reported 1 or more activations with peak coordinates falling within BA 10, according to the atlas of Talairach and Tournoux (1988) or as defined by the Brodmann map in MNI space (Collins and others 2001). Therefore, we transformed into MNI space using a linear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml; Brett and others 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. Both “activations” (i.e., greater BOLD signal or rCBF in a task of interest than a control task) and “deactivations” (i.e., greater BOLD signal or rCBF in a control task) were included. In other words, any change in BOLD signal or rCBF was taken as potentially noteworthy, regardless of whether activity was greater in a task of interest than a control task or vice versa. Below, any difference in BOLD signal or rCBF between 2 experimental conditions is referred to as an activation. Each activation peak was classified as lateral or medial by calculating whether the x coordinate was closer to the midpoint or lateral edge of the MNI template brain, 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). Where a contrast yielded multiple activation peaks within BA 10, only the most statistically significant one was retained in the meta-analysis, to ensure that the activation peaks entered into the analysis resulted from independent contrasts. Contrasts were then categorized into 1 of the following task categories: “attention,” “perception,” “language,” “working memory,” “episodic retrieval,” “other memory,” “mentaling,” “multitask” (for full details of this classification procedure and for a complete list of studies included in the meta-analysis, see Gilbert, Spengler, and others 2006).

Results

Association between x Coordinates and RTs

Figure 1 shows a frequency histogram representing the number of activation peaks observed, according to the absolute x coordinate (i.e., the distance in millimeters from the midline of the MNI template brain in a lateral direction, regardless of hemisphere). In addition, each bar is colored according to the mean difference in RT between the condition provoking the activation and the control condition against which it was compared.

Two features of Figure 1 are noteworthy. First, the distribution of activation peaks appears to be bimodal, with 2 clusters representing peaks in medial (|x| < 15) and lateral (|x| > 20) BA 10. This appearance was confirmed by a Kolmogorov–Smirnoff test on the distribution of absolute x coordinates, showing that it differed significantly from a unimodal normal distribution (P < 0.01). The second noteworthy feature of Figure 1 is that these 2 clusters of activations appear to differ according to the associated RTs. The bars representing lateral activations have relatively pale colors, suggesting that such activations have typically arisen from contrasts where the mean RT in the experimental condition was slower than the mean RT in the control condition. By contrast, bars representing medial activations have relatively dark colors, suggesting that such activations, if anything, come from activations where the mean RT in the experimental condition was faster than the mean RT in the control condition. In order to further examine these RT effects, Table 1 indicates the mean RTs associated with the experimental and control conditions for activations with peak
coordinates in left lateral, left medial, right medial, and right lateral BA 10, as well as the mean difference in RT between experimental and control conditions for contrasts associated with activation in these regions (illustrated in Fig. 2).

As is clear from Figure 2, activations in left lateral and right lateral BA 10 were associated with slower RTs in the experimental than control conditions ($t_{129} = 2.6, P < 0.05$; $t_{125} = 2.2, P < 0.05$, respectively). By contrast, both left and right medial activation peaks were associated with faster RTs in the experimental than control conditions, but this difference was not significant in either case ($t_{127} = 0.9, P > 0.3$; $t_{120} = 0.8, P > 0.4$, respectively). To illustrate the different patterns of RT data associated with activations in different regions of BA 10, Figure 3 displays the smoothed RT data plotted on axial, coronal, and sagittal slices of a normalized structural scan. RT differences between experimental and control conditions were analyzed in an analysis of variance (ANOVA) with factors hemisphere (left and right) and region (lateral and medial). Neither the main effect of hemisphere nor the hemisphere × region interaction was significant ($F < 1$). However, there was a significant main effect of region ($F_{1,120} = 9.3, P < 0.005$), indicating that the RT difference between experimental and control conditions was significantly different between contrasts producing activations in lateral versus medial BA 10. Despite this highly significant difference in RT patterns associated with lateral versus medial activations, we note that this relationship was not perfect. Thus, for only 61% of activations in lateral BA 10 was the RT in the experimental condition slower than the RT in the control condition. The corresponding figure for activations in medial BA 10 was 42%.

**Consistency of RT Findings Across Task Categories**

One potential explanation for the relationship between RT patterns and lateral versus medial activations is that it is mediated via the association between activations in different regions of BA 10 and different types of cognitive task. For example, Gilbert, Spengler, and others (2006) showed that studies involving episodic retrieval were associated with a higher proportion of activations in lateral BA 10 than studies in other categories. If studies involving episodic retrieval were also associated with a higher proportion of comparisons where RT was slower in the experimental than the control condition, this might account for the observed relationship between RT differences and lateral versus medial activations. In order to test this possibility, we subjected the experimental-control RT differences to a multiple regression analysis, with a variable representing region (lateral/medial) along with additional variables representing each of the 8 categories of task. In this analysis, there was still a highly significant effect of region ($t_{124} = 3.4, P < 0.001$). In other words, even after controlling for an effect of task category on RT differences, the effect of region was still highly significant. An ANOVA with factors task and region additionally showed that there was no significant task × region interaction ($F < 1$), despite a significant main effect of region ($F_{1,127} = 7.6, P < 0.01$). Thus, the association between RT effects and the location of activations within BA 10 (lateral vs. medial) was not attributable to the type of task involved; nor was this association reliably modulated by the type of task.

To illustrate this, Figure 4 plots the difference in RT between experimental and control conditions, separately for contrasts yielding lateral versus medial activations, split into the 8 categories of task investigated by Gilbert, Spengler, and others (2006). In general, contrasts yielding lateral activations were associated with slower RTs in the experimental than control conditions, regardless of the task. Contrasts yielding medial activations, if anything, were associated with faster RTs in the experimental than control conditions. Comparing the RT differences directly between contrasts yielding lateral versus medial activations showed that in 7 out of 8 domains these RT differences were more positive (i.e., slower for experimental than control) for lateral than medial activations. In the only domain where this was not true—mentalizing—there were only 3 contrasts that were associated with lateral activations, making it hard to draw any strong conclusions. Thus, the association between RT differences and lateral versus medial activations is relatively consistent across the 8 task domains investigated by Gilbert, Spengler, and others (2006), despite these domains differing reliably in the proportion of lateral versus medial activations.

Multiple regression analyses revealed that both task category and RT differences explained unique variance in the absolute $x$ coordinates of activation peaks. A full model, including dependent variables representing each of the task domains as well as an additional variable representing RT differences, accounted for 41% of variance in the absolute $x$ coordinates of activation peaks. The percentage of unique variance explained by RT differences was 7%; collectively, the variables representing task domain accounted for an additional 32%. Only 2% of variance was jointly attributable to the RT difference variable and the task domain variables (i.e., due to multicollinearity).

**Relationship between RT and RSI**

A further question that might be asked about the present results is whether the association between RT differences and lateral
versus medial activations might be related to the time from each response until the subsequent stimulus (i.e., RSI), rather than the time from each stimulus until the subsequent response (i.e., RT). Analysis of the difference in RSI between experimental and control conditions showed that activation peaks in lateral BA 10 were associated with shorter RSIs in experimental compared with control conditions ($M = -90$ ms), whereas activation peaks in medial BA 10 were associated with longer RSIs in experimental compared with control conditions ($M = 33$ ms). This resulted in a significant difference in RSI data associated with lateral versus medial activation peaks ($t_{117} = 2.6, P < 0.05$). However, there was a significant negative correlation between RT differences and RSI differences ($r = -0.64, P < 0.001$) because in many studies a slower RT led to a shorter interval until the next trial. In order to deconfound the effects of RT and RSI, we performed a multiple regression analysis with absolute $x$ coordinate as the dependent variable and RT and RSI as independent variables. This analysis showed that, even after controlling for the effects of RSI, the relationship between RT and the $x$ coordinate was still significant ($t_{116} = 2.3, P < 0.05$). However, there was no effect of RSI after controlling for RT ($t_{116} = 0.03, P > 0.7$). This suggests that the task used in the experimental and control conditions (and the associated RTs) is the decisive factor in influencing the location of activations in BA 10 (lateral or medial), rather than the amount of time between each response and the next stimulus.

Deactivations and Signal Change in Medial BA 10
Of the 133 contrasts included in the meta-analysis, 7 involved deactivations, that is, greater BOLD signal or rCBF in a control or baseline condition than a condition of interest. These contrasts were disproportionately associated with signal change in medial rather than lateral BA 10 (86% of deactivations were in medial BA 10 vs. 41% of activations; $\chi^2 = 5.5, df = 1, P < 0.05$). In addition, for these 7 contrasts, RTs were faster in the control or baseline condition (i.e., the condition associated with greater BOLD signal or rCBF) than in the condition of experimental interest (821 vs. 1083 ms, $t = 3.1, P < 0.05$). This may account, in part, for the association between signal change in medial BA 10 and conditions involving relatively fast RTs, when all 133 contrasts were averaged. However, this cannot be a complete account. Even when these deactivations were excluded from the analysis, activations in medial and lateral BA 10 were still associated with significantly different patterns of RT data ($t_{124} = 3.1, P < 0.005$). Furthermore, when the RT data were
subjected to a multiple regression analysis with factors region (medial/lateral) and contrast type (activation/deactivation), the effect of region was still significant after controlling for contrast type ($t_{1,30} = 3.1, P < 0.005$), whereas the effect of contrast type was only marginally significant after controlling for region ($t_{1,30} = 1.8, P = 0.07$). Thus, the differing patterns of RT data associated with signal change in medial versus lateral BA 10 cannot be attributed entirely to the finding that deactivations generally involved signal change in medial BA 10. Instead, the present data suggest that greater signal in medial BA 10 was associated with conditions with relatively fast RTs, regardless of whether that condition was labeled as an experimental or control condition.

**Gradient of RT Effects between Medial and Lateral Activations?**

We next investigated whether the relationship between lateral versus medial activations and the RT difference between experimental and control conditions was best understood in terms of 2 discrete clusters of activation (lateral/medial), each associated with a different pattern of RTs, or in terms of a gradient of RT effects between relatively medial and relatively lateral activations. After controlling for variance in RT differences attributable to a binary classification of activations as lateral or medial, the distance of each activation peak from the midline did not account for any significant additional variance ($t_{1,30} = 1.2, P > 0.2$). Thus, there is no clear evidence for a gradient in RT effects between medial and lateral activations, rather than 2 discrete clusters.

**Additional Analyses**

In a final set of analyses, we investigated whether there was a significant relationship between RT effects and the $y$ coordinates (i.e., position along the rostral-caudal axis) or the $z$ coordinates (i.e., position along the superior-inferior axis) of activation peaks. There was no significant relationship between RT effects and the location of activation peaks along these 2 dimensions ($r < 0.09, P > 0.3$). In addition, we investigated whether results were consistent across studies using PET versus fMRI. The proportion of activation peaks in lateral versus medial BA 10, the mean $y$ and $z$ coordinates of activation peaks, the mean difference in RT and RSI between experimental and control conditions, and the proportion of activations versus deactivations were all similar between studies using PET and fMRI (all $P$ values > 0.2). Thus, there was no evidence that imaging modality (PET or fMRI) affected the results presented here.

**Discussion**

These results indicate that a distinction may be made between lateral and medial subregions of rostral PFC, both in the sense that there were distinct clusters of activation peaks corresponding to these 2 regions and in the sense that these clusters were associated with different patterns of RT data. Specifically, activations in lateral rostral PFC were associated with contrasts where the RT for the experimental condition was slower than the RT for the control condition. Activations in medial rostral PFC were associated with contrasts where RT in the experimental condition was, if anything, faster than RT in the control condition.

These findings provide new constraints for theorizing about the functions of these 2 brain regions. The most obvious implication for theoretical accounts of the functions of rostral PFC is that it is inadequate to consider this region as functionally homogenous (see also Koecchlin and others 2000; Weidner and others 2002). A similar conclusion was reached by Gilbert, Spengler, and others (2006), whose meta-analysis showed that the proportion of activations in lateral versus medial subregions of rostral PFC differed reliably according to the type of task under investigation. This contrasts with previous meta-analyses, which have yielded little evidence for functional specialization within more caudal PFC regions (e.g., dorsolateral vs. anterior cingulate cortex; Duncan and Owen 2000). This suggests that functional specialization within PFC may be particularly apparent in more rostral subregions. However, even in the meta-analysis of Gilbert, Spengler, and others (2006) no category of task was associated exclusively with activations in lateral or medial rostral PFC.

The present results extend these findings, by showing that analysis of the behavioral data associated with each contrast allows a distinction to be drawn between activations in lateral versus medial rostral PFC, independent of the task categorization performed by Gilbert, Spengler, and others (2006). This suggests that some commonality may be drawn between the type of situation provoking activations in lateral versus medial rostral PFC, across diverse cognitive domains. Below, we consider some of the potential explanations for the relationship between RTs and activation in lateral versus medial subregions of rostral PFC.

An explanation in terms of slow or fast RTs being themselves causally responsible for activations in different parts of rostral PFC should be dismissed, at least in the sense that the RT on a particular trial itself causes the corresponding BOLD signal or rCBF. Overt behavior and the hemodynamic changes measured with PET or fMRI are both consequences of underlying neural events and so cannot be thought of as causally responsible for one another in any direct sense (see Henson 2004). Of course, indirect relationships between RTs and hemodynamic changes are possible, for instance, if these hemodynamic changes reflect the operation of a performance monitoring process (e.g., Botvinick and others 2001). However, models in which precisely the same underlying events determine both RT and hemodynamic changes in a certain brain region (e.g., the idea that activations in lateral rostral PFC reflect nothing more than “time on task,” regardless of what the task is) are not consistent with the present data. Only 61% of contrasts associated with hemodynamic changes in lateral BA 10 involved a comparison between 2 conditions where RT was slower in the experimental than the control condition, compared with 42% of contrasts associated with hemodynamic changes in medial BA 10. Thus, although highly significant, the association between different RT patterns and activations in lateral versus medial rostral PFC was far from perfect.

One potential explanation for the association between RT effects and the observation of hemodynamic changes in lateral versus medial rostral PFC is suggested by the literature on “task-induced deactivations.” Many authors have reported that low-level baseline conditions, such as passive fixation of experimental stimuli, simple RT (i.e., pressing a button whenever any stimulus is presented, regardless of its identity), or “rest,” are associated with greater rCBF or BOLD signal in medial rostral PFC than conditions requiring more extensive processing of experimental stimuli (e.g., Shulman and others 1997; McKiernan and others 2003; Raichle and others 2001; Gilbert, Simons, and...
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