Rostral Prefrontal Cortex and the Focus of Attention in Prospective Memory

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Prospective memory (PM) denotes the function to realize intentions after a delay while being immersed in distracting ongoing (OG) activity. Here, we scrutinize the often-reported involvement of rostral prefrontal cortex (rPFC; approximating Brodmann area 10) in such situations: This region might mediate attention between external stimuli and the internally maintained intention, that is, between stimulus-oriented (SO) and stimulus-independent (SI) processing. Using functional magnetic resonance imaging (fMRI) we orthogonally crossed 1) PM versus OG activity only, with 2) SO versus SI attention. In support of the hypothesis, common regions of medial rPFC exhibited greater blood oxygen level-dependent (BOLD) signal for the contrasts of both OG task only versus PM and SO versus SI attending. However, activation related to the former contrast extended more superiorly, suggesting a functional gradient along a dorsal–ventral axis within this region. Moreover, region-of-interest analyses revealed that PM versus OG task only was associated with greater BOLD signal in left lateral rPFC, reflecting the requirement to maintain delayed intentions. Distinct aspects of this region were also transiently engaged at transitions between SO and SI conditions. These results are consistent with the hypothesis that some of the rostral prefrontal signal changes associated with PM performance reflect relative differences in SO versus SI processing.

Keywords: anterior prefrontal cortex, delayed intentions, frontopolar cortex, fMRI, task switching

Introduction

Prospective memory (PM) denotes the capacity to remember to carry out an intention after a delay (e.g., posting a letter), while being immersed in distracting ongoing activity (OG; e.g., commuting to work) (Ellis 1996; McDaniel and Einstein 2007). Typically, the implementation of the intention has to be self-initiated upon occurrence of a particular event (i.e., the PM target; e.g., presence of a postbox). Thus, PM requires a fine attentional balance between information that is externally derived (e.g., monitoring the traffic) versus internally maintained (e.g., the intention).

Realizing such delayed intentions critically depends on rostral prefrontal cortex functioning (rPFC; approximating Brodmann area [BA] 10): Lesions to this region lead to impairments in PM, typically in the context of spared episodic memory abilities (Burgess et al. 2000, 2009; Roca et al. 2010; Uretzky and Gilboa 2010; Volle et al. 2011). Neuroimaging studies have further specified the temporal involvement of this region. rPFC appears to be engaged during the delay period between intention formation and execution (Okuda et al. 1998, 2007; Burgess et al. 2001, 2003; den Ouden et al. 2005; Simons et al. 2006; Gilbert et al. 2009, 2011; Reynolds et al. 2009). These studies employed a great variety of different OG tasks, intentions, stimuli, and response modalities, often within single experiments (i.e., conjunction approach). Furthermore, a recent study by Gilbert (2011) found that although lateral rPFC (lrPFC) exhibited robust activation during maintenance of delayed intentions, the content of those intentions (i.e., the nature of the target stimuli and appropriate PM responses) could not be decoded from this region. These data suggest that rPFC subserves central aspects of PM, that is, those that are not specific to individual stimuli, responses, or tasks. Importantly, this region is recruited when participants are instructed to carry out delayed intentions, but no actual PM targets are embedded in the OG task (Burgess et al. 2001; Simons et al. 2006). Similarly, lrPFC exhibits increased blood oxygen level-dependent (BOLD) signal during PM performance, even when statistically controlling for transient signal changes at the moments of target detection (Reynolds et al. 2009). Therefore, Burgess et al. (2001) concluded that this region supports the maintenance of the delayed intention in the context of OG task activity rather than target detection or actual realization of the intention (see also Okuda et al. 1998). This account is consistent with functions attributed to rPFC, such as the preparation for upcoming task demands (Sakai and Passingham 2003; Rowe et al. 2007), the coordination of multiple tasks (Koechlin et al. 1999; Braver and Bongiolatti 2002; Benoit 2008), or the integration of independent cognitive operations (Ramnani and Owen 2004).

However, PM performance is not just associated with increased rPFC activation. Instead, BOLD signal typically exhibits a double dissociation within this region, when contrasting conditions that require either sole engagement in OG activity (OG blocks) or additional performance of delayed intentions (PM blocks) (Burgess et al. 2008). Activation in lateral rPFC is commonly greater for PM compared with OG blocks, whereas the reverse contrast is associated with medial rPFC (mrPFC) recruitment. A complete account of rPFC involvement in PM thus
needs to explain this full pattern, and the gateway hypothesis of rPFC function (Burgess et al. 2007, 2008) has recently provided such a comprehensive account.

It posits that mrPFC and lrPFC comprise a gateway mechanism that mediates competition between stimulus-oriented (SO; based on the current environment) versus stimulus-independent (SI; decoupled from the environment) processing. This mechanism is thought to be engaged when either processing mode needs to be biased to an unusual degree or in situations that require frequent switches between the 2 modes. Accordingly, engagement for sole OG task performance versus additional PM performance has been attributed to relative differences in such attentional demands (Burgess et al. 2003, 2008): Whereas OG task activity on its own primarily requires attention toward external stimuli (i.e., SO attending; e.g., monitoring the traffic), the additional PM component necessitates a relative disengagement from the external environment. That is, this condition also demands SI maintenance of the intention (e.g., thinking about posting the letter) and frequent matching of the external world and the internally represented PM target (e.g., watching out for a postbox).

The gateway hypothesis is supported by a number of neuroimaging studies, all of which provided evidence for a consistent functional dissociation between mrPFC and lrPFC. Gilbert et al. (2005), for instance, instructed participants to perform 3 tasks, alternately based on externally presented (SO phase) or internally generated (SI phase) stimuli (see also Gilbert et al. 2007; Dumontheil, Gilbert, et al. 2010). Consistent across all tasks, SO contrasted with SI phases were associated with sustained BOLD signal increases in mrPFC. In contrast, lrPFC was transiently recruited when participants switched between SO and SI phases. These findings have been extended to a variety of different forms of SO versus SI attending, and lrPFC has been observed to also exhibit sustained activation during phases of SI processing (Gilbert, Simons, et al. 2006; Dumontheil, Gilbert, et al. 2010; Dumontheil, Hassan, et al. 2010; Henseler et al. 2011). Taken together, this pattern supports the account that mrPFC is involved in SO attending, whereas lrPFC supports SI attending (cf. Christoff and Gabrieli 2000).

Thus, maintaining an intention may activate lrPFC due to increased reliance on SI attending, while mrPFC deactivation may reflect concurrent attenuation of SO processing of the OG task (Burgess et al. 2003; Simons et al. 2006). In this case, at least some of the neuronal populations involved in PM might also be sensitive to a manipulation of SO versus SI attending. However, to date, no study has examined if both functions in fact recruit overlapping regions. Indeed, rPFC exhibits a functional specialization on a fine spatial scale (on the order of a few millimeters) (Gilbert, Spengler, et al. 2006; Gilbert et al. 2007; Gilbert et al. 2010; see also Krueger et al. 2007; Benoit et al. 2010), suggesting that areas implicated in PM might be distinct from those associated with the attentional gateway mechanism.

To test the gateway account of rPFC involvement in PM, we employed functional magnetic resonance imaging (fMRI) in a factorial design. Specifically, we crossed the requirements to engage in 1) PM versus OG only and 2) SO versus SI attending. This allowed us to assess whether at least some aspects of rPFC involved in PM performance are also involved in mediating between SO versus SI attending. Moreover, the factorial design enabled us to explore the general functional properties of rPFC in more detail, in addition to examining functional overlap versus segregation. If, for example, both the SI (vs. SO) condition and the PM (vs. OG only) condition recruit overlapping aspects of lrPFC, they might yield additive or multiplicative effects on BOLD signal. This would suggest that increasing the demand on SI processing increases the engagement of this region. On the other hand, an interaction effect between the 2 factors (i.e., the PM condition has an effect during SO but not SI phases) may suggest that this region does not need to be further engaged once the system is already in a state of SI processing.

Materials and Methods

Participants

Nineteen volunteers participated in this experiment. They were all right handed, had normal or corrected-to-normal vision, and reported good health with no known history of neurological or psychiatric illness. Prior to the experimental session, they gave written informed consent. All participants received £ 30 reimbursement as approved by the local research ethics committee. Of the 19 participants, 3 had to be excluded from further analysis either due to technical problems, miscomprehension of task instructions, or chance performance. Thus, 16 participants (9 females; mean age = 22.51 years, age range = 19–28 years) remained for further analyses.

Tasks and Procedure

Participants performed 2 tasks (Fig. 1 and description below) that required responses either based on visually presented information (i.e., SO condition) or internally generated information (i.e., SI condition). These stimulus conditions changed randomly within experimental blocks. Thus, both tasks alternated between phases of SO and SI processing. Apart from this critical commonality, they were designed to differ in other aspects of required cognitive operations, that is, spatial navigation versus line discrimination (see below; Gilbert et al. 2005). Engagement in the basic tasks constituted the OG condition, whereas the PM condition additionally required carrying out delayed intentions. Participants only learned about the PM condition in the MRI scanner, after they had performed the OG task alone.

In the “shape task,” participants continuously navigated around the edges of a shape in clockwise direction. For each corner, they indicated whether they would have to take a left or right turn. In SO phases, the actual shape was presented, which resembled the outlines of the letters H and F attached to each other (Fig. 1). In contrast, during SI phases, the HF shape was replaced by a distractor, that is, a mirrored version of the joined letters T and E. Participants were instructed to continue the task by picturing the HF shape in their head, while keeping their eyes open and fixated on the center of the screen. At transitions between stimulus phases, they continued the sequence from where they had left off. The outlines of both shapes were white and covered approximately 6° of the visual field. The PM targets were 2 junctions on the HF shape, which participants memorized at the beginning of each PM block. Whenever they got to these corners, they had to indicate their detection rather than making the right/left decision.

In the “alphabet task,” participants classified capital letters based on perceptual features. Specifically, they indicated whether any given letter was composed entirely of straight lines (e.g., A, H) or included any curved lines (e.g., C, P). In the SO condition, letters were presented in alphabetical order one at a time. As soon as a response was made, the letter was replaced by the next. When the end of the alphabet was reached, the sequence continued at “A” again. Letters were presented either in red or blue during SO phases. In contrast, during SI phases, letters were presented in random order and in the other color (i.e., blue or red) (Fig. 1). In this condition, participants had to ignore the distracting random letters and mentally continue the correct alphabetical sequence whilst carrying on with the classification based on the imagined letters. At transitions to the SO condition, the letter was
presented that participants would have imagined if they had correctly continued the alphabetical sequence throughout the SO condition. Letters always covered approximately 1° of the visual field. The PM targets were 3 letters, which were presented as a word (e.g., CUP) at the beginning of each PM block (see Supplementary Material). Presenting the targets as a word made them more memorable, which served to reduce the episodic memory component of the PM condition. Whenever participants reached one of the target letters, they had to perform an alternative response instead of the classification judgment.

Each block started at a unique position or letter but always with an SO phase for 2 s (Fig. 1). The starting point for the shape task was indicated by a green arrow, which disappeared after the first response. Blocks lasted for 7.5 s and were comprised of miniblocks. Their duration varied between 3 and 7 s to allow for an efficient estimation of BOLD signal changes and capped at 7 s to ensure a sufficient number of transitions between stimulus phases (Gilbert et al. 2005). Stimuli were presented at 1 of 2 possible screen locations (separated diagonally by ca. 6°) throughout a miniblock. At the beginning of each miniblock, the stimulus changed position to the other location, and the current stimulus phase (SO, SI) was randomly selected (Fig. 1). A "stay" trial is the first one of a new miniblock, if the stimulus phase has not changed relative to the last miniblock. In contrast, a "switch" trial marks the beginning of a miniblock after a change of stimulus phase. (All other OG trials are "non-switch" trials.) Changing the stimulus location on stay trials provided a baseline for switch events, controlling for visual transients at the transition between stimulus phases. Furthermore, PM targets, that is, either junctions marked on the shape or the 3-letter word, were presented for 10 s directly before the blocks started.

The frequency of the PM targets was similar in both tasks (alphabet: 11.54%; spatial: 11.11%). They were chosen so that the delayed intention could not easily be incorporated in the OG task (see Burgess et al. 2003). Specifically, at least 4 OG trials preceded the appearance of the first target, and successive targets were separated by at least 4 intervening OG trials. The minimum gap between subsequent targets ensured that detection of one PM target could not act as a strong retrieval cue for the imminent next target. Thus, processes involved in target detection and intention realization had to be engaged for each individual target. Moreover, to avoid automatized processing of PM targets, each was used for a single block only, and the gap between targets varied pseudorandomly across blocks. This rendered the target sequence unpredictable and served to minimize the awareness for any rule underlying the sequence. In addition, half of the targets were from either half of the shape or alphabet, and they were equally often associated with either OG response (e.g., left or right key). Finally, the 3-letter words were chosen to lack strong emotional connotations. Participants responded with the index, middle, or ring finger of their right hand, each of which was assigned to 1 of 3 keys. A left key press indicated left turns or "just-straight" letters, whereas a right one was used for right turns or letters including curved lines. A middle button was associated with PM target detection.

In addition, participants performed a simple reaction time task. The target was a row of 5 white "X" (XXXXX), which were oriented alternately vertically or horizontally. They remained on the screen until a response was made and were replaced by a black screen until onset of the next target after a random ISI of 300–700 ms. Participants indicated target detection by pressing the left button with their index finger. A block lasted for 20 s. This task served as a baseline to allow comparison of contrasts across fMRI runs (see below).

The experiment was divided into 4 sessions, one for each combination of PM condition (OG, PM) and task (shape, alphabet). The OG session of a particular task was directly followed by its PM session. A session consisted of 6 blocks of the task, each succeeded by a block of the simple reaction time task. Thus, including presentations of short reminders of the instructions before each block (10 s for the experimental, 2 s for the reaction time task), a session lasted for approximately 12 min. Participants were allowed to rest between sessions. Order of tasks and assignment of color to stimulus condition in the alphabet task were counterbalanced. Before entering the scanner, participants were familiarized with the HF shape and practiced both OG tasks.

fMRI Recordings
A 3-T Siemens Allegra MRI scanner was used to acquire $T_2^*$-weighted echoplanar images (64 × 64, 3 × 3 mm pixels; time echo: 30 ms; time repetition: 2.34 s) sensitive to BOLD contrast. The whole brain was covered by volumes that comprised 36 oblique axial slices (2 mm thick, separated by 1.7 mm) oriented at approximately 10° to the AC-PC plane to diminish the susceptibility artifact from the sinuses. For each of the 4 sessions, a separate functional scan of 305 volumes was acquired, of which the first 6 volumes were discarded to allow for $T_1$ equilibration effects. Stimuli were projected on a mirror in direct view of the participant.

Data Analysis
Behavioral Analysis
Response times (RTs) for correct responses and accuracy of the ongoing trials (i.e., all trials of the OG condition and those of PM blocks that were not associated with a PM response) were analyzed separately for stay, switch, and nonswitch trials. The initial trial of each experimental block was excluded from analysis.
Due to the continuous nature of the shape task and the lack of an external marker for the subjects’ position on the shape, accuracy of single responses cannot be assessed. Thus, accuracy for this task was estimated by examining consecutive overlapping sequences of 4 responses. It was then coded if a given sequence made up a valid response sequence given the shape (for details, see Gilbert et al. 2005 and Supplementary Material). Similarly, a PM response was taken for a hit, if it was embedded in a valid sequence of 5 responses (see Supplementary Material).

fMRI Analysis
fMRI data were analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). The volumes were first realigned, corrected for different slice acquisition times, normalized into 2 mm cubic voxels, using the Montreal Neurological Institute reference brain, by fourth-degree B-spline interpolation, and smoothed with an isotropic 8-mm full-width at half-maximum Gaussian kernel.

The 4 sessions were treated as separate time series, and variance in BOLD signal was decomposed in a general linear model (GLM) (Friston et al. 1995). Regressors coded for sustained activation in the 4 main conditions of interest (OG_SO, OG_SI, PM_SO, and PM_SI) and the baseline condition (i.e., the RT task). Transient activation associated with switch and stay events was modeled by delta functions (coding for stimulus onsets). Additional regressors modeled the first miniblock of each epoch, the respective instruction periods for the baseline and the task blocks, and PM responses in either stimulus phase. These regressors were all convolved with a canonical hemodynamic response function (HRF) and comprised the full model for each session, in addition to regressors representing residual movement artifacts and the mean over scans. A 1/128-Hz high-pass filter was applied to the data and the model.

Parameter estimates for each regressor were calculated from the least-mean-squares fit of the model to the data. Effects of interest were assessed in a random effects analysis as follows: Eight contrasts were performed, each individually assessing the variance explained by a regressor representing 1 of the 4 main conditions of interest in the 2 tasks (i.e., shape OG_SO, alphabet OG_SO, etc.). These were taken relative to the baseline condition of the relevant functional run. Assuming that cognitive processes associated with the RT task and their neural correlates are invariant over time, this allows comparison of conditions scanned in different functional runs (Simons et al. 2006; see also Supplementary Material). The 8 contrasts of each subject were entered into a repeated-measures analysis of variance (ANOVA) using nonsphericity correction (Friston et al. 2002). Appropriate contrasts for effects of interest were conducted at this second level. Here, the data were analyzed averaged across tasks (e.g., Burgess et al. 2001, 2003; Gilbert et al. 2007). Hence, reported activations are unlikely to result from task-specific effects. A further second-level analysis was performed to assess transient BOLD signal changes associated with changes in stimulus condition (i.e., switch vs. stay trials). This analysis included contrast estimates for switch and stay events as a function of stimulus and PM condition. Contrasts were averaged across tasks and also corrected for session differences by the RT baseline task. Finally, to analyze brain-behavior relationships in the RT task, a separate GLM was estimated with 3 additional regressors created by a series of delta functions, each convolved with the HRF. One of the regressors coded for onset of the first stimulus; another one for all other stimuli onsets. A third regressor represented the parametric modulations of the second regressor by log(RT). Since RT distributions are positively skewed (Luce 1986), log(RT) rather than RT were employed so that slow response trials do not account for a disproportional fraction of the behavioral variance (Gilbert, Simons, et al. 2006).

For BA 10, the a priori region-of-interest (ROI), contrasts were thresholded at F < 0.05, familywise error (FWE) corrected for multiple comparisons within this brain volume (as defined by the MRICro Brodmann map: http://www.mricro.com; Rorden and Brett 2000). Small volume correction (SVC) was used for further ROI analyses as indicated in the Results. Moreover, regions outside BA 10 are reported if they survived a whole-brain-volume FWE correction at F < 0.05.

Results
Behavioral Results
Nonswitch Trials
Inspection of the nonswitch trials indicated slowed responses for SI compared with SO phases and for PM compared with OG blocks (Fig. 2). Moreover, the shape task was associated with greater RT than the alphabet task. This pattern was reliable, as confirmed by an ANOVA with the factors task (shape, alphabet), PM condition (OG, PM), and stimulus phase (SO, SI), which revealed all main effects (task: F_{1,15} = 12.29, P < 0.006; PM: F_{1,15} = 46.22, P < 0.001; stimulus: F_{1,15} = 47.92, P < 0.001). In addition, all interactions including the task factor were significant (task × PM: F_{1,15} = 19.85, P < 0.001, task × stimulus: F_{1,15} = 21.74, P < 0.001; task × PM × stimulus: F_{1,15} = 46.22, P < 0.005). However, both main effects (i.e., PM condition and stimulus phase) were significant for both tasks (see Supplementary Material).

Accuracy was generally high for both tasks (>84%). While it was greater for PM than OG blocks of the alphabet task, the reverse pattern was associated with the shape task. This was statistically confirmed by an ANOVA with the factors of task, PM, and stimulus phase. The analysis revealed a main effect of task (F_{1,15} = 20.02, P < 0.001), indexing higher accuracy for the alphabet task as well as interactions between task and PM (F_{1,15} = 13.63, P < 0.005) and PM and stimulus phase (F_{1,15} = 4.71, P < 0.05). The former interaction reflected a crossover pattern, as corroborated by follow-up analyses establishing significant PM condition effects for both shape (F_{1,15} = 8.54, P < 0.05) and alphabet task (F_{1,15} = 7.68, P < 0.05). Note, however, that performance estimates for the shape task were more conservative for PM than OG data (Supplementary Material). The latter interaction between PM condition and stimulus phase resulted from a significant effect of the stimulus-phase factor (i.e., lower accuracy for SI than SO) for PM blocks only (F_{1,15} = 6.37, P < 0.05).

Switch versus Stay Trials
For each task a separate ANOVA was performed on RT with the factors trial type (switch, stay), PM condition, and stimulus phase (Fig. 2). For the alphabet task, all main effects were significant (i.e., slower responses for switch trials, the PM condition, and SI phases), and so were all interactions (all F > 9.17, all P < 0.01). The interactions indicate that the trial type effect varied with PM condition and stimulus phase. Bonferroni-corrected comparisons of stay and switch trials were significant for all combinations of these factors (all P < 2.97; all P < 0.005). Except for OG_SO, switch trials were always associated with slower responses. For the shape task, the interactions between trial type and PM (F_{1,15} = 5.03, P < 0.05) and trial type and stimulus phase (F_{1,15} = 11.92, P < 0.005) were significant. Follow-up analyses revealed a trial type effect for SO phases (F_{1,15} = 9.02, P < 0.01) and a trend for PM blocks (F_{1,15} = 4.34, P < 0.06) (i.e., switch slower than stay trials in both cases). Thus, whereas RT were generally influenced by trial type in the alphabet task, this was only the case for SO phases of the shape task.

Analysis of the accuracy data revealed main effects of PM condition (F_{1,15} = 4.83, P < 0.05) and stimulus phase (F_{1,15} = 5.85, P < 0.05) for the alphabet task, indexing higher performance in OG blocks and SO phases. The shape task was associated with a main effect of PM condition (F_{1,15} = 8.93, P < 0.01) and an
interaction between PM condition, stimulus phase, and trial type ($F_{1,15} = 6.47$, $P < 0.05$). However, Bonferroni-corrected paired samples $t$-tests did not reveal a trial type effect on accuracy for any combination of stimulus phase and PM condition (all $|t| < 1.9$, all $P > 0.08$).

**PM Targets**

An ANOVA of RT data with the factors task and stimulus phase revealed no significant main effects (task: $F_{1,15} = 10.23$, $P < 0.01$; stimulus: $F_{1,15} = 7.48$, $P < 0.05$), reflecting slower responses for the shape task and the SI phases, respectively (Table 1). Analysis of hit rates yielded an effect of stimulus condition ($F_{1,15} = 11.56$, $P < 0.005$), indicating a greater hit rate for SO phases (Table 1). Thus, participants were faster and more reliable in detecting PM targets during SO phases.

**fMRI Results**

**Sustained Engagement of mrPFC: Functional Overlap**

Significant BOLD signal changes for the contrasts of PM condition (OG vs. PM) and stimulus phase (SO vs. SI) are summarized in Table 2. Contrasting OG with PM blocks (OG > PM) revealed increased BOLD signal within mrPFC, including aspects of the medial frontal gyrus, extending caudally into the cingulate gyrus, and more rostral parts of the superior frontal gyrus (Fig. 3a). SO compared with SI phases (SO > SI) elicited more widespread activation, covering bilateral occipital cortex, right superior parietal lobe, temporal lobe, and precuneus as well as right parahippocampal gyrus and left dorsal striatum. Importantly, this comparison was also associated with mrPFC activation (Fig. 3b).

Table 1

<table>
<thead>
<tr>
<th>Task</th>
<th>Stimulus phase</th>
<th>Hit rate</th>
<th>RT (hits)</th>
<th>Mean</th>
<th>SE</th>
<th>Mean</th>
<th>SE</th>
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<tr>
<td>Alphabet</td>
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<td>0.03</td>
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<tr>
<td></td>
<td>SI</td>
<td>0.86</td>
<td>0.04</td>
<td>1135.5</td>
<td>160.2</td>
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<td></td>
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<tr>
<td>Shape</td>
<td>SO</td>
<td>0.64</td>
<td>0.08</td>
<td>1422.6</td>
<td>239.2</td>
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<tr>
<td></td>
<td>SI</td>
<td>0.73</td>
<td>0.10</td>
<td>1566.9</td>
<td>326.4</td>
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</table>

Note: SE, standard error; SO, stimulus-oriented; SI, stimulus-independent.

Table 2

<table>
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<tr>
<th>Contrast</th>
<th>Region</th>
<th>BA</th>
<th>Side</th>
<th>MNI coordinates</th>
<th>$Z_{max}$</th>
<th>Voxels</th>
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<td>l</td>
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<td>2</td>
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<td>10</td>
<td>r</td>
<td>$8$ $62$ $20$</td>
<td>4.33*</td>
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<td>4.13*</td>
<td>11</td>
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<td>11</td>
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<td>$52$ $12$ $12$</td>
<td>3.93*</td>
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<tr>
<td></td>
<td>MFG/ACC</td>
<td>32</td>
<td>r/l</td>
<td>$6$ $42$ $–6$</td>
<td>5.17</td>
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Note: l, left; r, right; MFG, medial frontal gyrus; MFG, middle frontal gyrus; ACC, anterior cingulate cortex; PHG, parahippocampal gyrus; SPL, superior parietal lobe; TC, temporal cortex; LDC, lateral occipital cortex; PC, parietal cortex; n/a, not applicable; MNI, Montreal Neurological Institute.

*small-volume corrected for BA 10.
was further assessed by analyzing baseline-corrected estimates of the 4 regressor coefficients (i.e., OG_SO, OG_SI, PM_SO, and PM_SI) that were extracted from the peak voxel of the more caudal cluster (Fig. 3c). (Virtually identical results were obtained for the other cluster.) Consistent with the individual contrasts, the ANOVA revealed main effects of PM condition ($F_{1,15} = 17.0, P < 0.001$) and stimulus phase ($F_{1,15} = 18.07, P < 0.001$), reflecting greater recruitment for OG blocks and SO phases. The interaction was not significant ($F_{1,15} < 1, P > 0.5$), also indicating that the effects of stimulus and PM condition were additive. This pattern also emerged for analyzing the data separately for each task (Supplementary Material).

**Sustained Engagement of mrPFC: Relation to Performance**

One might suggest that activation of this mrPFC region merely reflected task-unrelated processes during the easier conditions (i.e., SO and OG) that are less likely to occur during the more difficult conditions (i.e., SI and PM). Therefore, we examined if within-subject signal changes as a function of PM condition (OG > PM) or stimulus condition (SO > SI) can be accounted for by associated differences in performance (as indices of relative “task difficulty”). Neither RT nor accuracy differences were significantly correlated with the parameter estimates ($-0.25 < r < 0.08$; all $P > 0.36$). Furthermore, signal changes within the peak voxel during the RT task were analyzed. This task primarily requires SO processing, that is, attending toward the externally presented stimuli. If mrPFC supports task-related processes during such low-demand situations, we expected to observe greater activation on faster trials. On a trial-by-trial basis, RTs were negatively associated with BOLD signal, that is, greater activation was associated with better performance ($z = 1.87, P < 0.05$). (Note that RT and response–stimulus interval were uncorrelated [Fisher’s $z = -0.007 \pm 0.008$ (mean $\pm$ standard error of mean); $t_{15} = -0.82, P > 0.4$], implying that participants did not “rest” longer on trials associated with fast responses.) Thus, BOLD signal in mrPFC did not seem to merely decrease as a function of task difficulty (i.e., when task-unrelated processes have to be suspended). Instead, this region seems to support task-related processes during low-demand situations such as the RT task that require SO processing.

**Sustained Engagement of mrPFC: Functional Segregation**

In addition to recruiting overlapping aspects of mrPFC, the contrasts SO > SI and OG > PM were also associated with unique activations within this region. Particularly, segregation along a dorsal-ventral axis was observed, where the contrast of PM conditions was associated with more superior activation (Fig. 4a). To formally test for systematic spatial differences, $y$- and $z$-coordinates of each contrasts’ peak voxels were extracted. This was done for each sagittal slice within medial BA 10 (defined as $-8 \leq x \leq 8, y \geq 40, -12 \leq z \leq 30$), separately for each task and each subject (Fig. 4b for a similar approach, see Gilbert et al. 2007). Consistent across tasks, the PM contrast was associated with more superior peak coordinates ($z = 8.4$ vs. $z = 3.65$; $F_{1,15} = 4.83, P < 0.05$), whereas no significant difference on the caudal-rostral axis was obtained.

**Sustained Engagement of lpPFC**

The reverse contrast PM > OG was associated with activations of the left parietal lobe, bilateral precuneus, and posterior medial and middle frontal gyrus (Table 2), while no suprathreshold activation was observed for SI > SO (for activations at a lower threshold of $P < 0.001$, uncorrected, and at least 10 contiguous voxels, see Supplementary Material). Thus, neither contrast yielded activation of lpPFC. Since this area had previously been implicated in PM, ROI analyses were conducted at reported peak voxels in the left ($x = -30, y = 64, z = -4$) and right ($x = 40, y = 52, z = 4$) lateral lobes (Burgess et al. 2001). Specifically, SVC were applied for 3 mm spheres, to test for the main effect PM > OG as well as for interactions between PM condition and stimulus phase. Both PM > OG and the interaction contrast [(PM_SO > OG_SO) > (PM_SI > OG_SI)] revealed significant BOLD signal changes in the left ROI ($z = 1.96$ and $z = 1.88, x = -30, y = 62, z = -2$). The right ROI ($z = 2.8, x = 40, y = 52, z = 6$) was associated with the interaction only.

To further assess the nature of these effects, baseline-corrected estimates of the 4 conditions were extracted from the peak voxels revealed by the SVC analysis (Fig. 5). For the left hemisphere data, the effect of PM condition (PM > OG) was only significant for SO ($t_{15} = -4.1, P < 0.005$) but not SI phases ($t_{15} = -0.95, P > 0.36$). In contrast, right hemisphere activation was associated with greater activation for OG than PM blocks during SI phases ($t_{15} = 2.54, P < 0.05$) for parameter estimates by task, see Supplementary Material).

Thus, whereas PM compared with OG blocks were associated with left rostrolateral activation during SO phases only, activation of the right ROI was actually greater for OG than PM blocks during SI periods. To assess the reliability of this lateralization effect, an ANOVA was computed with the factors ROI (left, right), PM condition, and stimulus phase. In addition to revealing an interaction of ROI and PM condition ($F_{1,15} = 6.73, P < 0.05$), the analysis also showed a trend for the interaction between PM condition and stimulus phase ($F_{1,15} = 4.48, P < 0.06$). The 3-way interaction, however, was not significant ($F_{1,15} < 0.01, P > 0.96$). Hence, only the effect of PM condition differed significantly between the ROIs.
Figure 4. (a) BOLD signal changes for the contrasts 1) ongoing only versus prospective memory (OG > PM) and 2) stimulus-oriented versus stimulus-independent (SO > SI), and 3) for the overlap between both contrasts (thresholded at \( P < 0.001 \), uncorrected; averaged across both tasks). (b) Mean \( z \)-coordinates of the peak voxels for the individual contrast within each sagittal plane of rostromedial prefrontal cortex. Error bars indicate standard error of means.

Table 3

<table>
<thead>
<tr>
<th>Region</th>
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<th>MNI coordinates</th>
<th>( Z_{\text{max}} )</th>
<th>Voxels</th>
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</table>

Note: small-volume corrected for BA 10. l, left; r, right; MNI, Montreal Neurological Institute.

Figure 5. Parameter estimates from the ROI analyses within (a) left and (b) right rostralateral prefrontal cortex. Error bars indicate standard error of means. OG, ongoing only; PM, prospective memory; SO, stimulus-oriented; SI, stimulus-independent.

**Transient Engagement of rPFC**

Regions within BA 10 exhibiting BOLD signal changes for switch versus stay trials are listed in Table 3. Whereas no area was more strongly activated for stay compared with switch trials, the reverse contrast was associated with several foci. These were primarily located laterally in both hemispheres but also a medial cluster was identified (Fig. 6). Activation patterns within these regions were further examined by analyzing baseline-corrected estimates of the regressor coefficients for switch and stay trials of the 4 main conditions (Fig. 6). Site-specific ANOVAs with the factors PM condition, stimulus phase, and trial type (switch, stay) revealed greater BOLD signal for switch versus stay trials at both the left lateral (\( x = -32, y = 60, z = 12; F_{1,15} = 14.72, P < 0.005 \)) and the medial site (\( x = -6, y = 68, z = 14; F_{1,15} = 6.73, P < 0.05 \)). The right rostralateral site, in contrast, yielded a main effect of trial type (\( x = 22, y = 56, z = 6; F_{1,15} = 14.45, P < 0.005 \)) and the interaction between trial type and PM condition (\( F_{1,15} = 5.61, P < 0.05 \)). Follow-up analyses revealed that the trial type effect was restricted to OG blocks (\( F_{1,15} = 22.14, P < 0.001 \)). Thus, switch compared with nonswitch trials were associated with greater recruitment of left IrPFC and mrPFC, whereas such an effect was only present for OG blocks in right IrPFC. This pattern was largely corroborated by an ANOVA with the additional factor ROI (left, middle, right), which revealed a strong trend for the 4-way interaction (\( F_{2,30} = 3.2, P < 0.06 \)) in addition to the trial type main effect (\( F_{1,15} = 39.34, P < 0.001 \)).

**Table 3**

Significant BOLD signal changes within BA 10 for the contrast of switch versus stay trials, averaged across PM conditions, stimulus phases, and tasks

<table>
<thead>
<tr>
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Note: small-volume corrected for BA 10. l, left; r, right; MNI, Montreal Neurological Institute.
regressor estimates for (a) left lateral, (b) medial, and (c) right lateral rPFC (thresholded at $P < 0.05$, FWE corrected for BA 10). OG, ongoing only; PM, prospective memory; SO, stimulus-oriented; SI, stimulus-independent; Sw: switch; St: stay.

Figure 6. BOLD signal changes for the contrast switch versus stay and associated regressor estimates for (a) left lateral, (b) medial, and (c) right lateral rPFC.
that a gradient of connectivity runs along the genu of the corpus callosum (Amadio and Frith 2006). In the rhesus monkey, most superior aspects (BA 9) have strong connections with motor control regions (i.e., lateral premotor cortex, supplementary motor cortex, and cingulate motor area) but, at most, few connections with the rhinal cortex. In contrast, the latter brain region is highly connected with the most inferior and caudal medial PFC regions (BAs 25, 24, and 32; Barbas et al. 1999). Additionally, the inferiorly adjacent orbitofrontal cortex is primarily connected with sensory association areas (Ongur and Price 2002).

Thus, dorsal rPFC might primarily be connected with areas involved in the control of actions. Accordingly, the superior peak for the PM contrast may reflect differences in SO versus SI control of actions, that is, whether to perform the OG activity that is triggered by the stimulus or the internally represented intention that is less strongly prompted. Consistent with this idea, dorsal mrPFC has recently been found to be more strongly engaged when PM intentions were more directly cued by the environment (Gilbert et al. 2009). This hypothesis could be tested by contrasting PM conditions that vary in association strength between PM target and intention (cf. McDaniel et al. 2004). If, in contrast, ventral parts of rPFC are more strongly linked to sensory association cortices, they might be involved in mediating competition between perceived and imagined stimuli, which are processed in partly the same perceptual areas (Kosslyn et al. 2001).

Taken together, mrPFC is jointly associated with 1) OG task activity compared with additional maintenance of delayed intentions and 2) SO compared with SI processing. Thus, reduced recruitment of this region during PM performance might indeed reflect attenuation of SO attending. Concurrently, however, spatial segregation of peak activation suggests a functional gradient along a dorsal-ventral axis, which might reflect the regulation of different aspects of SO versus SI attending. This study thus contributes to the increasing knowledge about functional variations within mrPFC (Gilbert, Spenger, et al. 2006; Krueger et al. 2007; Gilbert et al. 2010; Volle et al. 2010).

Lateral rPFC

Sustained Engagement of Left IrPFC for Maintaining PM Intentions

Consistent with previous evidence (Okuda et al. 1998, 2007; Burgess et al. 2001, 2003; den Ouden et al. 2005; Simons et al. 2006; Gilbert et al. 2009; Reynolds et al. 2009), BOLD signal in the left IrPFC ROI was greater when participants performed a PM task in addition to OG activity. Burgess et al. (2001) demonstrated recruitment of this region when participants were prepared to carry out an intention in the absence of any actual PM targets (see also Simons et al. 2006; Reynolds et al. 2009). Thus, IrPFC appears to support the maintenance of an intention in the context of OG activity rather than actual target detection or task execution.

However, what processes supported by left IrPFC might be engaged while participants maintain a delayed intention? This region has been implicated in the adaptation to upcoming task demands (Sakai and Passingham 2003; Rowe et al. 2007). It thus might be involved in the preparation for intention execution. Alternatively, this region might subserve the interposition of the PM task in the OG activity (cf. Koechlin et al. 1999; Braver and Bongiolatti 2002). Consistently, lesions of left IrPFC have been associated with frequent rule breaks during such multitasking (Burgess et al. 2000). Both accounts, however, associate this region with processes that are not directly contingent on externally presented stimuli (i.e., task preparation precedes PM target onset; task coordination is not externally guided).

If this region is recruited to bias attention toward internally maintained information (i.e., the PM intention), one might expect an interaction between PM condition and stimulus phase. Specifically, the difference between PM and OG blocks might be smaller for SI than SO phases, since the system would already be in a relative mode of SI processing in the OG condition of SI phases. Consequently, there would be less need to bias attention toward this processing mode for the PM task. Thus, one may expect an underadditive effect of PM and stimulus condition. In contrast, accounts that implicate IrPFC in the integration of the outcomes of 2 or more cognitive operations would predict the opposite pattern, that is, a “superadditive” effect of the 2 factors (e.g., Ramnani and Owen 2004). The data yielded an underadditive pattern: The effect of PM condition was significant for SO phases only.

However, a more caudally located region in the right hemisphere exhibited an unexpected activation profile, that is, BOLD signal was greater for OG than PM blocks during SI phases. The functions supported by this subregion need to be further elucidated in future studies.

Transient Engagement of IrPFC for Shifting the Attentional Focus

In addition to supporting SI versus SO processing (Dumontheil, Gilbert, et al. 2010; Dumontheil, Hassan, et al. 2010), IrPFC also seems to be involved in shifting between both modes more generally (Gilbert et al. 2005; Dumontheil, Gilbert, et al. 2010). This was the case for the present data, where subregions of both mrPFC and left IrPFC were invariantly associated with greater BOLD signal for switch than for stay trials. The recruitment of IrPFC during switch events may accordingly reflect changes of task-relevant stimuli (i.e., externally presented vs. internally generated) (see also Pollmann et al. 2000; Braver et al. 2003).

In contrast, for right IrPFC, the trial type effect was restricted to OG blocks. If SO phases of PM blocks already require more SI processing than SO phases of OG blocks, there would be less need to shift between the 2 attentional modes in PM blocks. Hence, right IrPFC seems to be primarily engaged when the alternative processing mode needs to be strongly imposed (cf. Gilbert et al. 2005; Burgess et al. 2007).

Summary and Conclusions

Overlapping parts of mrPFC exhibited BOLD signal increases both during 1) mere OG task activity compared with additional PM performance and 2) SO compared with SI attending. This pattern supports the hypothesis that some of the rPFC activations associated with prospective memory reflect the demands that PM tasks make for the control of stimulus-oriented versus independent attending (Burgess et al. 2009). Thereby, this study corroborates a major prediction derived from the gateway hypothesis of rPFC function (Burgess et al. 2007). At the same time, the PM contrast was consistently associated with more dorsal peak activation than the stimulus contrast, implying additional engagement of distinct processes.
This finding suggests that mPFC might be functionally fractionated along a dorsal-ventral gradient. However, the nature of this putative gradient needs to be systematically examined in future studies. Moreover, left InPFC recruitment for PM compared with OG blocks may reflect processes involved in maintaining and/or implementing delayed intentions in the context of distracting OG activity. The observed underadditive interaction between PM and stimulus condition, however, argues against accounts that implicate rPFC in the integration of the outcomes of multiple cognitive operations (e.g., Ramman and Owen 2004).

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

Funding
Wellcome Trust (047963/Z/96/C to C.D.F.), the Royal Society (University Research Fellowship to S.J.G.), and the Medical Research Council (R.G.B.).

Notes
Conflict of Interest: None declared.

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