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Regional Brain Differences in the Effect of Distraction During the Delay Interval of a Working Memory Task

Florin Dolcos^a, Brian Miller^b, Philip Kragel^a, Amishi Jha^c, and Gregory McCarthy^{a,d,e}

^aDuke-UNC Brain Imaging and Analysis Center (BIAC), Duke University, Durham, NC

^bUniversity of California, Berkeley, CA

^cUniversity of Pennsylvania, Philadelphia, PA

^dDepartment of Psychology, Yale University, New Haven, CT

^eDurham Veterans Affairs Medical Center, Durham, NC

Abstract

Working memory (WM) comprises operations whose coordinated action contributes to our ability to maintain focus on goal-relevant information in the presence of distraction. The present study investigated the nature of distraction upon the neural correlates of WM maintenance operations by presenting task-irrelevant distracters during the interval between the memoranda and probes of a delayed-response WM task. The study used a region of interest (ROIs) approach to investigate the role of anterior (e.g., lateral and medial prefrontal cortex - PFC) and posterior (e.g., parietal and fusiform cortices) brain regions that have been previously associated with WM operations. Behavioral results showed that distracters that were confusable with the memorandum impaired WM performance, compared to either the presence of non-confusable distracters or to the absence of distracters. These different levels of distraction led to differences in the regional patterns of delay interval activity measured with event-related functional magnetic resonance imaging (fMRI). In the anterior ROIs, dorsolateral PFC activation was associated with WM encoding and maintenance, and in maintaining a preparatory state, and ventrolateral PFC activation was associated with the inhibition of distraction. In the posterior ROIs, activation of the posterior parietal and fusiform cortices was associated with WM and perceptual processing, respectively. These findings provide novel evidence concerning the neural systems mediating the cognitive and behavioral responses during distraction, and places frontal cortex at the top of the hierarchy of the neural systems responsible for cognitive control.

Keywords

Declarative Memory; Interference; Functional Neuroimaging

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Corresponding author: Gregory McCarthy, PhD Department of Psychology Yale University Box 208205 New Haven, Connecticut, 06520-8205 USA Phone: +1-203-432-7435 gregory.mccarthy@yale.edu.

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Classification Terms: Neural Basis of Behavior / Cognition / Learning and Memory: Systems and Functions

1. Introduction

The ability to maintain focus on goal-relevant information while ignoring goal-irrelevant and potentially distracting information depends upon a set of operations whose coordinated actions contribute to *cognitive control*. Cognitive control is necessary to bridge the gap between the processing of incoming sensory input and the execution of actions adaptively suited to the current goals and environment (Miller and D'Esposito, 2005). Two main categories of operations have been identified to contribute to cognitive control (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001): operations that allow active maintenance of goals and goal-relevant information in mind (working memory – WM; Baddeley, 1997) and operations that allow keeping goal-irrelevant information out of mind (cognitive inhibition).

Despite recent progress in identifying the neural circuitry contributing to cognitive control, the neural substrates of various mnemonic (WM maintenance) and non-mnemonic (cognitive inhibition) components of cognitive control are as yet incompletely specified. While the available evidence strongly implicates prefrontal cortex (PFC), controversy remains about the exact role various PFC subregions play in cognitive control (MacDonald et al., 2000, Milham et al., 2001, Badre and Wagner, 2004, Botvinick et al., 2004, Miller and D'Esposito, 2005). For instance, it is not clear what the exact contributions of different lateral PFC subregions are to operations subserving cognitive control operations engaged to counteract the presence of task-irrelevant distraction. Thus, the main goal of the present study was to investigate the influence of distraction upon lateral PFC activity during the delay interval of a delayed-response WM task. Investigation of these mechanisms using a WM task with distraction has the potential of clarifying the role of the PFC in cognitive control operations, as these operations are particularly engaged in challenging and non-routine situations (Botvinick et al., 2004).

Lateral PFC has repeatedly been associated with both mnemonic (e.g., WM maintenance) and non-mnemonic (e.g., interference inhibition) processes, both of which are essential for cognitive control (for comprehensive reviews concerning the role of the PFC in mnemonic and non-mnemonic processing, see Smith and Jonides, 1999, Shimamura, 2000, Badre and Wagner, 2004, Postle, 2006, Ranganath, 2006). The studies associating lateral PFC with mnemonic processes have typically used varieties of a delayed-response working memory task, and have demonstrated that sustained activity spans the interval occurring between the items to remember (the memoranda) and the probe item to be recalled. This sustained activity has been interpreted by some investigators as the neural substrate of WM maintenance (e.g., Goldman-Rakic, 1995, Courtney et al., 1997, Smith and Jonides, 1999, Curtis and D'Esposito, 2003), while others have interpreted it as a reflection of other more general, non-mnemonic, processes such as those related to preparatory states (e.g., Jha and McCarthy, 2000).

Lateral PFC has also been linked to other non-mnemonic functions. Increased lateral PFC activity in response to monitoring/manipulation demands (e.g., Petrides et al., 1993, D'Esposito et al., 1998) and to the recruitment of inhibitory processes (e.g., Jonides et al., 1998, D'Esposito et al., 1999, Jha et al., 2004) are particularly important in the context of cognitive control. These findings derived from functional neuroimaging studies (D'Esposito et al., 1998, Jonides et al., 1998, D'Esposito et al., 1999, Jha et al., 2004) are consistent with evidence from lesion studies, which have identified frontal patients as being particularly sensitive to distracting information, possibly due to an inability to inhibit task-irrelevant information (Richer et al., 1993, Chao and Knight, 1995, Chao and Knight, 1998, Shimamura, 2000).

One way to parse the contributions of PFC regions to cognitive control is to examine regional changes in activity while WM tasks are performed with concurrent distraction. For instance, a recent study by Dolcos and McCarthy (Dolcos and McCarthy, 2006) investigated the effect of distraction on sustained delay activity by presenting neutral or emotional distracters during the delay interval of a delayed-response WM task. In the absence of meaningful distracters, sustained activation occurred in the dorsolateral PFC/middle frontal gyrus (dlPFC/MFG) during the delay interval. However, the emotional distracters evoked strong relative *deactivation* (or negative activation relative to a prestimulus baseline) during the delay activity in this same region and impaired WM performance. Simultaneous with this deactivation of dlPFC, the emotional distracters evoked increased activation in ventrolateral PFC/inferior frontal gyrus (vlPFC/IFG), consistent with a role of this region in processes associated with inhibition (Aron et al., 2004, Dolcos and McCarthy, 2006). These contrasting findings are consistent with evidence linking dlPFC with WM maintenance operations (Goldman-Rakic, 1995, Courtney et al., 1997, Smith and Jonides, 1999) and vlPFC with inhibitory processes (Jonides et al., 1998, D'Esposito et al., 1999, Aron et al., 2004, Jha et al., 2004).

It is not clear, however, whether the pattern of relative deactivation in the dlPFC and increased activation of vlPFC was specifically associated with the processing of emotional distracters, or similar effects may be observed in the presence of other non-emotional distracters. Such non-emotional distracters that may interfere with WM performance could be novel stimuli that are highly similar, and thus more confusable, to the content of the memoranda. As the emotional distracters used by Dolcos and McCarthy (2006) were quite distinct from the memoranda, it was unlikely that subjects would confuse the distracters with the memoranda. The use of distracters that are confusable with the memoranda would likely also result in poor memory performance as Dolcos and McCarthy (2006) had observed with emotional distracters, but perhaps through a completely different mechanism. Thus, the first goal of the present study was to investigate the role of the lateral PFC regions during a delayed-response WM task in which the distracters could be confused with the memoranda (Jha et al., 2004, Yoon et al., 2006). In the present study, pictures of human faces were used as memoranda, and so novel faces and scrambled faces were presented as distracters during the delay interval.

As ample evidence demonstrates a role for posterior brain regions (i.e., parietal and occipito-temporal cortices) in WM processing (Chafee and Goldman-Rakic, 1998, Courtney et al., 1998, Rowe et al., 2000, Druzgal and D'Esposito, 2003), we also examined the influence of distraction upon delay activity in posterior brain areas (i.e., intraparietal sulcus = IPS and fusiform gyrus = FG). Previous WM studies have reported that the IPS shows similar patterns of activity as the MFG (Chafee and Goldman-Rakic, 1998, Courtney et al., 1998, Rowe et al., 2000), and thus suggest a role of IPS in WM, but the response of this region to distraction is largely unspecified (but see Sakai et al., 2002). Models for the interaction between the PFC and posterior perceptual areas (e.g., FG) suggest that activity in these latter regions is sensitive to top-down modulatory signals from the PFC (Chao and Knight, 1998, Shimamura, 2000, Miller and Cohen, 2001, Sreenivasan and Jha, in press), which may result in increased processing of task-relevant information and/or inhibition of task-irrelevant information. The FG sensitivity to modulatory influences from PFC implies that the FG may be involved in WM processes. However, the functional neuroimaging evidence for this role is mixed and has primarily turned on whether sustained activity is observed in the FG, as sustained activity is frequently interpreted as evidence for WM maintenance. Some studies have argued for a role of FG in WM (e.g., Druzgal and D'Esposito, 2003, Ranganath, 2006), while others suggest a role of FG in perceptual rather than mnemonic processing (e.g., Belger et al., 1998, Jha and McCarthy, 2000).

In the current study, event-related fMRI data were obtained while subjects performed a delayed-response WM task with distracters presented during the delay interval (Figure 1). The following three levels of distraction were investigated: *high distraction* (novel faces similar in form to memoranda), *low distraction* (scrambled faces), and *no distraction* (absence of any stimuli during delay period). An anatomical region of interest (ROI) approach was used as the primary analysis to accurately assess activity in those specific brain regions previously associated with WM and cognitive control processes, and included both anterior (i.e., from lateral and medial PFC) and posterior (i.e., IPS and FG) ROIs. In regard to the behavioral results, we hypothesized that the condition associated with the highest level of distraction would have the greatest interfering effect on WM performance. In regard to the fMRI results in the anterior ROIs, we hypothesized that dlPFC/MFG would show a pattern consistent with its involvement in WM maintenance, whereas vlPFC/IFG would show a pattern consistent with its involvement in cognitive inhibition. As for the posterior ROIs, we hypothesized that IPS would show a pattern consistent with a role in WM maintenance, whereas the FFG would show a pattern supporting its involvement in perceptual rather than mnemonic processing.

2. Results

Behavioral Results

Analysis of the behavioral data showed that subjects performed worse for the high distraction condition (*High*) than for both low distraction (*Low*) and no distraction (*None*) conditions. Accuracy scores were as follows (%/SD): *High* (74/12), *Low* (83/10), and *None* (80/9), and paired *t* tests confirmed that WM performance in the *High* trials was significantly lower than WM performance in both *Low* [$T(21) = 3.67, p < 0.005$] and *None* trials [$T(21) = 3.05, p < 0.007$], and that there was no significant difference between the WM performance in the *Low* and *None* conditions [$T(21) = 1.43, p > 0.16$].

fMRI Results

Anterior Brain Regions

Lateral PFC: Overall, a similar pattern of activity was observed in the lateral PFC ROIs, in which the *High* distraction condition systematically produced greater delay activity than both *Low* and *None* conditions (see Figure 2 and Table 1). In striking contrast to our previous delayed-response WM study that used emotional distracters (Dolcos and McCarthy, 2006), the confusable distracter condition that produced the most detrimental effect on WM performance (i.e., *High*) was associated with the highest *increase* (not *decrease*) of delay activity in the MFG/dlPFC (*High* > *Low* = *None*). Also, MFG was the only PFC ROI that displayed sustained activity during the delay interval in all conditions.

It is notable that both MFG and IFG showed greater differences among the three trial types than the SFG (Figure 2 and Table 1). However, while the MFG showed equivalent activation for the *Low* and *None* distraction conditions, activity in the IFG showed a gradient of increasing activation with increasing distraction (*High* > *Low* > *None*). This impression was confirmed by two-way ANOVAs including ROI (MFG and IFG) and Distraction (High, Low, and None) as within-subjects factors. ANOVAs performed at time points 18 and 21 sec following the memoranda onset (which showed the highest differential effects between the MFG and IFG activity - see Figure 2), yielded significant ROI x Distraction interactions (18 sec: $F(2, 22) = 4.92, p < 0.02$; 21 sec: $F(2, 22) = 7.87, p < 0.003$), which were explained by the fact that the three distraction conditions produced differential effects in the MFG (*High* > *Low* = *None*) and the IFG (*High* > *Low* > *None*) ROIs. Finally, as also illustrated by Figure 2, the three types of distracters did not

differentially affect activity in the anterior cingulate gyrus (ACG) ROI (*High* = *Low* = *None*).

Posterior Brain Regions—Activity in the IPS and FG ROIs showed both similarities and differences with the patterns observed in the anterior ROIs (see Figures 2 vs. 3 and Table 1). First, similar to the MFG, the IPS displayed sustained activity during the delay interval in all three trial types. Second, similar to the IFG, the FG showed no sustained activity for the *None* condition; i.e., in the absence of stimuli during the delay interval, FG activity returned to baseline. The main difference between activity in the anterior and posterior ROIs was that both the IPS and FG showed larger differences between levels of distraction (see Figure 3 and Table 1). ANOVAs performed on delay activity in these regions on a time point by time point basis identified significant main effects of distraction (see Table 1), and post-hoc analyses confirmed that both IPS and FG showed a gradient in the delay activity: *High* > *Low* > *None* (all *p* values < 0.05).

It is important to note that the patterns described in both the anterior and the posterior ROIs were observed in conditions where there were no significant differences in the number of active voxels contributed by each distracter condition, thus confirming that each distracter condition contributed to the abovementioned analyses with relatively equal numbers of active voxels (see Figure 6 in the Experimental Procedure section).

3. Discussion

Anterior Brain Regions

The present study investigated the effect of distraction on delay activity in brain regions previously associated with cognitive control processes when those distracters were highly confusable with the memoranda. With the exception of the anterior cingulate, these confusable distracters (*High*) elicited greater delay interval activity than the non-confusable distracters (*Low*) or the absence of distraction (*None*) at all anatomical ROIs examined, and subjects performed more poorly when confusable distracters were presented compared to non-confusable distracters and no distracters. These results are in striking contrast to the study of Dolcos and McCarthy (2006), where emotional distracters elicited relative deactivation during the delay interval (compared to prestimulus levels) within the MFG, while increasing activation in the adjacent IFG. Similar to the current study, the presence of emotional distracters resulted in poor subject performance in the WM task. Dolcos and McCarthy (2006) interpreted their MFG deactivation as an interruption of WM maintenance, and their increased IFG activation as evidence for an active inhibitory process that attempts to limit the impact of incoming distracting stimuli.

How can we reconcile the present results, where performance-disrupting distraction increased MFG activity, to those of Dolcos and McCarthy (2006), where performance-disrupting distraction decreased MFG activity to below baseline levels? We favor an interpretation based upon the prior findings of Jha and McCarthy (2000) who found that, within MFG in a delayed-response WM task, memory load effects occurred in the early part of the delay interval, where larger memory loads led to greater activation than smaller memory loads. However, despite this initial load-dependent effect, sustained activity at the end of the delay interval was equivalent in amplitude for all memory load levels. Jha and McCarthy (2000) interpreted the initial load-dependent delay activity in terms of a memory encoding process, and the later non-load-dependent delay activity as a general process related to the maintenance of a preparatory state. As the faces presented in the high distraction condition appeared randomly and asynchronously within a matrix of possible locations, and were by design confusable with the faces in the memoranda, we argue that the increased MFG activation observed here might have reflected the encoding of the distracter

faces into WM. As the confusable faces were presented throughout the delay interval, the encoding process was engaged throughout the interval, leading to an apparent increase in sustained activity. The non-confusable scrambled faces used in the low distraction condition, on the other hand, might have easily been filtered by attention, and thus these distracters were not encoded into working memory. Thus, there was no increase in delay activity for the low distraction condition over the level of the no distraction condition.

An alternative interpretation is that increased delay activity in the MFG reflects neural activity associated with enhanced resistance against distraction (Sakai et al., 2002), similar to the interpretation Dolcos and McCarthy (2006) offered for IFG in their experiment. The finding that the condition associated with the highest level of distraction (*High*) produced the greatest increase in the MFG delay activity supports the involvement of this region in processes subserving cognitive control operations. Based on findings from studies investigating WM processes and cognitive control {Miller, 2005 #92} one may predict *enhanced* (not *reduced*) dlPFC engagement associated with the distracter condition demanding increased WM monitoring and cognitive control (i.e., the memoranda-confusable distracters in the present study). Also, given that MFG was the only PFC region that also showed overall sustained delay activity, it is reasonable to posit that delay activity in the MFG reflects both active WM maintenance and the engagement of cognitive control processes to protect the task-relevant WM representations against distraction (Sakai et al., 2002). This interpretation, however, is not consistent with findings from studies that manipulated the domain of distracters relative to the content of the WM memoranda (i.e., congruent vs. incongruent), which provided evidence consistent with a role of MFG in WM maintenance but linked processing supporting delay-spanning interference resolution with activity in the IFG (e.g., Jha et al., 2004).

Similarly, while it is difficult to rule out this interpretation for the present IFG results, it is not consistent with the MFG deactivation results of Dolcos and McCarthy (2006). If the MFG activity was associated with enhanced resistance against distraction (Sakai et al., 2002), we might expect that MFG activity would also increase for the low distraction condition. Increased activity for both distracter conditions was found for the adjacent IFG, where a gradient of activity was found (high distraction > low distraction > no distraction). This pattern is consistent with a role in inhibitory processes: i.e., the condition requiring the highest level of inhibition (*High*) showed the highest level of delay activity, while the condition requiring the lowest level of inhibition (*None*) showed no delay activity (*High* > *Low* > *None*). These findings are consistent with Dolcos and McCarthy (2006) and other functional neuroimaging studies that have linked IFG activity with inhibition (reviewed in Aron et al., 2004). The early studies investigating this issue using the Sternberg Proactive Interference task (e.g., Jonides et al., 1998, D'Esposito et al., 1999) identified a role of the IFG in the inhibition of distraction that is endogenous to the task (i.e., information that was initially needed, but which is not longer necessary to perform the task). The present study, along with other recent functional neuroimaging studies of WM with distraction (Jha et al., 2004, Dolcos and McCarthy, 2006, Yoon et al., 2006), investigated the brain mechanisms mediating the effect of distraction that is exogenous to the WM task (i.e., distracters that are presented concurrently with the task-relevant stimuli), and provides evidence supporting the idea that IFG also plays a role in the inhibition of exogenous distraction (Jha et al., 2004, Dolcos et al., 2006, Dolcos and McCarthy, 2006). It should be noted, however, that given the similarity between activity in the IFG and FG observed in the present study, this interpretation needs further validation from studies directly investigating the interplay between these two regions putatively associated with different aspects of information processing (cognitive inhibition – IFG vs. perceptual processing - FG).

Turning to the medial anterior brain regions, the fact that delay activity in the ACG was equivalent across the three distraction conditions was surprising given the evidence linking the anterior cingulate cortex with conflict detection/resolution and cognitive control (Bench et al., 1993, MacDonald et al., 2000, Milham et al., 2001, Botvinick et al., 2004). While it is reasonable to expect that the presence of memoranda-confusable distraction may induce a conflict (as also suggested by the behavioral data) whose resolution is expected to involve activity in this region, the present ACG results does not support the involvement of this region in the detection/resolution of such conflict.

Posterior Brain Regions

The patterns of activity observed in the posterior cortical regions are consistent with evidence supporting a role of the IPS in WM maintenance and with the evidence associating the FG with perceptual processing. Although IPS has long been included in the network of brain areas associated with WM, its contribution to WM processes in the presence of task-irrelevant distraction has been less well investigated (but see Sakai et al., 2002). One finding that is systematically reported in previous WM studies concerns the similarity between activity in IPS and MFG (Chafee and Goldman-Rakic, 1998, Courtney et al., 1998, Rowe et al., 2000). Consistent with this idea, previous work from our group reported similar MFG and IPS patterns of activation across various behavioral manipulations in working memory (e.g. Jha & McCarthy, 2000). Similarly, the present finding that IPS activity showed sustained activity in all three conditions also suggests a role of this region in WM maintenance, although given the paucity of studies investigating the role of the IPS in WM tasks with distraction, additional studies are needed to further specify the contribution of this region to WM processes with and without distraction.

The increased delay activity in the FG to both face and scrambled face distracters and the absence of sustained activity in the absence of distracters suggest that the contribution of FG in the present task is related to perceptual rather than to mnemonic processing. The FG showed sustained activity whenever perceptual stimuli were present during the delay (*High* and *Low* trials), but in the absence of perceptual stimuli (*None* trials) the FG activity returned to baseline. Consistent with the role of the FG in face processing (e.g., Puce, Allison, Gore, & McCarthy, 1995; Kanwisher et al., 1997, McCarthy et al., 1997), activity in this region was present during the whole length of the *High* trials, which consisted of novel faces. Additionally, consistent with its sensitivity to perceptual information, FG activity was also present during the scrambled face condition (*Low* condition), although at a significantly lower level compared to the *High* trials. This finding is consistent with the results of a previous study from our group using a similar design (Jha and McCarthy, 2000), which manipulated the WM load to identify the brain regions associated with WM maintenance operations. Similar to the present findings, this study did not find evidence supporting the involvement of FG in WM maintenance operations, as FG did not show sustained delay activity in even the highest load condition. Collectively, these findings suggest that delay activity in the FG does not reflect processing associated with WM maintenance, but rather the involvement of this region in the processing of perceptual information (see also Belger et al., 1998). These findings are inconsistent with the evidence supporting a role of the fusiform cortex in WM maintenance for faces (e.g., Miller et al., 1991, Druzgal and D'Esposito, 2003, Ranganath et al., 2004). One possible explanation for this discrepancy may be that only the face-specific areas of the fusiform gyrus are involved in WM for faces (Druzgal and D'Esposito, 2003, Ranganath et al., 2004), whereas the FG as a whole is not. Of course, this explanation is *ad hoc* and should be the focus of future investigations.

Conclusions

In summary, the present study provides evidence concerning the neural systems mediating the effects of memoranda-confusable distracters presented during the delay interval of a delayed-response WM task. The findings concerning the anterior brain regions fit the expected pattern of activity for brain regions involved in higher-order processing that subserves cognitive control. The patterns of activity observed in the lateral PFC are consistent with a role of the MFG in encoding items into WM and maintaining a preparatory state, and a role of the IFG in inhibition. The findings concerning the posterior brain regions link IPS activity with mnemonic processing and FG activity with perceptual processing. Collectively, these findings are consistent with previous lesion, electrophysiological, and functional neuroimaging evidence that places the frontal lobes at the top of the hierarchy of a neural network responsible for cognitive control, and extend the evidence concerning the neural systems mediating the cognitive and behavioral responses in the face of distraction.

4. Experimental Procedure

Subjects

Twenty-six young (age range 19-22 yrs, average age = 20 yrs; 10 females), right-handed, healthy volunteers participated in the study. Fourteen subjects (age range 19-22 yrs, average age = 20.6 yrs; 7 females) participated in a behavioral study outside the scanner and twelve subjects (age range 19-21 yrs, average age = 19.6 yrs; 3 females), were scanned while performing the WM task. Data from four of the scanned subjects were excluded from the behavioral analyses because of software failures in recording the behavioral responses. All subjects provided written informed consent for a protocol approved by the Duke University Institutional Review Board, and received monetary compensation for their participation.

Task & Procedure

Subjects performed a delayed-response working memory task with distracters, while event-related functional magnetic resonance imaging (MRI) data were recorded. For each trial, the memorandum consisted of three human faces, which subjects had to encode and maintain in WM for a short delay (Figure 1). Then, subjects were presented with a single face probe and asked to decide whether that probe matched the content of the memoranda. In half of the trials, the probe stimulus matched one of the faces in the memory array, while the probes of the other half were novel foils. In 2/3 of the trials, either new faces (1/3 of the trials: *High*-level distraction) or scrambled faces (1/3 of the trials: *Low*-level distraction) were presented as distracters during the delay interval. Subjects were instructed to maintain focus on the WM task, despite the presence of the distracters, and to make fast and accurate responses to the probes. The rest of the trials (1/3) did not contain any distracters (no-distraction trials = *None*).

The order and timing of the events in each trial type were as follows (Figure 1). Each three-face memorandum was presented for 3 seconds and followed by an 18-second delay interval. All memorandum faces were unfamiliar faces, and there were no repeats across trials. The probes were presented for 1.5 seconds and followed by a 27-second inter-trial interval. The distracters were presented asynchronously (McCarthy et al., 1997) on the screen during the last 15 seconds of the delay interval – each individual face appearing for a brief interval (400-1000 ms) in one of a 3×3 matrix of possible spatial locations. Since the distracters were presented during the delay interval, their presence did not affect the overall timing. Thus, the total trial length was of 49.5 seconds. The subjects made a choice-button response with the index finger of their left or right hand to indicate whether the probe did, or did not, match one of the memory items (50 % of the probes matched the content of the memoranda).

There were a total of 90 trials equally divided into the three task conditions (i.e., 30 *High*, 30 *Low*, and 30 *None* trials). To prevent habituation or strategy shifts associated with blocked designs, these trials were randomly intermixed, and then divided into 10 runs, each consisting of 9 trials. The only difference between the 3 trial types was the level of distraction, which was defined by the nature of the distracters. The face distracters consisted of fast asynchronous presentation of sixty faces stimuli, which began 3 seconds after the offset of the cue and continued until the probe was presented. The distracter stimuli were chosen from a different set of faces than the faces used as memoranda or cues, so that there was no overlap between the memoranda/cues and distracter face stimuli. The gender of the face distracters always matched the gender of the faces in the memoranda. The scrambled face distracters were similarly presented as the face distracters. The scrambled faces were created by computing a two-dimensional Fourier transform of the face distracters, by randomly permuting the phase spectrum and then computing the inverse Fourier transform. Although unrecognizable as faces or objects, these images preserved the spatial frequency and luminance of the original face images allowing for a perceptual control. The face and scrambled face distracters were presented randomly in a 3×3 matrix of possible locations directly surrounding the fixation point, to avoid shifts of spatial attention during the delay interval.

Stimuli were presented on an LCD projector, located behind the subjects' head, which subjects could see via angled mirror glasses. Stimuli were presented using custom software from Duke University's Brain Imaging and Analysis Center (BIAC). Subjects were instructed to maintain a constant gaze on the central fixation point of the screen, where all of the memoranda, probes and distracting stimuli appeared. Subjects were asked to look at, but not to actively name or remember the distracter stimuli, while trying to maintain the memoranda faces in working memory. During the inter-trial interval, subjects were instructed to maintain fixation in preparation for the next trial.

MRI Data Acquisition

Scanning was performed on a General Electric 1.5 T NVi scanner. T1-weighted sagittal localizer images were first acquired. The anterior commissure (AC) and posterior commissure (PC) were identified in the mid-sagittal slice and 34 contiguous axial slices were prescribed parallel to the AC-PC plane, and high-resolution T1-weighted structural images were acquired (TR=450-ms, TE= 20-ms, FOV=24-cm, 256² matrix, slice thickness= 3.75-mm). A second series of coronal images (perpendicular to the AC-PC) were then acquired using the same imaging parameters. Thirty-four contiguous echo-planar images (EPIs) sensitive to blood-oxygenation-dependent (BOLD) contrast were acquired parallel to the AC-PC plane using the same slice prescription described above for the axial structural images (TE= 40-ms, 24-cm FOV, 64² image matrix, 90° flip angle, TR = 3-sec, slice thickness=3.75-mm resulting in 3.75-mm³ isotropic voxels). The resulting EPI volumes could then be viewed with the same uninterpolated resolution in coronal, axial, and sagittal orientations. Images were superimposed on a slice-by-slice basis upon both the axial and coronal high-resolution anatomical images. **fMRI Data Analysis.** Data analysis consisted of preprocessing and statistical analyses performed on fMRI data extracted from anatomically defined regions of interest (ROIs). These analyses involved methods derived from previous WM studies conducted by our group (Jha and McCarthy, 2000, Dolcos and McCarthy, 2006), and were performed with SPM99 and in-house BIAC tools programmed in MATLAB.

Preprocessing included slice timing (TR alignment), to compensate for the interleaved slice acquisition order within each TR interval and co-registration of the anatomical and the functional images. The fMRI data were analyzed completely within each individual's

anatomy – i.e., no normalization to a standard template or smoothing was performed. Prior to preprocessing, fMRI data were individually screened for motion (the center of mass for each EPI image volume within each time series was computed and plotted to measure head movement), and data from subjects who had excessive motion (a deviation in the center of mass greater than 2 voxels) were excluded from analysis and replaced.

ROI Tracing—Anatomical regions of interest (ROIs) were manually drawn on each subject's high-resolution coronal image, based on established anatomical landmarks and diagnostic gyral and sulcal patterns (Damasio, 1995, Duvernoy et al., 1999), and using the same procedures as Jha and McCarthy (2000). This anatomical ROI identification preceded statistical analysis (see below) and was thus blind to functional activation patterns. Both anterior (superior frontal gyrus = SFG, middle frontal gyrus = MFG, inferior frontal gyrus = IFG, and the anterior cingulate gyrus = ACG), and posterior ROIs (intraparietal sulcus = IPS and fusiform gyrus = FG) were isolated (Figure 4). The anterior ROIs were drawn on 11 slices ranging from 41.25 to 3.75-mm anterior to the AC the posterior ROIs were drawn on 7 slices ranging from 41.25 to 63.75-mm posterior to the AC. For the anterior ROIs, the SFG was traced between the superior frontal sulcus (identified on the lateral aspect) and the cingulate sulcus (identified on the medial aspect), the MFG was traced between the inferior and the superior frontal sulci (both identified on the lateral aspect), the IFG was traced between the inferior frontal sulcus and the lateral fissure, and the ACG was identified between the cingulate and the callosal sulci (both identified on the medial aspect). For the posterior ROIs, IPS was identified as the gray matter proximally surrounding the intraparietal sulcus, and the FG was identified between the collateral and the occipitotemporal sulci. A white matter (WHM) region was also traced and used as a control. ROIs were drawn on each slice on which the structure appeared, and the ROI slices were labeled based on the distance in mm from the anterior commissure (AC). Each subject contributed a total of 140 ROI slices. These anatomical ROIs were used to extract the averaged fMRI signal from each subject's data set, as a function of experimental condition, brain region, slice, time point, and hemisphere, which were then used as input for random-effects group analyses (i.e., *t* tests/ANOVAs, and post-hoc analyses performed with Fisher's PLSD). Anatomical ROI analysis has the advantage of measuring activation within a structure as defined by each individual's anatomy without the inaccuracies and smoothing introduced by normalizing each brain to a common coordinate system. However, the loci of activation within the predefined anatomical ROI can only be ascertained at the smallest unit of measurement which, for our study, was the level of each brain slice in which the ROI was drawn. These slices were numbered in millimeters from the anterior commissure, and so it was possible to group data from individuals at this level of precision.

Statistical Analyses—Both individual and group analyses were performed. For individual analyses, anatomically defined ROIs were used to identify and count the *active* voxels associated with each condition. Active voxels were identified based on the correlation of the fMRI signal for each condition with a reference waveform (Figure 5A), which was empirically derived from a previous study using a similar working memory paradigm (Jha and McCarthy, 2000). To avoid missing regional and/or task-related differences in the waveshape of the HDR (as some voxels might show sensitivity only to some phases of the WM task - e.g., encoding but not maintenance or retrieval), before extracting the fMRI signal from the active voxels, the average signal changes for *all* voxels within each anatomically defined ROI were computed for each time point and plotted for inspection of the hemodynamic response (HDR) profile (Jha and McCarthy, 2000). This analysis was independent of the reference waveform, and as Figure 5B illustrates, the overall shape of the average HDR profiles was very similar to the reference waveform and across the ROIs. This does not, however, exclude the possibility that some voxels might have had

time-activation profiles that differed from the reference waveform, but were too few in number to produce identifiable effects in the analysis of mean activity from all voxels contained in the anatomical ROIs (but see Jha and McCarthy, 2000).

In each subject's ROIs, the active voxels were identified as those whose activity significantly correlated with the reference waveform at $p < 0.05$ (see Figure 4 for examples of slices showing active voxels). The averaged fMRI signal was extracted from the active voxels of each subject's data set, as a function of experimental condition (i.e., *High*, *Low*, and *None* trial types), brain region, slice, hemisphere, and time point, using in-house BIAC software.

To avoid possible condition-related biasing in statistical analyses, the fMRI time courses for each subject were extracted for each distraction condition from the union of the active voxels, which were independently identified for all three trial types in each ROI and then collapsed together. These counts were then converted to percentages relative to the total number of voxels within each anatomical ROI. As Figure 6 illustrates, there were no significant differences in the number of active voxels contributed by each distracter condition, thus confirming that within each ROI the three distracter conditions contributed with relatively equal numbers of active voxels.

Finally, the average MR signal values were converted to percent signal change relative to a pre-memorandum onset baseline, which was calculated as the mean intensity of the two volumes (6-sec) preceding the presentation of the memoranda, and the resulting averaged time-epochs were subject to further random-effects group analyses, to determine whether activity differed as a function of distraction type and ROI. Statistical analyses focused on comparing the delay brain activity observed at the peak time points (i.e., the time points of the delay interval showing the highest statistical significance for the contrasts of interest) within the 9-24 sec period following the memoranda onset, when the differential effects of the distraction upon delay activity were most likely to occur (see Figures 2 and 3). As our ROI approach was focused upon a relative few preselected brain regions, a threshold of $p < 0.005$ (uncorrected) was used to identify significant main effects of distraction, and a threshold of $p < 0.05$ was used for post-hoc analyses.

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Figure 1.

Diagram of the delayed-response working memory (WM) task with distraction. Three categories of trials were involved, as follows: 1/3 of the trials contained novel faces (*High*-load distracters), 1/3 contained scrambled faces (*Low*-load distracters), and 1/3 contained no distracters (*None*). Subjects were instructed to encode and maintain the memoranda into WM, look at the distracters while maintaining focus on the WM task, and then indicate by pressing a response button whether the probes were part of the memoranda or not.

Figure 2.

Brain activity in the anterior ROIs. Lateral anterior ROIs showed similar general pattern of activity in which face distracters (*High*) produced greater delay activity than both scrambled (*Low*) and no-distraction (*None*) conditions. However, differences were also noticed, particularly in the MFG, IFG, and ACG. Specifically, MFG was the only PFC ROI that displayed sustained activity during the delay interval in all conditions, the IFG showed a gradient in the activation pattern ($High > Low > None$), and the ACG did not distinguish among the three experimental conditions ($High = Low = None$). S1 and S2 mark the onsets of the memoranda and the probes, respectively.

Figure 3.

Brain activity in the posterior ROIs. Activity in IPS and FG showed both similarities and differences with the patterns observed in the anterior ROIs. First, similar to the MFG, IPS displayed sustained activity during the delay interval in all three trial types. Second, similar to the IFG, the FG showed no sustained activity for the *None* condition: without perceptual stimuli during the delay, the FG activity returned to baseline. Different from the anterior ROIs, activity in the posterior ROIs showed more systematically significant differences across all conditions: *High* > *Low* > *None*.

Figure 4.

Anatomically-defined regions of interests (ROI) in anterior and posterior brain regions. The figure illustrates representative coronal slices showing the location in the brain of the anatomical ROIs. Analyses involved identification of active voxels (highlighted in red) in each subject, as a function of trial type, brain region, slice, hemisphere, and time point, whose activity was further examined across subjects using random-effects group analyses. SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, ACG = Cingulate Gyrus, IPS = Intraparietal Sulcus, FG = Fusiform Gyrus, and WHM = White Matter.

Figure 5.

Similarity between the shape of the reference waveform and the shape of the hemodynamic response (HDR) profiles of the anatomical ROIs. **A.** The left panel illustrates the shape of the reference waveform used to identify the active voxels; **B.** The right panel illustrates the shape of the average HDR profiles of the anterior and posterior ROIs that resulted from averaging the signal changes from all voxels within each anatomically defined ROI, across all three trial types and as a function of time point. The overall shape of the average HDR profiles was very similar to the reference waveform and across the ROIs.

Figure 6.

Similarities in the number of active voxels across the three trial types. No significant differences in the number of active voxels contributed by each distracter condition were observed, thus confirming that within each ROI the three distracter types contributed with relatively equal numbers of active voxels. The numbers of active voxels identified for each ROI are expressed in percentages relative to the total number of voxels within each anatomical ROI.

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Table 1

The effect of distraction load on activity in the anterior and posterior ROIs. The F values corresponding to one-way ANOVAs comparing the three categories of trial types are presented for representative time points. These statistics complement those reported in the main text, as well as the graphic representation of the comparisons across the three conditions illustrated in the figures showing the time course of activity in the ROIs. SFG = superior frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, and FG = fusiform gyrus; L = Left, R = Right.

Time Following the Memoranda Onset (sec)													
9		12				15				18			
ROI / Hemisphere		L	R	L&R	L	R	L	R	L&R	L	R	L	R
Anterior ROIs	SFG	4.6 [*]	11 ^{*****}	8.3 ^{*****}	1.7	7.0 ^{***}	4.0 [*]	2.7	3.2	2.1	2.5	2.4	2.2
	MFG	3.5 [*]	6.2 ^{***}	5.0 [*]	6.0 ^{**}	9.3 ^{***}	8.2 ^{***}	5.9 ^{**}	6.0 ^{**}	3.5 [*]	4.9 [*]	4.5 [*]	5.0 [*]
	IFG	3.6 [*]	10 ^{*****}	7.0 ^{***}	6.0 ^{**}	11 ^{*****}	9.1 ^{***}	4.2 [*]	7.0 ^{***}	5.6 [*]	7.8 ^{***}	7.3 ^{***}	7.6 ^{***}
Posterior ROIs	IPS	3.3	9.3 ^{***}	6.3 ^{**}	10 ^{*****}	20 ^{*****}	17 ^{*****}	5.8 ^{**}	14 ^{*****}	6.0 ^{**}	21 ^{*****}	15 ^{*****}	15 ^{*****}
	FG	6.4 ^{**}	6.5 ^{**}	7.0 ^{***}	25 ^{*****}	27 ^{*****}	30 ^{*****}	20 ^{*****}	23 ^{*****}	15 ^{*****}	18 ^{*****}	18 ^{*****}	18 ^{*****}

^{*}
p < 0.05
^{**}
p < 0.01,
^{***}
p < 0.005,
^{****}
p < 0.001,
^{*****}
p < 0.0001.