

Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task

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Abstract

Performance in delayed-response working memory (WM) tasks is typically associated with sustained activation in the dorsolateral prefrontal cortex (dlPFC) that spans the delay between the memoranda and the memory probe. Recent studies have demonstrated that novel distracters presented during the delay interval both affect sustained activation and impair WM performance. However, the effect of the performance-impairing distracters upon sustained dlPFC delay activity was related to the characteristics of the distracters: memoranda-confusable distracters *increased* delay activity, whereas memoranda-nonconfusable emotional distracters *decreased* delay activity. Because these different effects were observed in different studies, it is possible that different dlPFC regions were involved and the paradox is more apparent than real. To investigate this possibility, event-related fMRI data were recorded while subjects performed a WM task for faces with memoranda-confusable (novel faces) and memoranda-nonconfusable emotional (novel scenes) distracters presented during the delay interval. Consistent with previous findings, confusable face distracters increased dlPFC delay activity, while nonconfusable emotional distracters decreased dlPFC delay activity, and these opposing effects modulated activity in the same dlPFC regions. These results provide direct evidence that specific regions of the dlPFC are generally involved in mediating the effects of distraction, while showing sensitivity to the nature of distraction. These findings are relevant for understanding alterations in the neural mechanisms associated with both general impairment of cognitive control and with specific impairment in the ability to control emotional distraction, such as those observed in aging and affective disorders, respectively.

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1. Introduction

Studies investigating the neural correlates of delayed-response working memory (WM) tasks have demonstrated sustained activity in the dorsolateral prefrontal cortex (dlPFC) regions that spans the interval between the memoranda and the probe stimulus. Several groups have associated the presence

of this sustained activity with working memory maintenance (Courtney, Ungerleider, Keil, & Haxby, 1997; Curtis & D'Esposito, 2003; Funahashi, Bruce, & Goldman-Rakic, 1993; Goldman-Rakic, 1995; Smith & Jonides, 1999), although others have suggested that this activity might reflect other processes such as the maintenance of a preparatory set, mental timing, or the control of distraction (Jha & McCarthy, 2000). Task-irrelevant stimuli presented during the delay period typically interfere with WM performance, and so the effect of such distracters on sustained activation in delayed-response tasks has generated considerable interest. Indeed, evidence from recent functional neuroimaging studies suggests that sustained activity in the dlPFC is affected by distraction, but the nature of this effect has not been consistent.

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One study from our group has shown that the presence of emotional distracters in the delay interval was associated with impairments in WM performance and a marked decrease in sustained activity to below prestimulus baseline levels (Dolcos & McCarthy, 2006). This finding suggests that, possibly because of their relevance for survival, emotional stimuli can capture and divert attention, and thus may reallocate processing resources from task-relevant to task-irrelevant emotional stimuli. Other evidence from studies using non-emotional distracters (e.g., Yoon, Curtis, & D'Esposito, 2006) suggests that such effects are not specific to emotional distraction *per se*, and that similar decreases in sustained activation occur with memoranda-confusable non-emotional distracters (e.g., novel face presented as distracters in a WM task for faces). However, when our group tested memoranda-confusable neutral distracters (Dolcos, Miller, Kragel, Jha, & McCarthy, 2007), we found the expected impairments in memory performance, but *increased* not *decreased* dlPFC activity.

While the similar decreases in dlPFC-sustained activity in the studies of Dolcos and McCarthy (2006) and Yoon et al. (2006) that used different types of distracters suggests the operation of similar neural mechanisms mediating the effects of task-irrelevant distraction, the contradictory findings from Dolcos et al. (2007) suggest that the same behavioral outcome might occur through different mechanisms. However, because these contradictory effects were observed in different studies, using different subjects and analytical strategies, their comparability is open to question.

A possible explanation for these contradictory findings is that the dlPFC may show a subregional specificity with respect to its involvement in operations that are generally engaged in the processing of distraction, and/or are differentially sensitive to the nature of distraction. It is not clear whether the opposing effects of distraction type upon dlPFC-sustained activity (compare Dolcos & McCarthy, 2006 with Dolcos et al., 2007) modulate delay activity in the same dlPFC regions, or in different regions linked to the nature of distraction. As Dolcos et al. (2007) used an anatomical region of interest (ROI) analysis, it is possible that the ROIs may have summed brain activity over subpopulations of voxels with different activation profiles. Investigation of these issues has relevance for understanding the alterations in neural mechanisms that lead to general impairment of cognitive control (e.g., observed in frontal patients and in healthy and clinical aging Chao & Knight, 1995; Richer et al., 1993; Shimamura, 2000), and to the impairment in the ability to control emotional distraction (e.g., observed in mood and anxiety disorders, Mayberg et al., 1999; Watts, MacLeod, & Morris, 1988).

The goal of the present study, therefore, was to directly compare the effect of memoranda-confusable and memoranda-nonconfusable emotional distracters on delay activity in the dlPFC. Event-related functional magnetic resonance imaging (fMRI) data were acquired while subjects performed a delayed-response item recognition working memory task for faces. Distracters presented during the delay interval were either faces that were cropped and posed similarly as the faces comprising the memoranda (confusable distracters) or scenes with

strong emotional content (nonconfusable distracters). Additional control distracters were also included. Based on evidence from our prior studies that separately investigated this issue (Dolcos & McCarthy, 2006; Dolcos et al., 2007), we predicted that the memoranda-confusable distracters would increase dlPFC-sustained activity while the memoranda-nonconfusable emotional distracters would decrease dlPFC-sustained activity. Of critical interest was whether these predicated opposing patterns of sustained activity would occur in the same or different areas of the dlPFC.

2. Materials and methods

2.1. Subjects

Analyses were performed on data from fourteen healthy young (19–30 years of age) right-handed adults from Duke University community who participated in the study. Because other investigators have reported gender differences in the processing of emotional information (Lang, Greenwald, Bradley, & Hamm, 1993; Shields, 1991), we restricted our study to female participants to maintain homogeneity of the subject sample. The experimental protocol was approved by the Institutional Review Board at Duke University Medical Center and all subjects provided informed consent.

2.2. Stimuli

Subjects performed a delayed item recognition working memory task with novel distracters presented during the delay interval (Fig. 1). The memoranda consisted of sets of three human faces (50% females/50% males) that were photographed face forward and cropped closely above the neck. There were two main distracter types. The memoranda-confusable distracters consisted of similarly posed and cropped faces, having the same gender as the memoranda on that trial (overall, 50% females/50% males). The memoranda-nonconfusable emotional distracters consisted of high-arousing and negative pictures (e.g., depictions of violence, mutilations) selected from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1997). Due to differences in compositional complexity between these two distracter types, each had their own control. The control for the memoranda-confusable face distracters were scrambled faces that had the same average spatial frequency and luminance as the distracter faces, and thus served as a low-distraction perceptual control. The controls for the emotional scene distracters were low-arousing neutral scenes (e.g., depictions of everyday activities) selected from the IAPS that were supplemented by an in-house picture collection used in previous studies (Yamasaki, LaBar, & McCarthy, 2002) to equate emotional and neutral pictures for complexity and human presence. The IAPS means in the 1–9 arousal and valence scales, respectively, were as follows: 6.2/2.0, for negative scenes, and 3.5/5.2 for neutral scenes. All emotional and neutral pictures contained human characters, and all memoranda and distracters were presented in color. A total of 160 experimental trials (40 emotional, 40 neutral, 40 faces, and 40 scrambled faces) were acquired.

2.3. Experimental procedures

The pool of 160 trials was divided into 10 sets of 16 trials (four emotional, four neutral, four faces, and four scrambled faces), which were randomly assigned to 10 study blocks. Ten different block orders were randomly assigned to the participants. To avoid inducing long-lasting mood states, the order of trials within each block were constrained so that no more than three trials of the same type were consecutively presented. As illustrated in Fig. 1, each trial started with a 3 s presentation of the face memoranda, which subjects encoded and maintained in working memory over the 13 s delay interval between the offset of the memoranda and the onset of the memory probe. Three seconds after the offset of the memoranda, two distracters of the same category were presented consecutively for a total time of 5 s (2.5 s each). The subjects were instructed to look at the distracters but maintain focus on the working memory task. At

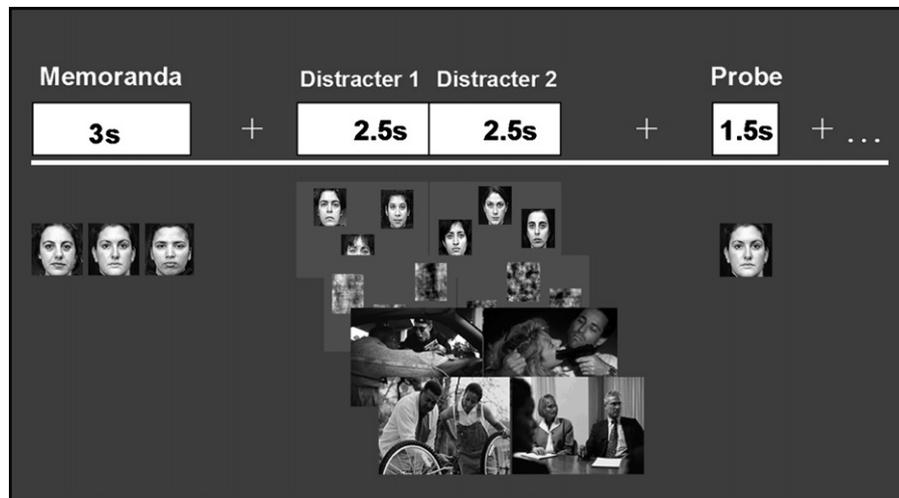


Fig. 1. Diagram of the delayed item recognition working memory (WM) task with distraction. Four categories of distracters were used: faces, scrambled faces, emotional scenes, and neutral scenes. Subjects were instructed to encode and maintain the memoranda into WM, look at the distracters while focusing on the WM task, and then indicate whether a single-face probe was part of the memoranda (*Old*) or not (*New*).

the conclusion of the delay interval, a single face was presented for 1.5 s. The subject's task was to indicate by pressing a button whether the probe face was one of the three faces that comprised the memoranda or whether it was a new face (50% of the probes were old, and 50% were new). Subjects were instructed to make quick and accurate responses while the probes were on the screen. Each probe was followed by a 12.5 s fixation interval to allow the hemodynamic response to return to the baseline (the total length of each trial was 30 s). Following scanning, subjects rated the emotional intensity of the emotional and neutral scenes using a four-point Likert scale (1 = lowest, 4 = highest). Based on these ratings, individual indices of emotional reactivity were calculated by averaging each subject's ratings of the emotional and neutral distracters. Emotional ratings were not obtained from three of the subjects because of mechanical failures in recording the behavioral responses. Thus, group emotional rating analysis was performed on data from eleven subjects.

2.4. Imaging protocol

Scanning was conducted on a 4T GE scanner (General Electric, Milwaukee, WI). After localizer, anatomical series, and high-order shimming, a series of 30 functional slices were acquired (axial plane; echo time, 31 ms; field of view, 25.6 cm²) using an inverse-spiral pulse sequence. Functional voxels were isotropic (4 mm³), and the acquisition repetition time (TR) was 2000 ms, allowing full-brain coverage. Anatomical scans consisted of high-resolution three-dimensional spin-echo structural images, which were acquired coplanar with the functional slices (anatomical–functional ratio = 4:1); anatomical voxels were also isotropic (1 mm³).

2.5. Data analysis

Statistical analyses were preceded by the following preprocessing steps performed with SPM99 and with custom Brain Imaging and Analysis Center (BIAC) tools: quality assurance, TR alignment, motion correction, coregistration, normalization, and smoothing (8 mm³ kernel). Data analysis used custom MATLAB scripts for voxel-wise analyses to compare brain activity associated with the conditions of interest (e.g., face distracters versus emotional distracters). Peri-event epochs time-locked to memoranda onset were extracted from the image time series, and separated by distracter type. No assumption was made about the shape of the hemodynamic response function.

Analyses were performed at both individual and group levels. For individual analyses, the peri-event epochs were selectively averaged for each subject as a function of trial type (i.e., faces, scrambled faces, emotional scene, and neutral scene) and time point (one pre- and 13 post-memoranda onset), and then pairwise *t* statistics for the contrast of interest (e.g., face versus scrambled face, emotional

versus neutral scene distracters, etc.) were calculated for each subject. Because we hypothesized that the content of distraction (i.e., the memoranda-confusable and emotional scene distracters) would differentially modulate (increase or decrease) dIPFC activity regardless of their effects on WM performance, and to increase statistical power, fMRI analyses included data for all trials (i.e., 40 per condition) and so error trials were not excluded. The individual analyses produced whole-brain average and activation *t* maps for each condition, contrast of interest, and time point, which were used as inputs for second-level random-effects group analyses. Group analyses involved both voxel-wise and region of interest (ROI) analyses (i.e., *t* tests/ANOVAs and complementing post hoc analyses), focused on investigating the impact of distraction nature on activity in the dIPFC. As a general rule, voxel-wise analyses were performed using the individual activation *t* maps, and time courses were computed from functional ROIs that encompassed the activated voxels for the contrasts of interest.

The main focus of the present analyses was to identify the dIPFC areas showing similar or opposing patterns of delay activity in the presence of memoranda-confusable distracters (i.e., novel faces) and memoranda-nonconfusable emotional distracters (i.e., novel emotional scenes). The dIPFC areas showing similar patterns of activity were identified using conjunction analyses, which consisted of two steps. First, each distracter type was compared to its own control—i.e., separate *t*-maps were computed to identify voxels where face distracters were significantly different from scrambled face distracters ($p < 0.01$), and where emotional scene distracters significantly differed from neutral scene distracters ($p < 0.01$). Then, the overlapping significant voxels in these two independent maps were identified by inclusively masking these *t* maps independently dissociating the face and emotional scene distracters from their own controls. The statistical significance of the resulting combined *t* maps was computed using Fisher's method of estimating the conjoint significance of independent tests, such that the conjoint significance threshold was $p < 0.001$ (Fisher, 1950; Lazar, Luna, Sweeney, & Eddy, 2002). For example, the brain regions showing similar increases in sustained PFC activity to both faces and emotional scenes distracters were defined as those where faces > scrambled faces and emotional > neutral scenes, whereas those showing similar decreases were identified as those where faces < scrambled faces and emotional < neutral scenes. Similarly, the brain regions showing opposing patterns of dIPFC activity to face and emotional scene distracters were identified as those displaying a significant activation in the direct contrast ($p < 0.001$) and also distinguishing the face and emotional distracters from their controls. Specifically, voxels were sought where face > emotional and face > scrambled and emotional < neutral, or where emotional > face and emotional > neutral and face < scrambled. Finally, an extent threshold of four contiguous voxels was used in all analyses.

The brain regions identified using the whole-brain voxel-wise approach were subjected to further investigation using ANOVAs and planned *t* tests performed on fMRI data extracted from functional ROIs comprising anatomically contigu-

ous voxels for the contrasts of interest, and from homologous ROIs from the opposite hemisphere. The functional ROIs were defined on *t* maps resulted from group-level random-effects analyses, by tracing contiguous voxels around the peak voxel (i.e., the voxels showing the greatest effects in the comparisons of interest), and the homologous ROIs were identified as the corresponding (i.e., ‘mirror’) voxels from the opposite hemisphere. The time points of the delay period (defined as the interval between the disappearance of the memoranda and the presentation of the probes) showing statistical significance for the contrasts of interest were computed, and the time points showing the largest differences (typically peaking between 12 and 16 s after the onset of the memoranda—i.e., 6–8 TRs post-memoranda onset) were tabulated.

3. Results

3.1. Behavioral results

3.1.1. Emotional intensity ratings

As expected, subjects rated emotional distracters as more emotional than the neutral distracters. The average scores for emotional intensity (1 = lowest, 4 = highest) as rated by the participants were 2.8 (S.D. = 0.3) for the emotional distracters and 1.1 (S.D. = 0.1) for the neutral distracters. Pairwise comparison of the rating scores was highly significant ($t(10) = 21.22$, $p < 0.00001$), thus confirming that the subjects’ rating scores were consistent with the normative scores.

3.1.2. Working memory performance

The percentages of probes correctly identified as being *old* or *new* were as follows (average %/S.D.): face distracters (74.8/7.4), scrambled face distracters (75.9/5.2), emotional scene distracters (75.1/9.7), and neutral scene distracters (73.9/9.0). A one-way ANOVA yielded a non-significant main effect of distracter type ($F(3, 52) = 0.14$, $p > 0.93$). Statistical comparisons of the reaction time data also did not yield significant differences ($ps > 0.1$), thus suggesting that WM performance was equivalent across all four trial types. To investigate whether this null finding at the group level is related to individual differences in behavioral responses, we examined whether subsets of subjects showed different WM performance to face and emotional distracters relative to their corresponding control conditions (i.e., scramble faces and neutral scenes, respectively). These analyses identified that half of the subjects ($N = 7$) showed an increase in WM performance to face distracters (increased performance subgroup: face = 59.9, scrambled face = 49.9; $p < 0.01$) whereas the other half showed a decrease in WM performance (decreased performance subgroup: face = 39.3, scrambled face = 53.6; $p < 0.005$). Similarly, half of the subjects ($N = 7$) showed an increase in WM performance to emotional distracters (increased performance subgroup: emotional scenes = 54.3, neutral scenes = 34.9; $p < 0.001$), whereas the other half showed a decrease in WM performance (decreased performance subgroup: emotional scenes = 46.5, neutral scenes = 60.6; $p < 0.02$). These findings suggest that the overall absence of differences at the group level is due to individual differences in subsets of subjects that show opposing behavioral effects. Thus, we conducted additional analyses to investigate whether these behavioral patterns were linked to differences in brain activity.

3.2. fMRI results

3.2.1. Opposing PFC modulation by memoranda-confusable faces and emotional scene distraction

Confirming our prediction, dlPFC delay activity was differentially sensitive to the presence of memoranda-confusable faces and memoranda-nonconfusable emotional scene distracters: memoranda-confusable face distracters increased delay activity while memoranda-nonconfusable emotional distracters decreased delay activity. No significant clusters were found in the dlPFC for the opposite patterns (see Table 1A). These findings are illustrated in Fig. 2, which shows the time course of activity extracted from a functional ROI identified in the right dlPFC (BA 10/46, Talairach coordinates: $xyz = 44, 44, 22$). A one-way (distracter type: face, scrambled face, emotional scene, and neutral scene) ANOVA performed on fMRI signal extracted from this functional ROI yielded a significant main effect of distracter type ($F(3, 39) = 15.67$, $p < 0.0001$), and post hoc analyses showed that all paired comparisons were significant ($p < 0.01$ for all). It is notable that the decreased pattern of activity observed in the dlPFC in the presence of emotional distracters was coupled with increased activity in the amygdala (see Fig. 3), thus replicating our previous findings that emotional distracters produce opposing patterns of activity in these two brain regions (Dolcos & McCarthy, 2006).

Moreover, consistent with our previous findings (Dolcos & McCarthy, 2006) and with the role of the right hemisphere in processing negative emotions (Borod et al., 1998; Davidson, 1995), the emotional distracters produced a greater impact in the right hemisphere. These findings were confirmed by a two-way ANOVA with *hemisphere* (left versus right) and *distracter* (face, scrambled face, emotional, and neutral) as within-subject factors, which was performed on fMRI data extracted from homologous ROIs traced in the left and right dlPFC (BA 10/46). This analysis yielded a significant hemisphere \times distracter interaction ($F(3, 39) = 3.03$, $p < 0.05$), and post hoc analyses confirmed that the difference between the face and emotional distracters was greater in the right hemisphere ($t(13) = 4.97$, $p < 0.0001$) than in the left hemisphere ($t(13) = 2.36$, $p < 0.02$).

Hemispheric-related differences were also investigated in dlPFC regions that were identified in the left hemisphere (e.g., BA 9). Although activity in this region survived the present thresholds only in the left hemisphere, this region showed a pattern of activity similar to that observed in the right dlPFC. Confirming this idea, a two-way ANOVA on fMRI data extracted from homologous ROIs did not yield a significant hemisphere \times distracter interaction ($F(3, 39) = .61$, $p > 0.6$). Thus, although regions from the left dlPFC showed a similar pattern of activity with that identified in the right dlPFC, the general pattern is consistent with a right-lateralization of the opposing influences of the face and emotional distracters.

We also investigated whether activation effects in the dlPFC were linked to individual differences in behavioral performance. To investigate this issue, two separate analyses were performed to examine the brain activity associated with individual differ-

Table 1
Brain regions showing opposing (A) and similar (B) patterns of delay activity in the presence of memoranda-confusable and memoranda-nonconfusable emotional distracters

(A) Opposing patterns of delay activity						
Face > Emo and Face > SFace and Neu > Emo	Talairach coordinates (xyz)			Face > Emo	Face > SFace	Neu > Emo
R dlPFC (BA 10/46)	44	44	22	5.67	2.20	3.07
R dlPFC (BA 9/46)	25	36	22	4.99	2.56	2.22
L dlPFC (BA 9)	-44	26	37	4.68	2.93	2.22
R PFC (BA 6)	24	15	58	4.75	2.09	2.78
L LPC (BA 40)	-44	-52	43	5.77	3.31	2.75
R LPC (BA 40)	40	-56	47	5.24	2.86	2.56
L SPC (BA 7)	-12	-68	48	6.70	2.46	1.99
R SPC (BA 7)	12	-59	55	5.83	3.21	1.94
Emo > Face and Emo > Neu and SFace > Face				Emo > Face	Emo > Neu	SFace > Face
L sgCG	-8	11	-11	5.50	4.74	2.37
L Amy/Uncus	-24	3	-14	5.89	3.77	1.97
R Amyg/Uncus	20	-1	-10	4.78	3.66	2.68
mFC (BA 6/24)	0	-12	67	4.30	2.05	2.58
L Hipp	-28	-20	-9	5.33	2.42	1.78
L PG/FG (BA 36/37)	-32	-36	-12	6.22	4.19	1.88
(B) Similar patterns of delay activity						
Emo > Neu and Face > SFace				Emo > Neu	Face > SFace	
R lpFC (BA 6/9)	44	2	35	5.76	3.51	
R lpFC (BA 6/9)	36	5	30	6.47	3.64	
R lpFC (BA 6)	37	-5	46	3.65	3.79	
mFC (BA 6/8)	0	18	54	4.06	3.74	
R SPC (BA 7)	24	-56	43	4.46	5.76	
L SPC* (BA 7)	-28	-51	58	3.20	3.07	
R FG (BA 37)	40	-47	-14	4.12	3.57	
L FG* (BA 37)	-44	-51	-14	3.68	3.68	
L OC BA (18/19)	-44	-74	-3	3.41	3.21	
R OC BA (18/19)	44	-78	-10	3.72	3.29	
L OTC BA (19)	-48	-77	19	3.32	3.23	

T values of paired contrasts between the conditions of interest as resulted from whole-brain voxel-based analyses are shown for the contrasts of interest. The *xyz* coordinates denote the location of the peak voxel in Talairach space (Talairach & Tournoux, 1988). The effects identified during the delay interval typically peaked between 12 and 16 s following the onset of the memoranda. Face = face distracter trials, SFace = scrambled face trials, Emo = emotional scene trials, Neu = neutral scene trials. mFC = medial frontal cortex, lpFC = lateral posterior frontal cortex, PFC = prefrontal cortex, LPC = lateral parietal cortex, SPC = superior parietal cortex, sgCG = subgenual cingulate gyrus, Hipp = hippocampus, PG = parahippocampal gyrus, FG = fusiform gyrus, OC = occipital cortex, OTC = occipitotemporal cortex, BA = Brodmann area, L = left, R = right; *extent threshold ≥ 2 voxels.

ences in performance in the presence of memoranda-confusable and memoranda-nonconfusable emotional distraction, as follows: (1) to compare the face increase and the face decrease subgroups and (2) to compare the emotional increase and the emotional decrease subgroups. Given that identification of brain activity specifically linked to behavioral differences in WM performance requires analyses based on brain activity associated with trials reflecting the actual behavioral differences, only correct trials were these included in these analyses investigating whether behavioral differences in WM performance can be linked to differences in the dlPFC activity. These analyses identified regions in the left dlPFC that paralleled the differences observed behaviorally—specifically, it showed increased activity in the subjects showing an increase compared to those showing a decrease in WM performance. These effects were confirmed by two-sample *t* tests directly comparing delay activity in the left dlPFC in the subgroups showing increased versus decreased WM performance to face ($t(10) = 2.46, p < 0.02$) and emotional ($t(10) = 5.35, p < 0.0005$) distracters (see Fig. 2).

Interestingly, these independent comparisons identified overlapping areas of activation that were contralateral to the right dlPFC region showing opposing effects to the face and emotional distracters.

Furthermore, we also investigated whether activation effects observed in the amygdala may be linked to individual differences in emotional ratings. To investigate this issue, across-subjects correlations between brain activity to emotional and neutral distracters and subjective scores for emotional rating were calculated. This analysis showed that although activity in the amygdala positively correlated with the emotional ratings of both emotional and neutral distracters, specific amygdala areas correlated with the rating scores for the emotional distracters (see Fig. 3).

3.2.2. Similar PFC modulation by memoranda-confusable faces and emotional scene distraction

Analyses that searched for brain regions showing similar patterns of delay activity to both face and emotional scene

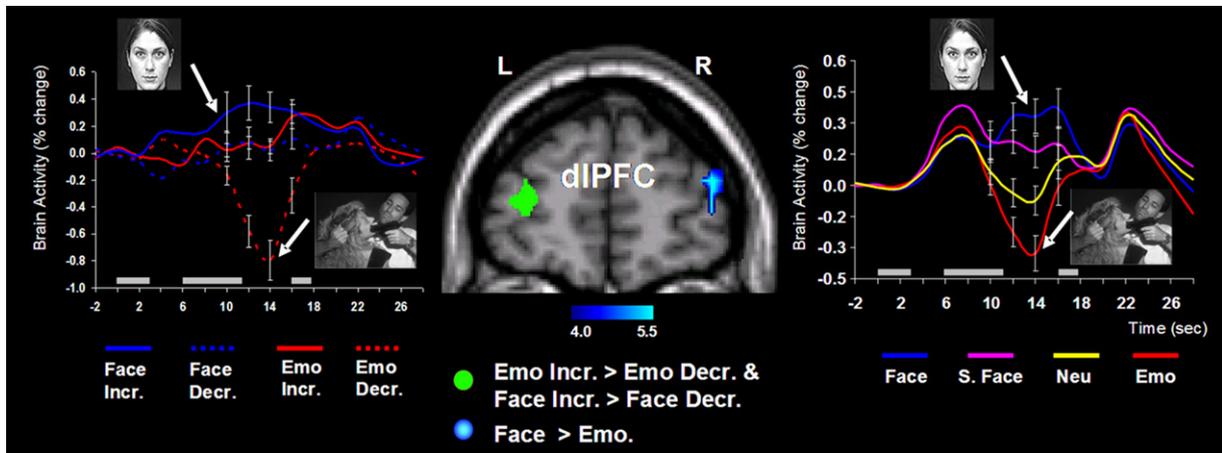


Fig. 2. Hemispheric asymmetry in the dlPFC. Specific areas of the right dlPFC (e.g., BA 10/46) showed opposing modulation linked to the nature of distraction (i.e., increased activity to face distracters, and decreased activity to emotional distracters). These findings were also confirmed when faces and emotional scene distracters were compared to their corresponding control conditions (i.e., scrambled faces and neutral scenes distracters, respectively). The blue blob on the middle panel shows the activation map of the direct contrast between delay activity to face and emotional distracters, superimposed on a high-resolution brain image displayed in a coronal view. The colored horizontal bar at the bottom of the brain image indicates the gradient of the *t* values. The line graph on the right side shows the time courses of activity in the right dlPFC ROI. In the left hemisphere, specific dlPFC areas (i.e., the green blob on the middle panel) showed similar modulation to face and emotional distraction linked to WM performance. The line graph on the left side shows the time courses of activity at peak voxels from overlapping areas of the left dlPFC (BAs 9/10) identified by the separate analyses examining differences in brain activity associated with individual differences in performance in the presence of memoranda-confusable (Face Increase > Face Decrease: Talairach coordinates –36, 48, and 27) and memoranda-nonconfusable emotional distraction (Emo Increase > Emo Decrease: Talairach coordinates –36, 59, and 12). For simplicity, the left-side graph is plotting the time courses of the face and emotional distracters alone. (i.e., with the scrambled face and neutral conditions omitted). The grey rectangular boxes above the x-axes indicate the onset and duration of the memoranda, distracters, and the probes, respectively. Face = face distracters, S. Face = scrambled face distracters, Emo = emotional scene distracters, Neu = neutral scene distracters; Incr. = increase group, Decr. = decrease group; L = left, R = right; BA = Brodman area. In all graphs, error bars represent the standard errors of means.

distracters identified posterior lateral frontal areas that showed greater delay activity to both distracter types than to their corresponding control conditions (i.e., faces > scrambled faces and emotional > neutral scenes). No significant clusters of voxels showed the opposite patterns of decreased activation to both face and emotional scene distracters (see Table 1B). Delay activity in BA 6/9 (Talairach coordinates: *xyz* = 44, 2, 35 T) showed a gradient in delay activity, with the perceptually more complex (i.e., relative to the face and scrambled face distracters)

and the semantically richest distracters (i.e., emotional scenes) producing the highest level of activity, and the simplest and meaningless distracters (i.e., scrambled faces) producing the lowest level of activity. These findings are illustrated in Fig. 4. A one-way (distracter type: face, scrambled face, emotional scene, and neutral scene) ANOVA performed on fMRI signal extracted from a functional ROI in the right lateral posterior PFC (see Fig. 4) yielded a significant main effect of distracter type ($F(3, 39) = 9.68, p < 0.0001$), and post hoc analyses showed that activ-

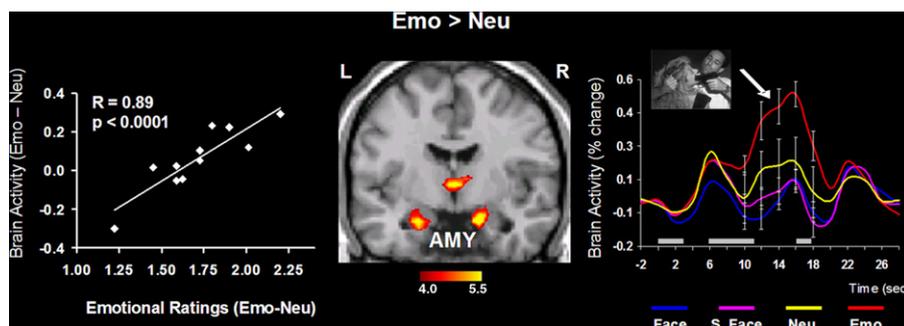


Fig. 3. Enhanced activity in the amygdala to emotional distracters. The panel in the middle shows the activation map of the direct contrast between delay activity to emotional and face distracters (Emo > Face), superimposed on a high-resolution brain image displayed in a coronal view. The colored horizontal bar at the bottom of the brain image indicates the gradient of the *t* values. Given that there were similar patterns of activity in the left and right amygdalae, the line graph on the right side of the figure illustrates the time courses of activity based on fMRI data extracted from functional ROIs traced around the peak voxels identified in the left (Talairach coordinates: –24, –5, –13, $t(13) = 6.02, p < 0.0001$) and right (Talairach coordinates: 16, –5, –13, $t(13) = 6.69, p < 0.00001$) hemispheres in the Emo > Face contrast, and averaged across hemispheres. The scatter plot on the left side illustrates the results of the correlation between individual indices of emotional reactivity and brain activity, as extracted from the peak voxel identified in the left amygdala (Talairach coordinates: –32, –4, –10). The voxels in the amygdala showing increased correlation with the subjective emotional ratings were identified by calculating across-subject whole-brain voxel-based correlations on the difference in the MR signal to the emotional and neutral distracters extracted at the peak time point of the effect in the amygdala (i.e., 16 s post-memoranda onset) and the difference in individual rating scores to emotional and neutral distracters.

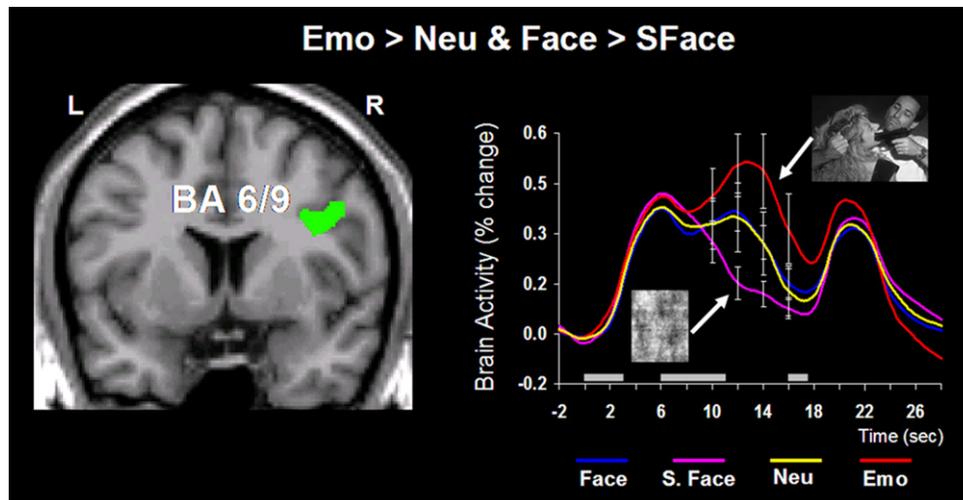


Fig. 4. Enhanced delay activity in the posterior lateral frontal cortex linked to processing of informational load. Delay activity in specific areas of the posterior lateral PFC (i.e., in the precentral gyrus and extending into the inferior frontal gyrus; BA 6/9) was modulated by the overall informational content of the distracters. Specifically, the distracters that were richest overall in informational content (i.e., emotional scenes) produced the highest level of activity, whereas the least complex and meaningless distracters (i.e., scrambled faces) produced the lowest level of activity.

ity in these regions was greater to face than to scrambled face distracters, and to emotional than to neutral scene distracters ($p < 0.001$ for both comparisons).

Finally, we also investigated whether the effects observed in these posterior PFC regions also showed a right-lateralized pattern of delay activity. Consistent with the idea that the effects of distraction differed across the two hemispheres, a 2 (hemisphere: left versus right) \times 4 (distracter: face, scrambled face, emotional, and neutral) ANOVA comparing delay activity from homologous posterior PFC ROIs (i.e., BA 6/9 identified above), yielded a significant hemisphere \times distracter interaction ($F(3, 39) = 9.06$, $p < 0.0001$). Moreover, consistent with a right-lateralized pattern of emotional distraction, post hoc analyses showed that this interaction was due to the fact that the effect of emotion differed across the two hemispheres. Compared to their control condition (i.e., neutral scenes), emotional distracters significantly affected the delay activity only in the right hemisphere ($t(13) = 4.94$, $p < 0.0002$), whereas the face distracters significantly affected delay activity in both hemispheres (right: $t(13) = 4.06$, $p < 0.001$; left: $t(13) = 2.32$, $p < 0.02$).

4. Discussion

The present study investigated the influence of different forms of distraction upon sustained activation in prefrontal cortex during the delay interval of a delayed item recognition working memory task. Consistent with our prior findings, the study identified dlPFC areas that showed opposing patterns of activity to memoranda-confusable (increased activity) and memoranda-nonconfusable emotional distracters (decreased activity). The opposite patterns were not observed. The present study also identified posterior lateral PFC regions where both types of distracters increased delay activity relative to their respective controls. These findings will be discussed in turn below.

The opposing patterns of activity evoked in the dlPFC by confusable face and nonconfusable emotional scene distracters

replicate, within the same study, our previous findings from separate studies (Dolcos & McCarthy, 2006; Dolcos et al., 2007). Importantly, our current results show that these opposing patterns occurred in the same dlPFC voxel clusters, and thus eliminate from consideration the possibility that different dlPFC subregions were responsible for these opposing effects observed in our prior studies. It is also notable that these dissociable patterns of dlPFC activity to emotional and memoranda-confusable distracters were observed in the absence of group-level behavioral differences, which rules out memory performance differences as the reason for these differing effects. The most parsimonious accounting of these opposing activations posits that the same process is influenced by both distracter types—i.e., the emotional distracters inhibit or otherwise diminish this process, while the face distracters increase its engagement.

Decreased dlPFC activity to novel emotional scenes suggests that this pattern of deactivation is a response specific to the presence of emotional distraction, rather than to distracters whose content is highly similar to the memoranda. We previously suggested that, perhaps of their relevance to survival, task-irrelevant emotional distracters momentarily commandeer the executive processing system and reallocate resources away from on-going tasks (Dolcos & McCarthy, 2006). Other work from our laboratory suggests that this effect may be observed even in the absence of apparent behavioral consequences (Yamasaki et al., 2002). The relative deactivation of dlPFC by emotional distracters is associated with increased activation of the amygdala and ventral lateral PFC by these same emotional distracters, suggesting that dlPFC deactivation may reflect an active inhibition from these or related ventral structures (Dolcos & McCarthy, 2006). We favor this interpretation in the present context, but recognize that it is not specific with respect to what executive control process is interrupted and/or inhibited.

One possibility is that increased dlPFC to novel faces may reflect enhanced processing demands necessary to monitor the

content of WM and inhibit the inclusion into WM of distracters that are highly confusable with the memoranda. This interpretation is consistent with evidence that dlPFC plays an important role in cognitive control mechanisms (e.g., Badre & Wagner, 2004; Miller & D'Esposito, 2005; Smith & Jonides, 1999), which are engaged to protect the WM content from task-irrelevant distraction (e.g., Sakai, Rowe, & Passingham, 2002). While this interpretation could account for the present results, it is inconsistent with prior results from our laboratory (Dolcos, Kragel, Wang, & McCarthy, 2006) and others (Aron, Robbins, & Poldrack, 2004; D'Esposito, Postle, Jonides, & Smith, 1999; Jha, Fabian, & Aguirre, 2004; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998) that have indicated that more ventrolateral regions of the PFC (primarily within the inferior frontal gyrus) are associated with inhibitory processes. The pattern identified in the left dlPFC is consistent with this idea, as participants that showed enhanced WM performance also showed increased brain activity in this region, compared to those that showed decreased WM performance in the presence of memoranda-confusable or memoranda-nonconfusable emotional distraction.

An alternative explanation for enhanced dlPFC activity to memoranda-confusable distracters is that it reflects the (perhaps partial) encoding of the memoranda-confusable faces into WM. This interpretation is consistent with Jha and McCarthy (2000) who argued that delay period activation associated with varying memory loads in delayed-response working memory tasks were evident in only the early part of the delay-interval, and suggested that this activity reflected differences in the initial encoding of the memoranda into working memory. If the face distracters were encoded into WM during the middle of the delay period, we would expect an increase in activity to occur later in the interval as was observed here. This interpretation is not incompatible with the interpretation posited above, as encoding of highly similar incoming novel stimuli might also lead to enhanced processing demands to monitor and protect the WM content.

The present findings also suggest a division of labor in the dlPFC across the two hemispheres, with the right hemisphere showing general sensitivity to the nature of distraction and the left hemisphere linking differences in activation with behavioral differences in the presence of confusable versus nonconfusable emotional distraction. This hemispheric asymmetry is consistent with a functional dissociation identified by our previous study in the ventrolateral PFC, with the right vlPFC being involved in coping with the general feeling of being distracted and the left vlPFC being involved in effective coping with the presence of emotional distraction (Dolcos & McCarthy, 2006, Dolcos et al., 2006).

The effect of increased activity to memoranda-confusable distracters identified in the right dlPFC is inconsistent with the findings reported by Yoon et al. (2006), who showed reduced dlPFC activity and with the results reported by Jha et al. (2004), who did not find differences in the dlPFC. There are two possible explanations for these discrepancies: the first related to differences in the experimental design and the second related to the manner in which the data analyses were performed. Concerning the first explanation, unlike the present study and that of Jha et al.

study, the distracters in the Yoon et al. study (and in other studies investigating similar issues—e.g., Postle, 2006; Postle, Druzgal, & D'Esposito, 2003) the distracters were relevant to the task and subjects were required to respond to them. Thus, it is possible that the difference in findings may reflect the engagement of different operations to perform the tasks. With regard to the second explanation, the analysis of the present study did not include any assumption about the shape of the expected hemodynamic response function. It should also be noted, however, that despite these differences there are also similarities between the studies. For instance, both Yoon et al. study and the analysis investigating individual differences in the present study linked reduced WM performance to reduced dlPFC activity following the disappearance of the distracters. The novel aspect of the present finding is that the effect observed in the left dlPFC was similar to both memoranda-confusable and memoranda-nonconfusable emotional distracters.

A different pattern of activity was found in more posterior lateral frontal regions, which were identified by the analyses investigating the PFC areas showing a similar pattern of response to face and emotional distracters. As Fig. 4 illustrates, delay activity in specific posterior lateral frontal areas (BA 6/9) showed a gradient in delay activity, with the emotional distracters (which were the richest in overall informational content) producing the highest level of activity, while the scrambled face distracters (which were the poorest perceptually and semantically) producing the lowest level of delay activity. Although BA 6 is not typically included as a part of the dlPFC, the patterns observed here are consistent with evidence that activity in this region is sensitive to manipulations of WM load (see review by Cabeza & Nyberg, 2000).

The pattern of activity observed in this region is slightly different than that observed in more anterior inferior frontal cortex (IFC) areas/vlPFC (BAs 45/47), which we also reported in our previous study (Dolcos & McCarthy, 2006). Different than the more posterior lateral frontal region identified here (BA 6/9), the more anterior IFC/vlPFC areas show a pattern of activity similar to that observed in the amygdala (i.e., greater activity to the emotional than to all other distracter categories). These findings suggest a possible functional dissociation along the anterior–posterior axis in the right lateral frontal cortex, with more anterior IFC areas showing a pattern of activity that increases proportional to the emotional content of the distracters, and the more posterior lateral frontal cortex showing a pattern of activity that increases proportional to the informational complexity (perceptual and/or semantic content) of the distracters. Thus, it is possible that activity in this posterior frontal region was sensitive to the 'informational load' of the novel distracters presented during the delay interval of the WM task, which might have been unintentionally processed even though they were task-irrelevant. However, this idea needs further empirical validation.

The right-lateralized pattern observed in the effect of emotional distracters replicates our previous findings (Dolcos & McCarthy, 2006) and is consistent with previous evidence concerning the role of the right hemisphere in processing negative emotions (Borod et al., 1998; Davidson, 1995; Dolcos, LaBar, & Cabeza, 2004), although this finding should be treated with cau-

tion given the evidence suggesting gender-related differences in the processing of emotional information (e.g., Cahill et al., 2001). Also, this right-lateralization seems to apply to brain activity reflecting general sensitivity to the nature of distraction but not to activity specifically linking differences in activation with behavioral differences in the presence of memoranda-confusable or memoranda-nonconfusable emotional distraction.

The fact that all of these activation effects were observed in the absence of clear differences in performance suggests that, to some extent, such effects might be detected in the brain even if they are not associated with measurable changes in behavior. On the one hand, if enhanced dlPFC activity reflected the engagement of cognitive control operations, the absence of behavioral differences might suggest that their engagement was efficient. Alternatively, if enhanced dlPFC activity reflected encoding operations, the absence of behavioral differences might suggest that automatic encoding of memoranda-confusable distracters did not reach the processing limit of the system, and thus did not lead to impaired performance. The latter logic may also be applied to explain the pattern of dlPFC deactivation in the presence of emotional distracters, which although produced effects detectable in the brain activity they might have not been powerful enough to reach the system's limit to cope with their presence. The present findings are consistent with both interpretations: while global patterns of activity may be identified in the absence of a direct link to behavioral differences, identification of patterns of brain activity specifically linked to behavioral differences can benefit from investigation of individual differences. Future studies should aim at investigating individual differences other than those related to the specific behavioral task scanned, that may affect brain activity associated with the ability to cope with emotional and non-emotional distraction (e.g., personality-related differences, etc.).

Collectively, identification of specific dlPFC regions that are sensitive to general modulation linked to the nature of distraction and specifically linked to behavioral differences in performance in the presence of distraction has relevance for understanding alterations in the neural mechanisms associated with general impairment of cognitive control (Chao & Knight, 1995; Richer et al., 1993; Shimamura, 2000) and with specific impairment in the ability to control emotional distraction (Mayberg et al., 1999; Watts et al., 1988). Moreover, the fact that activity in these regions may vary proportional to the engagement of cognitive control operations, even in the absence of clear behavioral consequences, has relevance for further investigations focusing on early detection of functional markers of cognitive control decline observed in healthy and pathological aging, for investigations focusing on detection of 'asymptomatic' susceptibility to affective disorders, as well as for investigations involving assessments of changes in brain activity as a result of therapeutic interventions.

5. Conclusions

In summary, the present study provides evidence concerning the role of the dlPFC in processing task-irrelevant distracters, and identified specific PFC regions that are sen-

sitive to the nature of distraction and linked with differences in performance in the presence of memoranda-confusable and memoranda-nonconfusable emotional distraction. The present findings suggest that the pattern of decreased delay activity observed reflects the reallocation of executive control resources by emotional distracters and, perhaps, the inhibition of current operations. The increased dlPFC activity in the presence of memoranda-confusable distracters may reflect the engagement of executive control mechanisms that monitor WM content and prevent the inclusion of highly confusable stimuli (left dlPFC), or by the partial encoding of these confusable items into WM (right dlPFC). These findings have relevance for understanding alterations in the neural mechanisms associated with both general and specific impairment in the ability to control cognitive and emotional distraction, respectively, and provide specific regions that can be targeted by studies investigating the neural mechanisms mediating the response to cognitive and emotional distraction, as well as by studies involving assessments of changes in brain activity resulted from therapeutic interventions.

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References

- Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, 8(4), 170–177.
- Badre, D., & Wagner, A. D. (2004). Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. *Neuron*, 41, 473–487.
- Borod, J. C., Obler, L. K., Erhan, H. M., Grunwald, I. S., Cicero, B. A., Welkowitz, J., et al. (1998). Right hemisphere emotional perception: Evidence across multiple channels. *Neuropsychology*, 12(3), 446–458.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neurosciences*, 12(1), 1–47.
- Cahill, L., Haier, R. J., White, N. S., Fallon, J., Kilpatrick, L., Lawrence, C., et al. (2001). Sex-related difference in amygdala activity during emotionally influenced memory storage. *Neurobiology of Learning and Memory*, 75(1), 1–9.
- Chao, L. L., & Knight, R. T. (1995). Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport*, 6, 1605–1610.
- Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature*, 386, 608–611.
- Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, 7(9), 415–423.

- D'Esposito, M., Postle, B. R., Jonides, J., & Smith, E. E. (1999). The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. *PNAS*, *96*(13), 7514–7519.
- Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. Davidson & K. Hugdahl (Eds.), *Brain asymmetry* (pp. 361–387). MIT Press.
- Dolcos, F., Kragel, P., Wang, L., & McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *NeuroReport*, *17*(15), 1591–1594.
- Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: An event-related fMRI study. *NeuroImage*, *23*(1), 64–74.
- Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *The Journal of Neuroscience*, *27*(6), 2072–2079.
- Dolcos, F., Miller, B., Kragel, P., Jha, A., & McCarthy, G. (2007). Regional brain differences in the effect of distraction during the delay of a working memory task. *Brain Research*, *1152*, 171–181.
- Fisher, R. A. (1950). *Statistical methods for research workers* (11th ed.). London: Oliver and Boyd.
- Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic “scotomas”. *J. Neurosci.*, *13*(4), 1479–1497.
- Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. *Ann N Y Acad Sci*, *769*, 71–83.
- Jha, A. P., Fabian, S. A., & Aguirre, G. K. (2004). The role of prefrontal cortex in resolving distractor interference. *Cognitive, Affective, and Behavioral Neuroscience*, *4*(4), 517–527.
- Jha, A. P., & McCarthy, G. (2000). The influence of memory load upon delay-interval activity in a working memory task: An event-related functional MRI study. *Journal of Cognitive Neuroscience*, *12*(2), 90–105.
- Jonides, J., Smith, E. E., Marshuetz, C., Koeppe, R. A., & Reuter-Lorenz, P. A. (1998). Inhibition in verbal working memory revealed by brain activation. *PNAS*, *95*, 8410–8413.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). *International affective picture system [pictures]*. Gainesville: NIMH Center for the Study of Emotion and Attention.
- Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology*, *30*(3), 261–273.
- Lazar, N. A., Luna, B., Sweeney, J. A., & Eddy, W. F. (2002). Combining brains: A survey of methods for statistical pooling of information. *Neuroimage*, *16*(2), 538–550.
- Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., et al. (1999). Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *American Journal of Psychiatry*, *156*(5), 675–682.
- Miller, B. T., & D'Esposito, M. (2005). Searching for “the top” in top-down control. *Neuron*, *48*(4), 535–538.
- Postle, B. R. (2006). Distraction-spanning sustained activity during delayed recognition of locations. *Neuroimage*, *30*(3), 950–962.
- Postle, B. R., Druzgal, T. J., & D'Esposito, M. (2003). Seeking the neural substrates of visual working memory storage. *Cortex*, *39*(4–5), 927–946.
- Richer, F., Decary, A., Lapiere, M. F., Rouleau, I., Bouvier, G., & Sainthilaire, J. M. (1993). Target detection deficits in frontal lobectomy. *Brain and Cognition*, *21*(2), 203–211.
- Sakai, K., Rowe, J. B., & Passingham, R. E. (2002). Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nature Neuroscience*, *5*(5), 479–484.
- Shields, S. A. (1991). Gender in the psychology of emotion: A selective research review. In K. T. Strongman (Ed.), *International review of studies on emotion* (pp. 227–245). New York: Wiley.
- Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. *Psychobiology*, *28*(2), 207–218.
- Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science*, *283*(5408), 1657–1661.
- Talairach, J., & Tournoux, P. (1988). *A Co-planar Stereotactic Atlas of the Human Brain*. Stuttgart, Germany: Thieme.
- Watts, F. N., MacLeod, A. K., & Morris, L. (1988). Associations between phenomenal and objective aspects of concentration problems in depressed patients. *British Journal of Psychology*, *79*, 241–250.
- Yamasaki, H., LaBar, K. S., & McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. *Proc Natl Acad Sci USA*, *99*(17), 11447–11451.
- Yoon, J. H., Curtis, C. E., & D'Esposito, M. (2006). Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex. *Neuroimage*, *29*(4), 1117–1126.