

Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex

Jong H. Yoon,^{a,b,c,*} Clayton E. Curtis,^d and Mark D'Esposito^{a,b,c}

^aHenry H. Wheeler Jr. Brain Imaging Center, 132 Barker Hall, University of California Berkeley, Berkeley, CA 94720-1650, USA

^bHelen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA 94720, USA

^cDepartment of Psychology, University of California, Berkeley, Berkeley, CA 94720, USA

^dDepartment of Psychology, New York University, 6 Washington Place, Room 859, New York, NY 10003, USA

Received 31 March 2005; revised 13 August 2005; accepted 23 August 2005

Available online 14 October 2005

Maintaining relevant information for later use is a critical aspect of working memory (WM). The lateral prefrontal cortex (PFC) and posterior sensory cortical areas appear to be important in supporting maintenance. However, the relative and unique contributions of these areas remain unclear. We have designed a WM paradigm with distraction to probe the contents of maintenance representations in these regions. During delayed recognition trials of faces, selective interference was evident behaviorally with face distraction leading to significantly worse performance than with scene distraction. Event-related fMRI of the human brain showed that maintenance activity in the lateral PFC, but not in visual association cortex (VAC), was selectively disrupted by face distraction. Additionally, the functional connectivity between the lateral PFC and the VAC was perturbed during these trials. We propose a hierarchical and distributed model of active maintenance in which the lateral PFC codes for abstracted mnemonic information, while sensory areas represent specific features of the memoranda. Furthermore, persistent coactivation between the PFC and sensory areas may be a mechanism by which information is actively maintained.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Working memory; Cognition; Prefrontal cortex; Visual association cortex; Event-related fMRI; Functional connectivity

Introduction

Working memory (WM) is a complex process and is composed of multiple component cognitive processes. A cardinal feature of

WM is the on-line maintenance of information to guide future behavior. The specification of the functional neuro-architecture subserving this process remains controversial. In tasks involving visual objects, one group of studies points to the lateral prefrontal cortex (PFC) (Courtney et al., 1997, 1998; Funahashi et al., 1989; Fuster, 1973; McCarthy et al., 1996; Miller et al., 1996; Scalaidhe et al., 1999) as the site of maintenance, while others implicate the visual association cortex (VAC) (Druzgal and D'Esposito, 2003; Postle and D'Esposito, 1999; Postle et al., 2003; Ranganath et al., 2004). Additionally, few studies have provided clear evidence for the nature of the representations coded by persistent delay period activity.

In the field of cognitive psychology, distraction paradigms have been instrumental in lending empirical support to influential models of WM (Baddeley et al., 1984; Logie et al., 1990). These paradigms rely on the logic that a distractor disrupts WM performance by engaging and interfering with a capacity-limited pathway that is common to distraction and WM processing. Monkey electrophysiology and human fMRI experiments have adopted delayed response paradigms with distraction to identify neural pathways subserving maintenance. They are based on the rationale that only regions whose activity persists after distraction can support maintenance during successful trials. This strategy has been employed to identify distinct regions thought to represent maintenance of verbal (Gruber, 2001) and visual information (Postle et al., 2003) in humans. Single unit studies investigating visual object maintenance have demonstrated delay period activity in the PFC (Fuster, 1973; Scalaidhe et al., 1999) and in IT (Miyashita and Chang, 1988; Nakamura and Kubota, 1995; Sakai and Miyashita, 1991); but only PFC activity has been shown to be resistant to task irrelevant distraction (Miller et al., 1993, 1996). Thus, IT activity may reflect bottom-up, perceptually-driven processes critical to stimulus representation, while PFC activity may reflect processes necessary for goal-directed behavior.

* Corresponding author. Department of Psychiatry, UC Davis School of Medicine, 2230 Stockton Blvd., Sacramento, CA 95817, USA. Fax: +1 510 642 3004.

E-mail addresses: jhyoon@ucdavis.edu (J.H. Yoon), clayton.curtis@nyu.edu (C.E. Curtis), despo@socrates.berkeley.edu (M. D'Esposito).

Available online on ScienceDirect (www.sciencedirect.com).

In our human event-related fMRI study, we attempted to clarify the contribution of the lateral PFC and VAC to maintenance by examining delay period activity while subjects performed a delayed response task with distraction. The persistence of delay period activity after distraction implicates that region's involvement in maintenance. To clarify the nature of representations in these areas, we manipulated the congruency of the memoranda and distractor by utilizing two categories of visual objects (faces and scenes) that engage object-specific areas of the PFC (Courtney et al., 1997, 1998; Sala et al., 2003) and VAC (Epstein and Kanwisher, 1998; Kanwisher et al., 1997). We anticipated that congruency would produce selective interference in WM performance (Jha et al., 2004), which would then allow us to examine the neural correlates of this effect and to make inferences on the nature of representations during maintenance in these areas.

Methods

Subjects

Twelve healthy volunteers (ages 23–33; 8 females) participated in this experiment. All participants were recruited from the University of California Berkeley community. This study was approved by the Committee for the Protection of Human Subjects at the University of California Berkeley. All experiments were conducted at the Henry H. Wheeler, Jr. Brain Imaging Center at the University of California Berkeley.

Behavioral paradigm

Stimulus presentation and response recordings were conducted with E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA;

<http://www.pstnet.com>) Stimuli were projected onto a screen viewed by participants through a mirror mounted on the head radiofrequency (RF) coil while the subject was lying prone in a scanner. Participants made their responses with the right index and middle fingers on a response pad.

Participants performed a modified version of a three-item delayed response working memory task (Fig. 1) while being scanned. We tested subjects with both face and scene memoranda; the behavioral data from both WM tasks are presented. The congruency effect was evident behaviorally only with faces. Accordingly, our ability to make inferences based on selective interference is limited to systems supporting face WM, and the fMRI data presented are for face WM. During the encoding phase, three faces were presented sequentially over a period of 3.1 s. The subjects were instructed to maintain these images over the entire delay period and make a match discrimination with the probe stimulus. The subjects were to press the left most button with a match, and the adjacent button with no match. In the middle of the delay period, a distractor stimulus, either a face or scene, was displayed for 0.9 s. The delay period is thus separated into two components, delay 1 and delay 2, of equal duration of 10.1 s. Prior to entry into the scanner, the subjects were shown one face target and one scene target stimuli. The subjects were instructed to make a match discrimination between the distractor stimulus and these targets. On one third of trials, the distractor stimulus matched one of the targets, while on the remainder of trials, the distractor was a unique stimulus. There were two responses given per trial: one for the WM delayed response task and one for the distractor target detection task. Responses were recorded on a 4-button response box. The subjects were to press the left most button if the distractor stimulus matched one of the targets and the adjacent button if it did not. The distractor stimulus was outlined in grey so as to help distinguish this portion of the task from the rest of the trial.

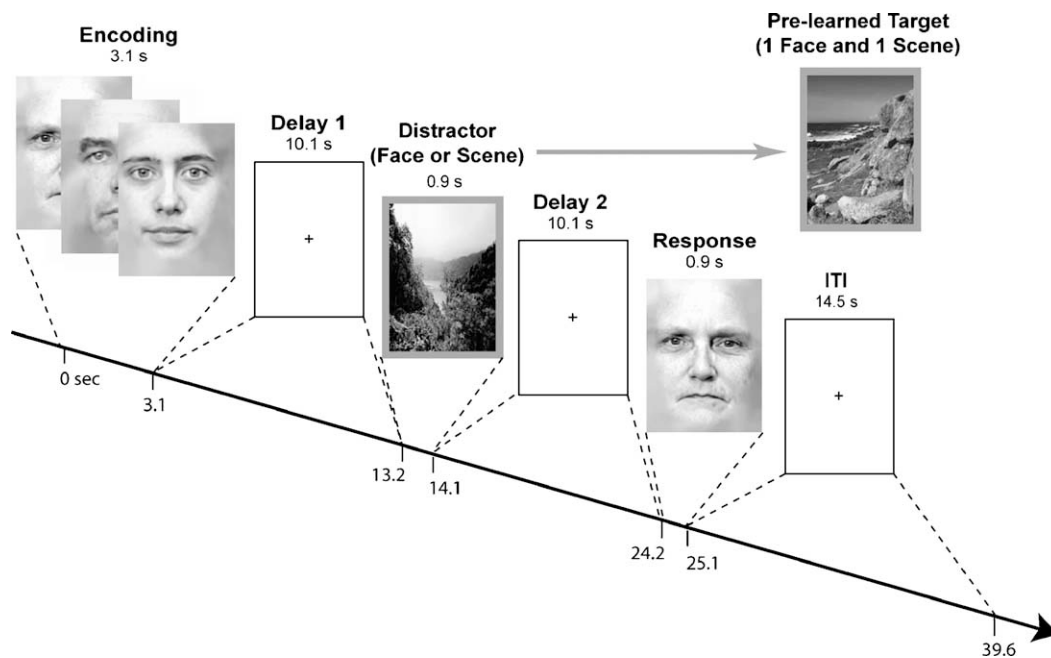


Fig. 1. Schematic diagram of the distractor task. During encoding, subjects remembered three faces shown sequentially over 3.1 s. After a 10.1 s delay period, they were shown a picture bounded by a grey border, of either a face or scene, which required them to make a decision whether this stimulus matched a pre-learned target face or scene. After another delay period of 10.1 s, the probe stimulus appeared during the response period and the subject responded whether this matched one of the encoded stimuli. After the 14.5 s ITI, the brief appearance of a red cross bar signaled the beginning of the next trial.

We employed two categories of visual stimuli, faces and natural outdoor scenes. All stimuli were novel, except in cases where the distractor and probe stimuli were matches to distractor targets and cues, respectively. Stimuli subtended a visual angle of 10°. Faces represented a random sampling of age groups and distribution between genders. They were edited so as to minimize peripheral mnemonic cues: faces were cropped to exclude the ears and hair; contour of the head and face was blurred with the background; any face with distinguishing characteristics such as facial hair, blemishes, or marks was not used; any face that displayed non-neutral affect was discarded. Pictures of natural outdoor scenes were obtained from the Digital Library Project, University of California (<http://www.elib.cs.berkeley.edu/photos/landscape>). Scenes that included any man-made object (e.g. cars, umbrellas, etc.) were discarded. The contents of these pictures represented a random sampling of outdoor scenes, e.g. mountains, plains, rivers, trees, etc.

There were 2 trial types: cue/distractor congruent (i.e. face/face) and cue/distractor incongruent (i.e. face/scene) with equal distribution of trials between these conditions. Overall, the probe matched the cue 50% of the time. Trials were grouped into 3 blocks with each block consisting of 12 trials to give a total of 36 trials for each subject. The order of trials within each block was pseudorandomized.

Behavioral data analysis

All behavioral data were collected while subjects were scanned. Only trials in which the subject made correct responses during the distractor target detection task were included in the behavioral and fMRI analysis. The logic in this is that we were only interested in analyzing trials in which we had behavioral verification of the engagement of the subject's attention to the distractor task. For similar reasons, we also discarded trials in which no responses were registered for the distractor target detection or probe response tasks. Finally, we excluded trials in which the RT for the probe response was more than two standard deviations from the mean for each condition. This resulted in only one or two trials per condition being excluded in each subject.

MRI data acquisition and processing

Functional images were acquired from a Varian INOVA 4 T scanner using a 2-shot gradient echo, echoplanar sequence (TR = 2200 ms, effective TR = 1100 ms, TE = 28 ms, flip angle 30°, 64 × 64 matrix, FOV = 22.4 cm) sensitive to BOLD contrast. Each volume consisted of 20 5 mm thick axial slices with a 0.5 mm gap between each slice. In plane resolution was 3.5 × 3.5 mm. Each fMRI run was preceded by 10 scans of dummy gradient RF pulses to achieve a steady state tissue magnetization and to minimize head movements often associated with a startle response elicited by the initiation of an EPI pulse sequence. Two high-resolution structural T1-weighted scans were also acquired; 20 axial slices in the same plane as the echoplanar images (TR = 200 ms, TE = 5 ms, matrix size = 256 × 256, FOV = 22.4 cm) and a 3D MPFLASH scan (TR = 9 ms, TE = 4.8 ms, TI = 300 ms).

fMRI data processing and general linear models (GLM) were completed with VoxBo (<http://www.voxbo.org>). Initial data processing included motion-correction using a six-parameter, rigid-body, least-squares alignment procedure (Friston et al., 1995). We imposed a maximal movement threshold of 4 mm in any one

direction for inclusion in this study. Consequently, one subject's fMRI data were excluded from the group level analysis. Data were spatially smoothed with an 8 mm full-width half-maximum Gaussian kernel.

MRI data analysis

Time series plots were generated by, first averaging within each subject, the BOLD signal across all voxels within an ROI, for all correct trials within a condition, and then averaging across all subjects. In each subject, percent signal change was calculated by normalizing each value in the time series by the mean fMRI signal across the entire WM scanning session. The percent change at time zero was then subtracted from every point in the time series.

Our method for analyzing within-trial patterns of activity has been described in detail elsewhere (Postle et al., 2000; Zarahn et al., 1997) and is summarized below. We modeled each task phase of each condition with unique covariates, giving us a total of 10 covariates of interest for correct trials. We also included a separate set of covariates for incorrect trials. The 5 task phases were modeled in the following manner: encoding—a mini-block spanning cue presentation (0–3.3 s); delay 1—a single covariate in the middle of first delay period (7.7 s); distraction—a single covariate during distractor presentation (13.2 s); delay 2—a single covariate in the middle of the second delay period (18.7 s); and response—a single covariate during probe presentation (24.2). Trial periods were modeled for each subject by convolving the covariates with an individually-derived hemodynamic response function (HRF) (Zarahn et al., 1997). Subject-specific HRFs were used in order to account for inter-subject variability of the HRF that could significantly affect subsequent BOLD analysis (Aguirre et al., 1998; Handwerker et al., 2004). The convolution matrix included filters to remove frequencies above 0.45 and below 0.025 Hz and nuisance covariates to model an intercept and trials excluded due to absence of responses and extreme RTs. Parameter estimates (i.e. beta values, an index of the magnitude of the BOLD response in which the magnitude of the beta value is proportional to the signal change at that stage of the trial and is estimated by fitting a HRF-convolved covariate placed into the design matrix at the various stages of the trial) yielded by the GLM for the trial phase of interest was extracted and averaged within each functionally-defined ROI (see below). These beta values served as the dependent measures for across-subject analyses. Because we were primarily interested in maintenance activity before and after distraction, group analyses was mainly focused on the covariates modeling these two task periods, delay 1 and delay 2. Additionally, to more sensitively measure the effect of distraction on delay period activity, we derived an index of delay period activity surviving distraction for each subject: Index = (Delay 2 Beta / Delay 1 Beta). All statistical analyses were conducted on SPSS (SPSS Inc., Chicago, IL).

Regions of interest (ROI)

We conducted all imaging data analysis in native space to maximize sensitivity to detect spatially variable activations in the prefrontal cortex (PFC). The generation of individual subject-specific functionally defined regions of interest (ROI) followed a two-step procedure: (1) manual drawing of anatomically defined masks; (2) identification of functionally defined ROIs by applying the anatomic mask onto whole brain activation maps. Delay period

activity was assessed in two areas: the lateral PFC and the visual association cortex (VAC).

Anatomic masks

We used the middle frontal gyrus (MFG) to define the lateral PFC ROI because this area, in addition to the inferior frontal gyrus (IFG), is consistently active during the delay period in face working memory tasks in human neuroimaging studies (Courtney et al., 1997, 1998; Jha and McCarthy, 2000; Sala et al., 2003). Additionally, electrophysiological studies in monkeys have shown activity near the principal sulcus, a region homologous to the MFG, during passive viewing and WM of faces (Scalaidhe et al., 1999). We were unable to identify functional ROIs in the IFG in a sufficient number of subjects, and we could not conduct an analysis of maintenance of this region in the PFC. The VAC mask was constructed from the fusiform gyrus of each subject. The creation of these individualized anatomic masks was facilitated by surface rendered high-resolution 3D MPFLASH and coplanar axial GEMS images, which revealed gyral and sulcal landmarks.

Functionally defined ROIs for univariate analysis

Within anatomically defined masks, linear contrasts between delay 1 covariate vs. baseline (i.e. the inter-trial interval) identified delay period active voxels. We used a functional ROI based on delay 1 activity, and not an anatomic ROI or a functional ROI based on cue activity, in order to maximize our ability to identify voxels specifically engaged in maintenance and our sensitivity to detect changes in delay period activity. Thus, for each individual, we created subject-specific ROIs in the lateral PFC and VAC. For the lateral PFC ROIs, statistical threshold corresponding to P value of <0.05 , corrected for multiple comparisons, yielded active voxels. In one instance, a threshold of $t = 3.0$ was used, because higher thresholds did not reveal any active voxels. For the VAC ROIs, we lowered the threshold until active voxels were revealed (one subject $t = 1.25$, all other subjects minimum $t > 2.0$). The lower threshold requirement for the VAC is consistent with electrophysiological results showing significantly lower percentage of neurons exhibiting delay period activity in this region compared to the PFC (Miller et al., 1996). The inclusion of subjects with relatively lower thresholds increases type II, but not type I error, rate. Furthermore, in a section below, we describe an additional set of analysis we conducted to address inferential issues raised by the use of variable thresholds.

Bivariate correlation analysis

Recently, we have developed a method that is capable of quantifying functional connectivity between regions during distinct trial periods (Rissman et al., 2004). This method, known as “beta series correlation analysis”, is implemented by using separate HRF-convolved covariates to model activity evoked during the component stages of each individual trial in the context of the GLM. The resulting trial beta values are sorted according to the stage from which they were derived to form a unique beta series for each stage. For example, each beta value in an encoding stage beta series reflects the amount of BOLD signal attributable to the encoding stage of a single WM trial. A voxel’s beta series thus reflects its trial-to-trial variability in stage-specific activity. Regions whose beta series are correlated during a given stage are inferred to be functionally interacting during that stage. Correlation computations are performed separately on data from each individual

subject. All correlation analysis was conducted with Matlab 6.5 (MathWorks, Natick, MA) with scripts specifically developed for this analysis. For a more detailed description of the beta series correlation analysis method, see Rissman et al. (2004).

ROIs for bivariate analysis

We focused on right hemisphere correlations between the VAC and PFC because it has been shown that face processing and recognition engage the right VAC greater than the left (Bentin et al., 1996; Grill-Spector et al., 2004; Kanwisher et al., 1997; Rossion et al., 2003). Moreover, a recent study from our lab has demonstrated high correlation in activity between the right VAC and PFC during the delay period of a face working memory tasks (Rissman et al., 2004). For most subjects, right-sided PFC ROIs were obtained from the ROIs representing areas of activation during the delay 1 period described above for univariate analysis. For subjects lacking right-sided ROIs, we progressively lowered the threshold until right-sided ROIs were revealed. These thresholds ranged between $t = 3.0$ and $t = 1.75$. Within each subject, the beta series of all voxels within each ROI was averaged, and the correlation between the VAC and PFC beta series was computed separately for each component stage of the task. Correlation coefficients were converted to z -scores by applying the r -to- z transformation (Fisher, 1921).

To confirm the robustness of our main fMRI results and to facilitate direct comparisons of fMRI data across regions and between univariate and bivariate analysis, we have conducted a secondary analysis. In this analysis, we applied uniform criteria for selection of functional ROIs across individuals and regions. We used these ROIs to generate BOLD data and conducted the same univariate and bivariate analysis outlined above. For each individual activation map, we imposed a threshold of $t = 2.0$ on a linear contrast between delay 1 covariate vs. baseline. We used right-sided PFC and VAC anatomic masks as described above to identify lateral PFC and VAC ROIs. In one subject, no active voxel in the VAC was identified and we did not include this subject’s data for the VAC univariate and PFC-VAC bivariate analysis. The remainder of the procedures for producing the univariate and bivariate data are identical as above. In the relevant sections, we provide data yielded by both ROI selection methods.

Results

Behavioral data

Mean accuracy and RTs for the face WM task are shown in Fig. 2. Selective interference, e.g. worse performance in the cue/distractor congruent condition, was observed for faces. Face distraction led to greater decrement in accuracy (73.7%) compared to scene distraction (82.4%) ($t = 2.64$, $df = 11$, $P < 0.05$). There was no significant difference in RTs, face/scene = 1242 ms, face/face = 1253 ms ($t = 0.54$, $df = 11$, $P = 0.60$). In the scene WM trials, no congruency effect was observed. Subjects performed at equivalent levels during scene/scene (81.4% accuracy and 1236 ms RT) and scene/face (77.7% accuracy and 1232 ms RT) (for all comparisons, $t < 0.9$, $df = 11$, $P > 0.3$). Subjects performed very well on both face and scene distractor target detection task with 96% and 95% accuracy, respectively ($t = 0.49$, $df = 11$, $P = 0.64$). There was also no significant difference between RTs in the

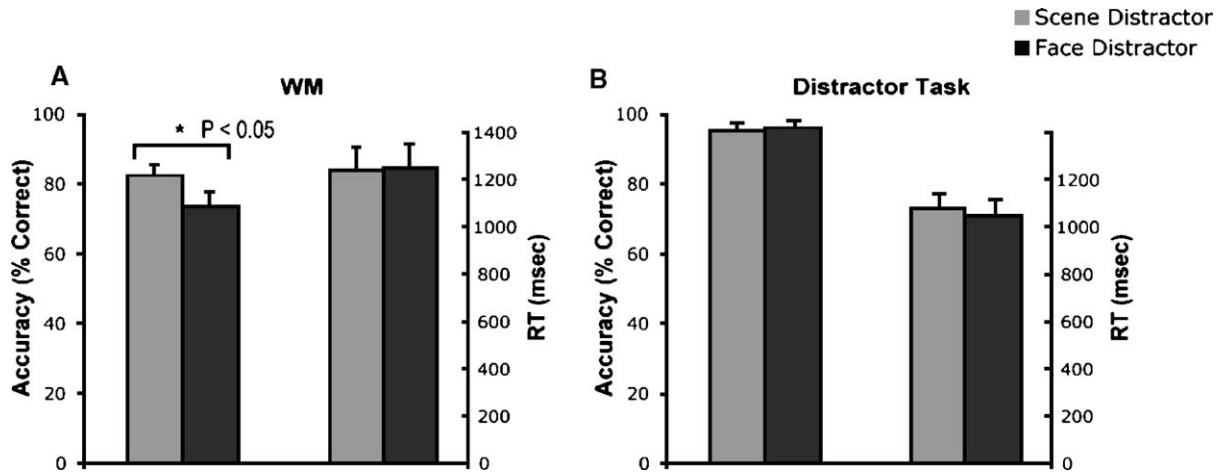


Fig. 2. Behavioral data. (A) Accuracy and reaction time (RT) for the delayed response task. (B) Accuracy and RT for the distractor target detection task.

distractor task, with 1063 ms for faces and 1100 ms for scenes ($t = 1.49, df = 11, P = 0.17$) (Fig. 2).

Imaging data

ROIs and BOLD time series

Representative examples of functional ROIs for the lateral PFC and VAC from one subject are displayed in Fig. 3A. There was significant inter-subject variability in the location of the PFC ROIs, which is consistent with other studies of face working memory (Druzgal and D’Esposito, 2003). Fig. 3B shows trial averaged BOLD time series plots from the PFC and VAC. The VAC displays equivalent levels of activity between conditions for all trial periods, including delay 2. This is not the case in the PFC, where delay 2

activity appears suppressed following face distraction compared to scene distraction. During other trial periods, no substantial differences between conditions are evident.

Univariate analysis

As our main hypothesis involves the measurement of maintenance activity, we have applied the following analysis to the parameter estimates for delay 1 and delay 2 in the lateral PFC and VAC (Fig. 4). A repeated measures ANOVA performed on PFC betas (parameter estimates) with factors of condition (congruent and incongruent) and trial epoch (delay 1 and delay 2) revealed a main effect of epoch [$F(1,10) = 77.55, P < 0.01$], but not of condition [$F(1,10) = 1.32, P = 0.28$], and no interaction [$F(1,10) = 1.54, P = 0.24$]. In the VAC, there was a main effect of epoch [$F(1,10) =$

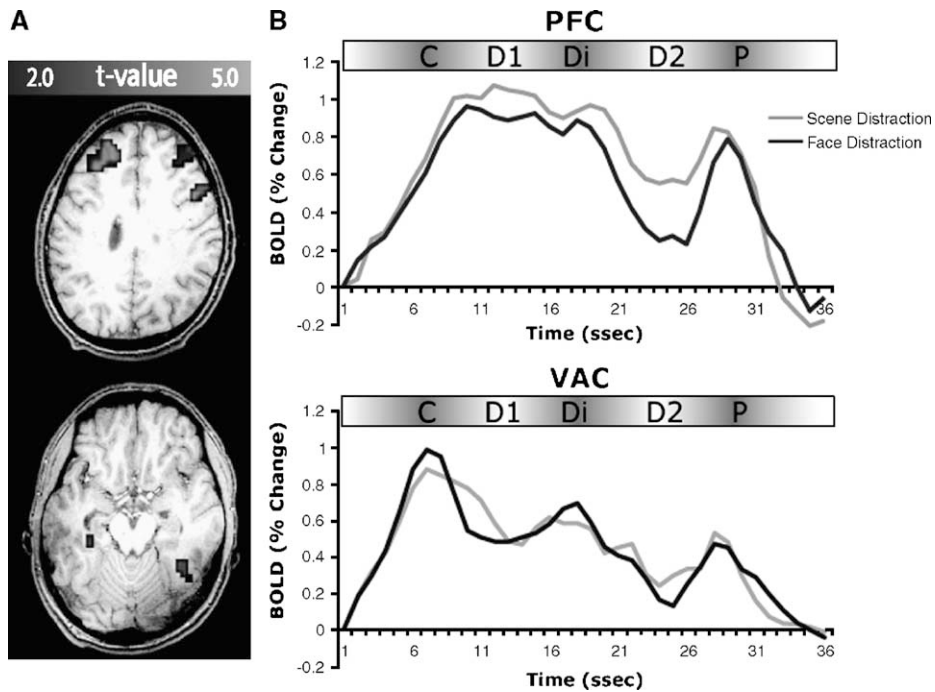


Fig. 3. Univariate BOLD time series. (A) Functional ROIs from a single subject demonstrating activations during delay 1 in the lateral PFC and VAC. (B) BOLD time series from the PFC and VAC. Percentage BOLD signal changes were averaged across trials, within ROI, and across all subjects. The intensity of the grey scale spectrum above the plots gives the approximate location of the expected peaks in activity associated with stimuli presentations; C = cue; D1 = delay 1; Di = distractor; D2 = delay 2; P = probe.

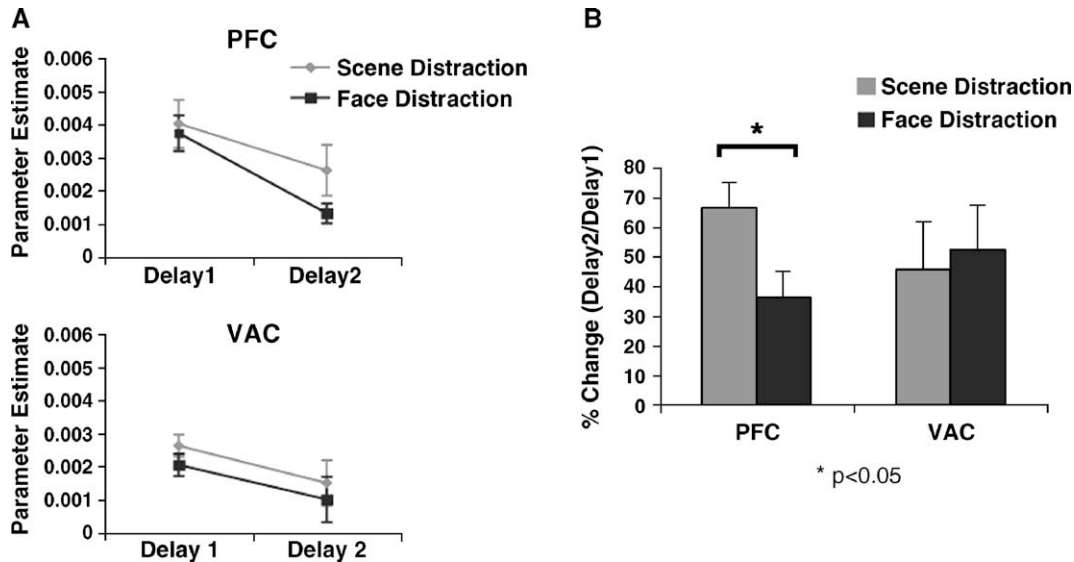


Fig. 4. Univariate BOLD data. (A) Delay period activity in the PFC and VAC before (delay 1) and after (delay 2) distraction. (B) Change in delay period activity expressed as an index of delay period activity surviving distraction (delay 2 beta/delay 1 beta).

26.12, $P < 0.01$], but no main effect of condition [$F(1,10) = 0.31$, $P = 0.59$] and no interaction [$F(1,10) = 2.16$, $P = 0.17$]. For all conditions, both PFC and VAC delay 2 activity remained significantly above baseline as revealed by a t test of beta values compared to baseline: PFC face/scene ($t = 4.12$, $df = 10$, $P < 0.01$), face/face ($t = 4.13$, $df = 10$, $P < 0.01$); VAC face/scene ($t = 2.4$, $df = 10$, $P < 0.05$), face/face ($t = 4.06$, $df = 10$, $P < 0.01$). In the PFC, there was a trend towards a significant congruency effect on delay period activity; face distraction resulted in less delay 2 activity compared to scene distraction ($t = 1.98$, $df = 10$, $P = 0.07$). In the VAC, there was no evidence of a congruency effect; the magnitude of delay 2 activity was not significantly different between face/scene and face/face conditions ($t = 0.74$, $df = 10$, $P = 0.45$). The index of delay period activity surviving distraction (delay 2 beta divided by delay 1 beta), a more sensitive measure of change in delay period activity (Fig. 4B), shows a significant difference between face/scene and face/face conditions in the PFC ($t = 2.94$, $df = 10$, $P < 0.05$), but not in the VAC ($t = 0.37$, $df = 10$, $P = 0.73$). The magnitude of activity during distraction did not differ between scene and face distraction in the PFC ($t = 0.89$, $df = 10$, $P = 0.40$) or VAC ($t = 0.40$, $df = 10$, $P = 0.82$).

Here, we present the results of univariate analysis on data obtained by applying uniform ROIs selection criteria across regions and subjects. These results are intended to confirm the robustness of the results from our primary analysis and to facilitate direct statistical comparisons across regions. In a repeated measures ANOVA on beta values, with within subject factors of condition, ROI, and trial epoch, there was no main effect of ROI [$F(1,9) = 0.001$, $P = 0.98$], condition [$F(1,9) = 1.66$, $P = 0.23$], or epoch [$F(1,9) = 2.37$, $P = 0.16$], and no interactions (for ROI \times epoch [$F(1,9) = 2.63$, $P = 0.14$]; for all other interactions [$F(1,9) < 1.35$, $P > 0.28$]). When an ANOVA was applied to the index of delay period activity surviving distraction, there were no significant main effects of ROI [$F(1,9) = 1.06$, $P = 0.33$] or condition [$F(1,9) = 2.17$, $P = 0.18$]. The interaction between ROI and congruency was also non-significant [$F(1,9) = 2.79$, $P = 0.13$]. t tests on the index of delay period activity surviving distraction revealed a significant difference between conditions in the PFC,

with greater activity in the face/scene condition ($t = 3.29$, $df = 10$, $P < 0.01$). In the VAC, no significant difference was detected ($t = 0.32$, $df = 9$, $P > 0.98$). In summary, these patterns of results are consistent with those results obtained from the first set of ROIs.

Bivariate analysis

The results of beta series correlation analysis (the correlation of trial-to-trial variability in stage-specific BOLD signal) between the lateral PFC and VAC are summarized in Fig. 5. As expected, during cue and delay 1, there was no significant difference in PFC-VAC correlation between face/scene and face/face trials (for all comparisons, $t < 0.90$, $df = 10$, $P > 0.20$). In addition, all correlations during these periods were above baseline (for all comparisons, $t > 3.0$, $df = 10$, $P < 0.01$). The pattern of correlation

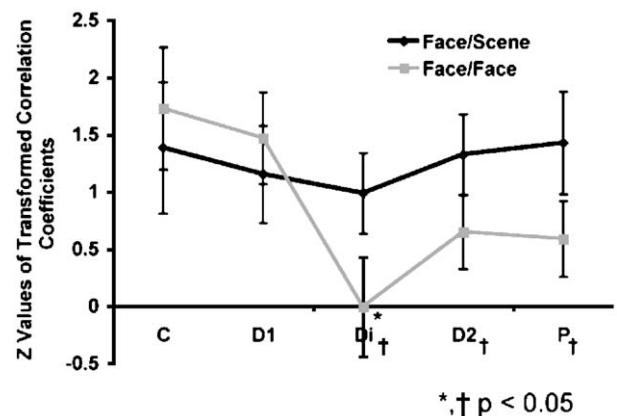


Fig. 5. Bivariate BOLD data. Trial to trial correlations of parameter estimates between the PFC and VAC. Face distraction results in the abolishment of PFC-VAC correlated activity. This effect persists throughout the remainder of the trial. Scene distraction does not significantly effect PFC-VAC correlations during distraction or subsequent stages. * t test between face/scene vs. face/face at Di; †repeated measures ANOVA over the periods Di, D2, and P, P value indicates level of significance for main effect of category of distractor. C = cue; D1 = delay 1; Di = distractor; D2 = delay 2; P = probe.

diverged over the subsequent epochs. For the face/scene condition, correlation remained significantly above baseline during distraction, delay 2, and probe (for all comparisons, $t > 2.8$, $df = 10$, $P < 0.01$). However, in the face/face condition, PFC-VAC correlation was abolished at distraction, no longer remaining above baseline ($t = 0.03$, $df = 10$, $P > 0.20$) and significantly diminished compared to the face/scene condition ($t = 2.43$, $df = 10$, $P < 0.05$). The correlation in the face/face condition remained suppressed in subsequent trial epochs compared to the face/scene condition, as confirmed by a repeated measures ANOVA restricted to the period over which the effects of congruency of distraction would have relevance (distraction, delay 2, and probe). This revealed a main effect of condition [$F(1,10) = 6.32$; $P < 0.05$], but no main effect of epoch [$F(2,20) = 1.49$, $P = 0.25$] or significant interaction between condition and epoch [$F(2,20) = 0.19$, $P = 0.83$]. t tests of correlations at other trial epochs were non-significant (cue, $t = 0.97$, $P > 0.36$; delay 1, $t = 0.02$, $P > 0.98$; delay 2, $t = 1.73$, $P = 0.11$; probe, $t = 1.40$, $P = 0.19$; for all comparisons $df = 10$).

Our reanalysis using uniform threshold revealed the same basic pattern of correlations. Repeated measures ANOVA with factors of condition and trial epoch on bivariate correlation data revealed a trend towards a main effect of condition [$F(1,9) = 7.05$, $P = 0.09$], with mean z -transformed correlations of 1.32 and 0.63 over these epochs for face/scene and face/face conditions, respectively. t tests between conditions at each epoch revealed that the only significant difference occurred during distraction, face/scene 1.45 compared to face/face 0.41 ($t = 2.48$, $df = 9$, $P < 0.05$).

Discussion

Behaviorally, we observed selective interference between faces. This was manifest as a significant decline in accuracy with face distractors compared to scene distractors during the retention of faces on a delayed response task. While we found sustained activity in the VAC and lateral PFC after distraction, selective interference in the BOLD maintenance signal, greater degradation of activity in the face distraction condition, was evident only in the lateral PFC and not in the VAC. Correlation analysis demonstrated disruption of functional connectivity between the PFC and VAC in the face congruent distraction condition. Our experimental design and results show consistency between behavioral and fMRI findings, and allow us to make inferences on the relative contributions of the PFC and VAC to maintenance and the mechanism underlying this sub-process of WM.

We interpret our findings to support a model of WM in which the on-line maintenance of the memoranda is an emergent function of cooperative activity between the lateral PFC and posterior unimodal cortex. In interpreting our results, we will adopt the terminology used by others (Miller and Cohen, 2001; Sakai et al., 2002) to differentiate the type of maintenance that occurs in the PFC from posterior sensory cortices. Active maintenance is an executive control process that provides top down modulation of information stored (simple maintenance) in lower cortical areas. Our work extends the conceptualization of active maintenance by providing evidence for the type of code being represented in the PFC. Based on prior theoretical and empirical work (Freedman et al., 2003; O'Reilly et al., 2002) and our own results showing differential effects of distraction on PFC and VAC activity, we infer that the PFC codes for higher order representations of the memoranda, possibly as a means of carrying out active maintenance.

The persistence of delay period signal surviving distraction in the VAC is consistent with our contention that this area supports maintenance. Prior animal and human studies have provided varying degrees of evidence for maintenance activity in the VAC. Lesions of the anterior portion of IT have been shown to disrupt performance on an object delayed response task in a delay dependent manner (Petrides, 2000). Although most single unit studies showing stimulus-specific delay period activity (Miyashita and Chang, 1988; Nakamura and Kubota, 1995; Sakai and Miyashita, 1991) can be criticized for not having demonstrated resistance to task irrelevant distraction (Desimone, 1996; Miller et al., 1996), there is at least one study that has demonstrated this in the ventromedial surface of the temporal lobe (Suzuki et al., 1997). Human imaging studies have been inconsistent in demonstrating the presence of delay period activity in the VAC. However, this inconsistency may be due to varying methodologies, and possibly, diminished sensitivity to detect this signal. Druzgal et al. failed to find above-baseline activity in the VAC across three memory loads of faces, although they did find evidence of a load effect in this area (Druzgal and D'Esposito, 2003). They used a contrast between face and scene blocks from a separate localizer experiment to identify the FFA as their VAC ROI. The FFA is presumably specialized for the processing of faces present in the environment. We conducted the delay 1 vs. baseline contrast to identify VAC neurons more specifically engaged in maintenance. A study by Postle employed a delayed recognition paradigm in which the number of distracting faces intervening between cue and probe varied between 0 and 2 (Postle et al., 2003). This study identified ROIs in the PFC and the VAC using the same strategy as our study and they found significant, above baseline activity surviving distraction in the VAC. Using a similar strategy, another recent study has also demonstrated a significant delay period activity in the VAC for faces and other objects (Sala et al., 2003).

There is a large body of studies supporting the lateral PFC's critical involvement in visual WM maintenance, including monkey lesion (Funahashi et al., 1993; Jacobsen, 1936; Mishkin, 1957), human lesion (Bechara et al., 1998), single unit (Funahashi et al., 1989; Fuster, 1973; Miller et al., 1993, 1996), and neuroimaging studies (Courtney et al., 1997, 1998; Druzgal and D'Esposito, 2003; Jha and McCarthy, 2000; Sala et al., 2003). These fMRI studies consistently found lateral PFC maintenance activity during face WM. For example, the Druzgal study found delay period activity in the PFC during the maintenance of faces which was sensitive to load manipulation. Prior fMRI studies employing a distraction paradigm can be interpreted as demonstrating maintenance in the PFC. In a WM study examining selective interference in the verbal domain (Gruber, 2001), worse behavioral performance resulting from verbal distraction was associated with diminished activity in regions supporting the phonological loop and increased activity in the lateral PFC. The author interpreted these findings as indicating the disruption of usual storage functions of the phonological loop by verbal distraction, and the transference of this function to lateral PFC buffers. Another fMRI study also supports the role of the PFC during temporary maintenance during distraction (Sakai et al., 2002). In a spatial delayed response task, the lateral PFC was active when cue congruent distractors were present. Moreover, there was significantly less PFC activity before and after distraction on error trials as compared to correct trials. The authors argued that PFC activity reflects executive processes that transform the maintained information into distraction-resistant representations. Miller and col-

leagues have conducted a series of studies that have clarified the unique contribution of the lateral PFC to maintenance of visual objects. Miller compared delay period activity in the IT and PFC, and found stimulus-specific delay period activity resistant to distraction only in the PFC. IT neurons appeared to be “reset” with a task irrelevant distractor. These empirical findings support the notion that VAC activity represents the most recent visual input regardless of its relevance, whereas PFC activity represents task relevant, distractor-resistant information. Similar results were also found in the parietal cortex during a spatial working memory task (Constantinidis and Steinmetz, 1996).

The question of what kind of task relevant information is being represented in the PFC remains controversial, however. Monkey studies showing stimulus-specific PFC activity led researchers to hypothesize that the PFC stores task relevant sensory information during WM (Funahashi et al., 1989; Fuster, 1973). Further, a functional topography of the PFC in which object and spatial information is represented in the ventrolateral and dorsolateral regions, respectively, has been specified based on electrophysiological (Scalaidhe et al., 1999), selective lesion (Levy and Goldman-Rakic, 1999; Mishkin and Manning, 1978; Passingham, 1975; Petrides, 1995), and human imaging studies (Courtney et al., 1997, 1998; Sala et al., 2003), showing segregation of function in lateral PFC according to the type of information being maintained. Yet, others have postulated a PFC topography based on process, in which the ventrolateral areas (BA 45/47) store sensory information (D’Esposito et al., 1999; Owen et al., 1996; Petrides, 1995, 2000), while more dorsal areas (BA 46/9) subservise executive control processes, such as monitoring or selective attention (Petrides, 2000; Rowe and Passingham, 2001).

The association in our study between worse performance and greater degradation of the lateral PFC signal during face/face trials compared to face/scene trials could be explained by greater perturbation in a critical executive control process. While this is a plausible alternative explanation for our findings, the fact that the only difference between the two conditions was the category of the stimulus (and, therefore, congruency with the cue) argues against this. First, the number of items to be monitored during the scene and face distraction tasks was identical. Thus, it would seem unlikely that face distraction would lead to greater perturbation of monitoring. Second, behavioral performance on face and scene distraction tasks was nearly identical. Thus, similar demands on attention should have been imposed by these tasks. A recent study that also found significant degradation of WM performance with object congruent distraction lends further support to our claim of code specificity of the distraction effect (Jha et al., 2004). However, we cannot exclude the possibility that both storage and executive control functions are represented concurrently in the PFC signal we have identified.

The different effects of cue/distractor congruency on PFC and VAC maintenance activity indicate that these areas represent different kinds of information. Greater decrement in PFC activity during congruent trials, compared to incongruent trials, suggests that face distraction activated representations that interfered with the maintenance of facial images in this region. Since unique faces were displayed during encoding and distraction, the representations coded by the PFC are likely more abstract than the particular faces being presented. The lack of a congruence effect in the VAC is consistent with the idea that VAC neurons code face identity information; therefore, unique faces during distraction would not disrupt the maintenance of cue faces. The Postle face WM study

cited above, demonstrated a similar pattern of findings in the PFC and VAC (Postle et al., 2003). VAC delay period activity persisted after face stimuli distraction, whereas PFC delay period activity diminished. On the surface, it may seem that the empirical finding in our study, as well as the Postle study, of persistent VAC activity during intervening stimuli is inconsistent with the monkey physiology data reported by Miller et al. (1996). However, it is important to underscore the obvious methodological difference between human and animal physiology studies. In Miller’s work, data are obtained from a single neuron that has been identified as being highly selective to a particular stimulus (i.e. butterfly). In contrast, fMRI measures neuronal population activity that will not code one particular stimulus. Thus, these studies provide complementary information and two interpretations of our VAC results, showing persistence of delay period activity after distraction and absence of selective interference can be made. We cannot differentiate neuronal activity emanating from neurons that are specific to different stimuli (i.e. cue vs. distractor). Consequently, delay period activity in the VAC before and after distraction may represent activity from the most recently viewed stimulus, the cue and distractor, respectively. The alternative interpretation would be that VAC delay period activity is resistant to distraction, as indicated by single unit studies in the entorhinal cortex (Suzuki et al., 1997). However, these neurons have thus far been only identified in the entorhinal cortex, a region of the medial temporal lobe. In either case, the absence of selective interference in the VAC is consistent with a model in which these neurons represent face identity information. Our interpretation of the divergent effects of stimulus congruency on PFC and VAC activity is also supported by the results of a recent study, which demonstrated that IT activity tends to reflect specific identity relevant visual features, while PFC activity tends to convey categorical information (Freedman et al., 2003).

Taken together, our results support the idea that the PFC and VAC maintain different types of representation that are necessary for guiding behavior, with the PFC and VAC representing higher-level and item-specific information, respectively. Our model of visual object WM is consistent with a model recently postulated by O’Reilly et al. (2002). These authors propose that the PFC represents task relevant information during maintenance, and that PFC representations are organized along a specific-abstract axis, with more ventral areas representing specific visual features and more dorsal (or anterior) areas coding higher-level features. It is important to emphasize, however, that postulating that the PFC represents sensory information does not exclude the possibility of this area also supporting executive control processes, e.g. pointer function. It is plausible that the PFC could efficiently support executive control processes by incorporating sensory relevant information in abstracted form (O’Reilly et al., 2002).

Theoretical (Bar, 2003; Goldman-Rakic, 1988; Miller and Cohen, 2001) and empirical works (Fuster et al., 1985; Rissman et al., 2004; Tomita et al., 1999) have suggested that the dynamic interaction of the PFC and posterior sensory association areas may be a critical feature of WM. In a remarkable series of studies involving the reversible deactivation of the dorsolateral PFC and IT by cooling, Fuster et al. (1985) demonstrated that lesions in one of these regions resulted in significant changes in delay period activity in the other, and that lesions of either region resulted in degradation of visual WM performance. Chao and Knight (1998) have proposed that PFC lesions lead to aberrant sensory processing

in sensory cortex through the perturbation of top down modulation of its activity. The distributed nature of WM maintenance is also suggested by other studies that have applied fMRI correlation analysis and have revealed prominent functional connectivity during maintenance between the PFC and posterior areas (Gazzaley et al., 2004; Rissman et al., 2004; Sakai et al., 2002). Our correlation data support this supposition by demonstrating the perturbation of functional connectivity between the PFC and VAC in the most difficult experimental condition (face/face). Two aspects of our data are particularly noteworthy. First, the disruption of correlated activity started at the time of face congruent distraction. Second, this disruption persisted through the remainder of the trial. These factors suggest a plausible mechanism for active maintenance—the coupling of abstracted, higher order information in the PFC and stimuli-specific sensory information in the VAC through reverberant activity between these areas. Our present work only hints at this mechanism and points to new lines of research to elucidate this proposed mechanism.

We were unable to pursue comparisons between correct and incorrect trials, a line of analysis that could have provided important confirmatory data regarding our results. Two factors prohibited us from effectively analyzing error trials. Firstly, the number of error trials per condition was too few to allow us to make useful inferences. Secondly, incorrect responses could be due to a failure in a number of processes. For example, it would be difficult to draw conclusions about delay period activity on trials where there was a failure of encoding the memoranda.

Our findings implicate a hierarchical organization of neural systems supporting maintenance, with different kinds of information represented by frontal and posterior sensory areas. The presence of selective interference in the PFC delay period signal by faces and the absence of this in the VAC suggest that the PFC maintains abstract, categorical information, while the VAC retains more stimuli-specific features. Our correlation data suggest that active maintenance may be an emergent function of coordinated, persistent activity representing reciprocal top down and bottom up interactions.

References

- Aguirre, G.K., Zarahn, E., D'Esposito, M., 1998. The variability of human, BOLD hemodynamic responses. *NeuroImage* 8, 360–369.
- Baddeley, A., Lewis, V., Vallar, G., 1984. Exploring the articulatory loop. *Q. J. Exp. Psychol.*, A 36, 233–252.
- Bar, M., 2003. A cortical mechanism for triggering top-down facilitation in visual object recognition. *J. Cogn. Neurosci.* 15, 600–609.
- Bechara, A., Damasio, H., Tranel, D., Anderson, S.W., 1998. Dissociation of working memory from decision making within the human prefrontal cortex. *J. Neurosci.* 18, 428–437.
- Bentin, S., Allison, T., Puce, A., Perez, E., McCarthy, G., 1996. Electrophysiological studies of face perception in humans. *J. Cogn. Neurosci.* 8, 551–565.
- Chao, L.L., Knight, R.T., 1998. Contribution of human prefrontal cortex to delay performance. *J. Cogn. Neurosci.* 10, 167–177.
- Constantinidis, C., Steinmetz, M.A., 1996. Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. *J. Neurophysiol.* 76, 1352–1355.
- 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.
- Courtney, S.M., Petit, L., Maisog, J.M., Ungerleider, L.G., Haxby, J.V., 1998. An area specialized for spatial working memory in human frontal cortex. *Science* 279, 1347–1351.
- Desimone, R., 1996. Neural mechanisms for visual memory and their role in attention. *Proc. Natl. Acad. Sci. U. S. A.* 93, 13494–13499.
- D'Esposito, M., Postle, B.R., Ballard, D., Lease, J., 1999. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cogn.* 41, 66–86.
- Druzgal, T.J., D'Esposito, M., 2003. Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *J. Cogn. Neurosci.* 15, 771–784.
- Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. *Nature* 392, 598–601.
- Fisher, R.A., 1921. On the “probable error” of a coefficient of correlation deduced from a small sample. *Metron* 1, 3–32.
- Freedman, D.J., Riesenhuber, M., Poggio, T., Miller, E.K., 2003. A comparison of primate prefrontal and inferior temporal cortices during visual categorization. *J. Neurosci.* 23, 5235–5246.
- Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., Frackowiak, R.S., 1995. Spatial registration and normalization of images. *Hum. Brain Mapp.* 2, 165–189.
- Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* 61, 331–349.
- 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, 1479–1497.
- Fuster, J.M., 1973. Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *J. Neurophysiol.* 36, 61–78.
- Fuster, J.M., Bauer, R.H., Jervey, J.P., 1985. Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Res.* 330, 299–307.
- Gazzaley, A., Rissman, J., Desposito, M., 2004. Functional connectivity during working memory maintenance. *Cogn. Affect Behav. Neurosci.* 4, 580–599.
- Goldman-Rakic, P.S., 1988. Topography of cognition: parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* 11, 137–156.
- Grill-Spector, K., Knouf, N., Kanwisher, N., 2004. The fusiform face area subserves face perception, not generic within-category identification. *Nat. Neurosci.* 7, 555–562.
- Gruber, O., 2001. Effects of domain-specific interference on brain activation associated with verbal working memory task performance. *Cereb. Cortex* 11, 1047–1055.
- Handwerker, D.A., Ollinger, J.M., D'Esposito, M., 2004. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *NeuroImage* 21, 1639–1651.
- Jacobsen, C.F., 1936. Studies of cerebral function in primate: 1. The functions of the frontal association areas in monkeys. *Comp. Psychol. Monog.* 13, 1–60.
- 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. *J. Cogn. Neurosci.* 12 (Suppl. 2), 90–105.
- Jha, A.P., Fabian, S.A., Aguirre, G.K., 2004. The role of prefrontal cortex in resolving distractor interference. *Cogn. Affect Behav. Neurosci.* 4, 517–527.
- Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* 17, 4302–4311.
- Levy, R., Goldman-Rakic, P.S., 1999. Association of storage and processing functions in the dorsolateral prefrontal cortex of the nonhuman primate. *J. Neurosci.* 19, 5149–5158.
- Logie, R.H., Zucco, G.M., Baddeley, A.D., 1990. Interference with visual short-term memory. *Acta Psychol. (Amst.)* 75, 55–74.
- McCarthy, G., Puce, A., Constable, R.T., Krystal, J.H., Gore, J.C., Goldman-Rakic, P., 1996. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cereb. Cortex* 6, 600–611.

- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202.
- Miller, E.K., Li, L., Desimone, R., 1993. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J. Neurosci.* 13, 1460–1478.
- Miller, E.K., Erickson, C.A., Desimone, R., 1996. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J. Neurosci.* 16, 5154–5167.
- Mishkin, M., 1957. Effects of small frontal lesions on delayed alternation in monkeys. *J. Neurophysiol.* 20, 615–622.
- Mishkin, M., Manning, F.J., 1978. Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Res.* 143, 313–323.
- Miyashita, Y., Chang, H.S., 1988. Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature* 331, 68–70.
- Nakamura, K., Kubota, K., 1995. Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. *J. Neurophysiol.* 74, 162–178.
- O'Reilly, R.C., Noelle, D.C., Braver, T.S., Cohen, J.D., 2002. Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. *Cereb. Cortex* 12, 246–257.
- Owen, A.M., Evans, A.C., Petrides, M., 1996. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb. Cortex* 6, 31–38.
- Passingham, R., 1975. Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). *Brain Res.* 92, 89–102.
- Petrides, M., 1995. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J. Neurosci.* 15, 359–375.
- Petrides, M., 2000. Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. *J. Neurosci.* 20, 7496–7503.
- Postle, B.R., D'Esposito, M., 1999. "What"–Then–Where" in visual working memory: an event-related fMRI study. *J. Cogn. Neurosci.* 11, 585–597.
- Postle, B.R., Zarahn, E., D'Esposito, M., 2000. Using event-related fMRI to assess delay-period activity during performance of spatial and non-spatial working memory tasks. *Brain Res. Brain Res. Protoc.* 5, 57–66.
- Postle, B.R., Druzgal, T.J., D'Esposito, M., 2003. Seeking the neural substrates of visual working memory storage. *Cortex* 39, 927–946.
- Ranganath, C., DeGutis, J., D'Esposito, M., 2004. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Brain Res. Cogn. Brain Res.* 20, 37–45.
- Rissman, J., Gazzaley, A., D'Esposito, M., 2004. Measuring functional connectivity during distinct stages of a cognitive task. *NeuroImage* 23, 752–763.
- Rossion, B., Schiltz, C., Crommelinck, M., 2003. The functionally defined right occipital and fusiform "face areas" discriminate novel from visually familiar faces. *NeuroImage* 19, 877–883.
- Rowe, J.B., Passingham, R.E., 2001. Working memory for location and time: activity in prefrontal area 46 relates to selection rather than maintenance in memory. *NeuroImage* 14, 77–86.
- Sakai, K., Miyashita, Y., 1991. Neural organization for the long-term memory of paired associates. *Nature* 354, 152–155.
- Sakai, K., Rowe, J.B., Passingham, R.E., 2002. Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nat. Neurosci.* 5, 479–484.
- Sala, J.B., Rama, P., Courtney, S.M., 2003. Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia* 41, 341–356.
- Scalaidhe, S.P., Wilson, F.A., Goldman-Rakic, P.S., 1999. Face-selective neurons during passive viewing and working memory performance of rhesus monkeys: evidence for intrinsic specialization of neuronal coding. *Cereb. Cortex* 9, 459–475.
- Suzuki, W.A., Miller, E.K., Desimone, R., 1997. Object and place memory in the macaque entorhinal cortex. *J. Neurophysiol.* 78, 1062–1081.
- Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., Miyashita, Y., 1999. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* 401, 699–703.
- Zarahn, E., Aguirre, G., D'Esposito, M., 1997. A trial-based experimental design for fMRI. *NeuroImage* 6, 122–138.