Brain (2001), **124,** 2074–2086

Prefrontal regions involved in keeping information in and out of mind

Silvia A. Bunge,[1] Kevin N. Ochsner,[2] John E. Desmond,[2,3] Gary H. Glover[3] and John D. E. Gabrieli[1,2,3]

[1]*Neurosciences Program and Departments of* [2]*Psychology and* [3]*Radiology, Stanford University, USA*

Correspondence to: Silvia Bunge, Department of Brain and Cognitive Sciences, NE-20, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
E-mail: sbunge@psych.stanfordalumni/org

Summary

Goal-directed behaviour depends on keeping relevant information in mind (working memory) and irrelevant information out of mind (behavioural inhibition or interference resolution). Prefrontal cortex is essential for working memory and for interference resolution, but it is unknown whether these two mental abilities are mediated by common or distinct prefrontal regions. To address this question, functional MRI was used to identify brain regions activated by separate manipulations of working memory load and interference within a single task (the Sternberg item recognition paradigm). Both load and interference manipulations were associated with performance decrements. Subjects were unaware of the interference manipulation. There was a high degree of overlap between the regions activated by load and interference, which included bilateral ventrolateral and dorsolateral prefrontal cortex, anterior insula, anterior cingulate and parietal cortex. Critically, no region was activated exclusively by interference. Several regions within this common network exhibited a brain–behaviour correlation across subjects for the load or interference manipulation. Activation within the right middle frontal gyrus and left inferior frontal gyrus was correlated with the ability to resolve interference efficiently, but not the ability to manage an increased working memory load efficiently. Conversely, activation of the anterior cingulate was correlated with load susceptibility, but was not correlated with interference susceptibility. These findings suggest that, within the circuitry engaged by this task, some regions are more critically involved in the resolution of interference whereas others are more involved in the resolution of an increase in load. The anterior cingulate was engaged to a greater extent by the load than interference manipulation, suggesting that this region, which is thought to be involved in detecting the need for greater allocation of attentional resources, may be particularly implicated during awareness of the need for cognitive control. In the present study, interference resolution did not involve recruitment of additional inhibitory circuitry, but was instead mediated by a subset of the neural system supporting working memory.

Keywords: prefrontal; working memory; inhibition; interference; fMRI

Abbreviations: BA = Brodmann area; fMRI = functional MRI; PFC = prefrontal cortex; ROI = region of interest; WM = working memory

Introduction

Prefrontal cortex (PFC) is important for actively maintaining relevant information in mind, a function referred to as working memory (WM) (Jacobsen, 1936; Fuster and Alexander, 1970; Baddeley, 1986; Goldman-Rakic, 1987). PFC also plays a critical role in the ability to ignore irrelevant information (interference resolution) and override prepotent responses (response inhibition) (Malmo, 1942; Luria, 1966; Perret, 1974; Drewe, 1975; Knight *et al*., 1981). These functions are referred to more generally as behavioural inhibition (Diamond, 1988; Bjork, 1989; Dempster, 1991). WM and inhibition appear to be highly interrelated functions. For example, the ability to suppress inappropriate responses decreases as a function of WM load (Roberts *et al*., 1994; Engle *et al*., 1995; Conway *et al*., 1999). The role of PFC in WM was first demonstrated by the finding that monkeys with lesions in lateral PFC were unable to maintain information in mind over a short delay (Jacobsen, 1936). Subsequently, it was shown that monkeys with these lesions were able to perform this WM task as well as control monkeys when the lights were turned out during the delay

period. Turning the lights off would remove competing visual stimuli from the monkey's environment (Malmo, 1942). Thus, the WM deficit of these PFC-lesioned monkeys can best be described as an inability to suppress the deleterious effects of interference on the maintenance of information in WM. These and other findings suggest that the ability to suppress interference is an integral component of WM.

The aim of the present study was to examine the relationship between prefrontal regions involved in WM and inhibitory processes. WM and behavioural inhibition long have been thought to rely on different regions of PFC, with dorsolateral regions important for WM and ventral regions important for behavioural inhibition (for summary, see Fuster, 1997). According to this view, WM relies on the active maintenance of goal-relevant information, whereas behavioural inhibition relies on the active suppression of goal-irrelevant information or inappropriate responses. However, a number of behavioural studies have shown that WM and behavioural inhibition are highly interdependent functions (Dempster, 1991; Roberts *et al*., 1994; Engle *et al*., 1995; Hasher and Zacks, 1998; Rosen and Engle, 1998; Conway *et al*., 1999; May *et al*., 1999). Several theorists have suggested that these functions may be two sides of the same coin (Kimberg and Farah, 1993; Desimone and Duncan, 1995; Cohen *et al*., 1996) and therefore both may be subserved by the same prefrontal regions (Miller and Cohen, 2001). According to this view, the ability to ignore distractions does not involve the active suppression of irrelevant information by frontal regions, but rather a frontally mediated biasing of competing streams of information processing in posterior association regions in favour of task-relevant information (Miller and Cohen, 2001).

In the present study, we employed functional MRI (fMRI) to examine whether WM and behavioural inhibition rely on common or distinct brain regions by separately manipulating WM and interference demands within the Sternberg item recognition paradigm (Sternberg, 1966). In one version of this WM task, subjects view a set of letters, maintain this set in mind across a short delay, and then indicate whether a probe letter corresponds to one of the letters in the set (Fig. 1). Relative to a condition involving a memory set of 4 letters (Load 4), the task was made more challenging in two separate ways. In the Load manipulation, the number of items to be retained in WM was increased to 6 items (Load 6). This manipulation increases WM demands, as demonstrated by slowed response times (Sternberg, 1966). In the Interference manipulation, proactive interference was increased by ensuring that the probe letter in a given trial had appeared in the target set of the immediately preceding trial. On negative trials (trials for which the correct response is 'no', because the probe letter did not appear in the current target set), subjects are slower to respond if the probe is highly recent (appeared in the immediately preceding trial) than if it is less recent (did not appear in either of the two preceding trials). This increase in response latency for negative trials is thought to be related to the need to resolve interference from the prior trial (Monsell, 1978; Jonides *et al*., 1998).

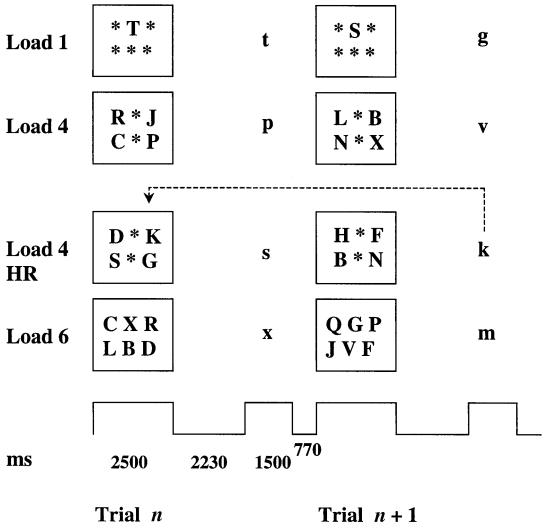

Fig. 1 Tasks performed in the scanner. A depiction of two successive trials of each condition. On a given trial, subjects viewed one, four or six letters on the screen and determined after a short delay whether a probe letter corresponded to one of the items in the target set. In blocks of Load 4 High Recency trials, each probe item was present in the memory set of the immediately preceding trial. In blocks of Load 4 trials, no probe item had appeared in the memory set of either of the two immediately preceding trials.

In addition to comparing activations between conditions, we compared activation levels between subjects by examining the relationships between behaviour and activation magnitudes. Such between-subject comparisons have proved useful for interpreting activations in functional neuroimaging studies (Cahill *et al*., 1996; Nyberg *et al*., 1996; Macdonald *et al*., 2000). Individual variability in this study is of particular interest because WM and inhibition are thought to be important factors underlying individual differences in cognitive ability (Dempster, 1991; Engle *et al*., 1995). Therefore, we asked whether level of activation in particular brain regions was correlated with variability in the level of susceptibility to interference and/or WM performance. Subjects were recruited widely from the community with the goal of achieving a high degree of variability in performance across subjects.

One region in particular, the left anterior inferior frontal gyrus [Brodmann area (BA) 45], has been associated with interference resolution in the Sternberg paradigm. This region was more active under a high-interference condition than a closely matched low-interference condition in a PET study of young adults (Jonides *et al*., 1998). In a subsequent study, it was shown that older adults, who were less effective at suppressing interference than younger subjects, did not show interference-related activation of this region (Jonides *et al*., 2000). An event-related fMRI study showed that the interference-related enhancement of activation in left BA 45 occurred specifically during the presentation of the probe,

the time during which previously encoded items are thought to interfere with task performance (D'Esposito *et al*., 1999*a*). These results suggest that activation of left BA 45 may be important for effective interference resolution. In the present study we asked whether activation of this region is specifically related to prior-trial interference resolution processes, or whether this region is also activated by an increase in WM load.

Material and methods

Subjects

Twenty-three paid volunteers were recruited from Stanford University and around the San Francisco Bay Area. Sixteen healthy right-handed volunteers (13 males, three females; ages 18–40 years, mean 27 years) were included in the study. Six subjects were excluded due to equipment malfunction. One additional subject was excluded because susceptibility to interference deviated by more than 2.5 SD from the mean of the group. Subjects' consent was obtained according to the declaration of Helsinki (*BMJ* 1991; 302: 1194) and the study was approved by the Stanford University Human Subjects Committee.

Tasks

Subjects were tested on the Sternberg item recognition paradigm while fMRI data were acquired. On a given trial, an array of 1, 4 or 6 upper-case consonant letters (the memory set) appeared briefly on the computer screen, followed by a fixation cross and then a lower-case probe letter. Subjects were asked to maintain the memory set in mind over the delay period and then press one of two buttons, as quickly and accurately as possible, to indicate whether or not the probe corresponded to one of the memory set items. Subjects performed four different types of trials in the scanner: Load 1, Load 4, Load 4 High Recency and Load 6 (Fig. 1). Each condition was associated with an equal number of positive probes (probes that had appeared in the memory set) and negative probes (probes that had not appeared in the memory set). In Load 4 High Recency trials, the probe had appeared in the memory set of the immediately preceding trial. In Load 1, Load 4 and Load 6 trials, the probe had not been presented (either as a memory set or probe item) for at least two trials prior to the current trial.

Testing procedure

Subjects practised the tasks by performing at least 10 trials of each type prior to the start of the scan session. Subjects performed 96 7-s trials over the course of two scans. Each scan contained three blocks of four trials for each condition, and the order of blocks was counterbalanced across subjects. Block order varied within and across scans and the order of lists was counterbalanced across subjects. Psyscope (Cohen *et al*., 1993) was used to generate stimuli and to collect responses. Upon completion of the experiment, subjects were asked whether they had noticed any trial groupings of trials other than the blocks of Load 1, 4 and 6 trials. They were then explicitly informed of the Interference manipulation and asked whether they had been aware of the presence of High Recency trials and of the grouping of High Recency trials into blocks. These verbal reports were used to assess whether subjects were conscious of having suppressed irrelevant information on the High Recency trials.

Data acquisition

Whole-brain imaging data were acquired on a 3 T MRI Signa LX Horizon Echospeed scanner (8.2.5 systems revision; GE Medical Systems, Waukesha, Wis., USA). T_2-weighted flow-compensated spin-echo anatomical images [2000 ms TR (repetition time); 85 ms TE (echo time)] were acquired in 17 contiguous 7-mm axial slices. Functional images were acquired in the same set of slices using a T_2*-sensitive gradient echo spiral pulse sequence (Glover and Lai, 1998) (30 ms TE, 1000 ms TR, 2 interleaves, 60° flip angle, 24 cm field of view, 80 × 80 data acquisition matrix).

Data analysis

Functional images were motion-corrected and normalized with SPM99 (Wellcome Department of Cognitive Neurology), interpolated to 2 × 2 × 4 mm voxels and spatially smoothed with a Gaussian filter (6 mm full-width half-maximum). Low-frequency noise and differences in global signal were removed. Data were analysed within the framework of the General Linear Model in SPM99 (Friston *et al*., 1994). Single subjects' data were analysed with a fixed effects model (Friston *et al*., 1994) and group data were analysed with a random effects model (Holmes and Friston, 1998). For the group analysis, functional images were averaged to create one image of mean activity per condition and subject. *t*-Tests were performed on these average images to create a series of SPM{Z} maps depicting differences in brain activity between conditions. Virtually no clusters survived correction for multiple comparisons using the Gaussian field correction in SPM99. Therefore, a voxel-level threshold of $P < 0.005$ uncorrected for multiple comparisons ($T = 3.09$) was used to examine individual contrasts in the group analysis. A further extent threshold of five contiguous voxels was applied to activations meeting the voxel-level threshold. A conjunction analysis was performed with the simple regression analysis tool in SPM99 to examine the extent of overlap between load-related and interference-related activations ($P < 0.005$ uncorrected for multiple comparisons). This analysis identified regions which exhibited a main effect of both load (Load 6 > Load 4) and interference (Load 4 High Recency > Load 4), and excluded regions for which activation differed significantly between the two manipulations. To avoid identifying regions that were

deactivated for Load 4 trials, we excluded from the analysis voxels that were deactivated for Load 4 relative to fixation trials ($P < 0.05$, uncorrected for multiple comparisons).

Regression analyses were performed in SPM99 to identify regions whose activation (as approximated by a comparison of the parameter estimates of the fitted haemodynamic response function for two conditions) was positively or negatively correlated with behavioural performance [voxel-level threshold $P < 0.005$ uncorrected for multiple comparisons ($T = 3.09$); extent threshold five contiguous voxels]. The adjusted mean signal intensity across each condition for each subject was computed for each of the regions of interest (ROIs) identified by the SPM regression analyses. These ROI analyses served two purposes. First, they allowed us to confirm the brain–behaviour correlations within regions identified by the SPM regression analysis. Secondly, they allowed us to examine the activation of each region across all conditions in the experiment. An additional ROI analysis was performed for a 1-cm^3 spherical ROI centred on the maximum in left inferior frontal gyrus ($x = -48$, $y = 21$, $z = 9$) reported previously (Jonides *et al*., 1998). All statistical tests reported in the present study were two-tailed except for planned contrasts on functional data. Maxima were reported in MNI305 coordinates, as in SPM99.

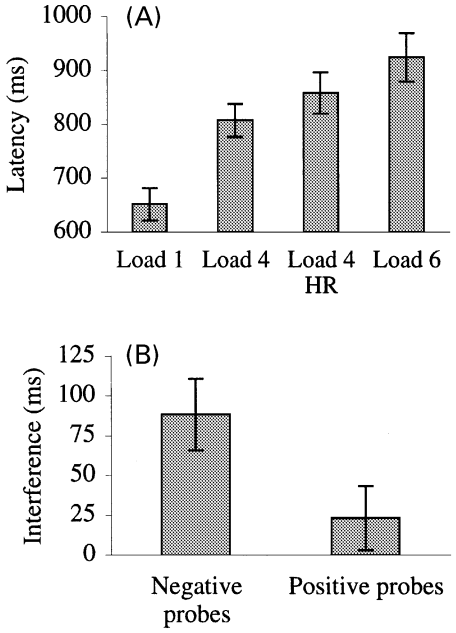

Fig. 2 Behavioural performance during scanning. (**A**) Average response times across the four conditions. Response times increased from Load 1 to Load 4 ($P < 0.0001$) and from Load 4 to Load 4 High Recency ($P < 0.005$), and tended to increase from Load 4 High Recency (HR) to Load 6 ($P = 0.057$). (**B**) Effects of interference on response times. Average response time differences between Load 4 and Load 4 High Recency for negative and positive probes. The interference effect was significant for the negative probes ($P < 0.001$) but not for the positive probes.

Results

Behavioural results

Repeated measures ANOVAs with condition (Load 1, Load 4, Load 4 High Recency and Load 6) and probe type (positive and negative) as within-subject factors were performed in the behavioural data. Performance was highly accurate on all four conditions (Load 1 99 ± 0.6%, Load 4 95 ± 1.5%, Load 4 High Recency 96 ± 0.8% and Load 6 93 ± 1.6%; mean ± SEM) but differed among them [$F(3,120) = 4.8$, $P < 0.005$]. Accuracy was greater for Load 1 than for other conditions [all $t(15) \geqslant 3.1$; $P \leqslant 0.01$]; accuracy on Load 4, Load 4 High Recency and Load 6 trials did not differ significantly. Subjects performed more accurately on positive trials (trials in which the probe was present in the memory set) than on negative trials [$F(1,120) = 35$; $P < 0.0001$]. The interaction between the effects of condition and probe type was not significant. Response times varied across conditions [Load 1 651 ± 21, Load 4 802 ± 22, Load 4 High Recency 858 ± 27 and Load 6 924 ± 32; mean ± SEM; $F(3,20) = 20$; $P < 0.0001$], but the interaction between condition and probe type was not significant.

Increasing WM loads resulted in response time increases from Load 1 to Load 4 [$t(15) = 11.1$; $P < 0.0001$] and from Load 4 to Load 6 [$t(15) = 3.8$; $P < 0.002$; Fig. 2]. Increasing inhibitory demands, through prior-trial presentation of the current probe, resulted in response time increases from Load 4 to Load 4 High Recency [$t(15) = 3.5$; $P < 0.005$]. Response times also tended to increase from Load 4 High Recency to Load 6 [$t(15) = 2.1$; $P = 0.057$]. The increase in response times on Load 4 High Recency trials relative to Load 4 trials was due to slowed responses to negative probes [average response time difference 88 ± 21 ms; mean ± SEM; $t(15) = 4.2$; $P < 0.001$] rather than positive probes [average response time difference 23 ± 19 ms; mean ± SEM; $t(15) = 1.2$; $P = 0.23$; Fig. 2].

The average response time difference between negative Load 4 High Recency and negative Load 4 trials was used as a measure of an individual's interference susceptibility. This measure revealed a high degree of variability in interference susceptibility across subjects (range –8 to 233 ms). The average response time difference between Load 6 and Load 4 trials, averaged over positive and negative trials, was used as a measure of an individual's load susceptibility. There was a high degree of variability in load susceptibility (range –2 to 153 ms). After being debriefed, only two out of 16 subjects reported noticing more than one or two High Recency trials and no subject noticed the grouping of High Recency trials into blocks.

Brain imaging results

Regions that exhibited greater activation for Load 6 than Load 4 trials were considered to be sensitive to WM load. Load-sensitive areas included bilateral regions of ventrolateral

Table 1 *Group activations for the load contrast (Load 6 > Load 4)*

Region of activation	Brodmann area	Talairach coordinates			*Z*-score	Volume (mm^3)
		x	*y*	*z*		
Left frontal						
Inferior frontal	L44/6	−42	−2	32	3.76	7040
Anterior insula	L13	−34	20	4	4.46	4768
Right frontal						
Inferior frontal	R45	36	24	4	4.55	11 264
	R47	36	30	−4	4.02	Local
	R10/44	38	46	0	3.21	288
Middle frontal	R46	40	34	20	3.53	Local
	R9	48	26	28	3.51	Local
	R6	26	2	56	3.19	912
Medial frontal	R32/8	8	20	44	3.41	6624
Anterior cingulate	R24	2	4	28	3.32	464
Inferior parietal/precuneus	L7/19	−28	−70	36	3.80	6768
Inferior parietal	R40/7	44	−50	48	3.74	8640
Cerebellum						
Anterior	R	16	−46	−16	3.34	240
Posterior	R	24	−62	−24	4.38	3808

'Local' indicates a local maximum. Regions that were less active in Load 4 than Load 1 are not shown. Clusters of five or more contiguous voxels whose maxima meet a *Z*-score threshold of 3.09 are reported.

and dorsolateral PFC, anterior insula, anterior cingulate and parietal cortex, as well as right-sided frontopolar cortex, caudate nucleus and cerebellum (Table 1 and Fig. 3). Regions exhibiting greater activation for Load 4 High Recency than Load 4 trials were considered sensitive to interference (Table 2 and Fig. 3). Interference-sensitive regions included right middle frontal gyrus, right anterior cingulate gyrus and right cerebellum (Table 2 and Fig. 3). To ensure that no interference-specific areas were overlooked on the basis of the choice of threshold, a more liberal threshold was used for the Interference manipulation ($P < 0.025$, uncorrected for multiple comparisons). At this threshold, additional activations were found in left inferior frontal gyrus (BA 47), left anterior middle frontal gyrus (BA 46/10), bilateral anterior insula and bilateral parietal cortex (left hemisphere BA 7; right BA 39) (Fig. 3). Critically, every area activated by the Interference manipulation was additionally activated by the Load manipulation and/or a conjunction of the Interference and Load manipulations ($P < 0.005$).

Two regions exhibited significant negative correlations between level of activation in the Interference manipulation and interference susceptibility. Subjects who were least susceptible to interference exhibited the greatest interference-related activation in the right middle frontal gyrus (BA 9) and right superior temporal gyrus (BA 22) (Table 3). No regions were identified as exhibiting a positive brain–behaviour correlation for the Interference manipulation. Regression analyses involving adjusted mean signal intensity in the clusters identified by the SPM regression analysis confirmed that greater activation in these regions was associated with less interference. For the right middle frontal gyrus, the brain–behaviour correlation was stronger for the negative trials ($r = 0.57$; $P = 0.02$) than the positive trials ($r = 0.42$; $P = 0.22$). Subjects who were least susceptible to interference on the negative High Recency trials had the highest levels of activation within this region (Fig. 4). In contrast, the correlation in the superior temporal gyrus was driven by the positive trials ($r = 0.67$; $P = 0.005$) rather than the negative trials ($r = 0.06$; $P = 0.84$). Thus, only the right middle frontal gyrus exhibited a pattern of activation consistent with a role in suppressing interference in the negative trials. An examination of the brain–behaviour relationships exhibited by these regions in the Load manipulation revealed that activity in the right middle frontal gyrus was not significantly correlated with performance for this manipulation (Table 3; Fig. 4). The region in right superior temporal gyrus, on the other hand, exhibited a tendency towards a positive correlation between response times and activation in the Load manipulation ($r = 0.42$; $P = 0.10$; Table 3). These results demonstrate that, across subjects, activation of the right middle frontal gyrus was correlated with the ability to suppress interference efficiently, but that it was not correlated with the ability to efficiently handle an increase in WM load.

Several brain regions exhibited a significant positive correlation between level of activation in the Load manipulation and the corresponding response time differences between Load 6 and Load 4. Subjects who were most susceptible to an increase in load (i.e. showed the greatest response-related slowing for Load 6 relative to Load 4) had the highest levels of activation within the anterior cingulate gyrus (BA 32/24) (Fig. 4 and Table 4) as well as regions in the thalamus, medial frontal gyrus (BA 6), left inferior frontal gyrus (BA 45/46), middle temporal gyrus (BA 22) and

posterior cerebellum (Table 4). Regression analyses involving adjusted mean images confirmed the presence of significant positive brain–behaviour correlations for the Load manipulation in the anterior cingulate and the thalamus. None of these regions exhibited a significant brain–behaviour correlation in the Interference manipulation (Table 4).

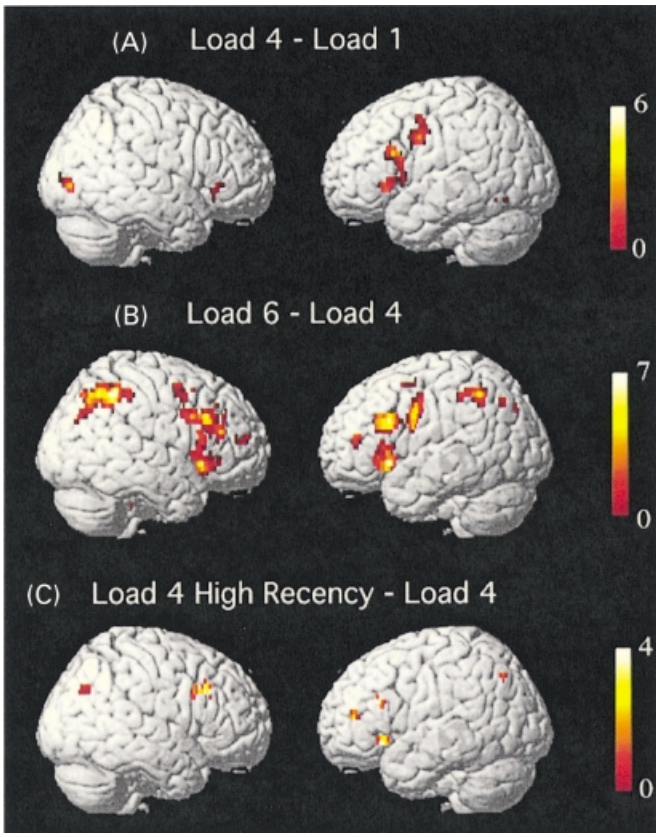

Fig. 3 Rendering of group-averaged brain activations. (**A**) Load-related activations identified by the contrast Load 4 > Load 1 ($P < 0.01$, 20 voxels). (**B**) Load-related activations identified by the contrast Load 6 > Load 4 ($P < 0.01$, 20 voxels). The rendered image was masked to exclude regions which were less active for Load 4 than Load 1 ($P < 0.05$). (**C**) Interference-related activations identified by the contrast Load 4 High Recency > Load 4 ($P < 0.025$, 20 voxels). The rendered image was masked to exclude regions which were less active for Load 4 than Load 1 ($P < 0.05$). Liberal thresholds were chosen to illustrate the overlap between regions activated by each contrast. The level of significance of activation at each voxel (T value) is colour-coded according to the scale on the right of each figure.

A region in left inferior frontal gyrus (BA 45), which has previously been activated by the Interference manipulation in the Sternberg paradigm (Jonides *et al*., 1998), was not significantly activated in the present study ($P > 0.05$). Because there was a high degree of variability in susceptibility to interference across subjects, we sought to determine whether magnitude of activation in this region was correlated with our behavioural measure of interference susceptibility. The adjusted mean signal intensity across conditions was calculated for a 1-cm^3 spherical ROI centred on the maximum reported by Jonides and colleagues ($x = –48$, $y = 21$, $z = 9$). Although activation in this ROI for the Interference manipulation did not reach significance [$t(15) = 1.6$; $P = 0.07$; one-tailed one sample t-test], the signal increase in left BA 45 from Load 4 to Load 4 High Recency was negatively correlated with the increase in response times for Load 4 High Recency relative to Load 4 trials ($r = –0.51$; $P = 0.04$). Thus, across individuals, greater activation in this region was correlated with less susceptibility to interference. However, the correlation between activation and the response time differences between High Recency and Low Recency probes was significant only when the response time differences were averaged over positive and negative trials, and not for the negative ($r = –0.35$; $P = 0.18$) or positive ($r = –0.37$; $P = 0.16$) trials alone. This finding suggests that activation in this region is correlated with increased processing in the Interference manipulation, but that it is not specifically related to suppression of interference on negative trials. Although the average signal intensity in this ROI did not differ across the Interference and Load manipulations [$t(15) = 1.0$; $P = 0.32$], load-related increases in activation were not correlated with load-related increases in response times ($r = 0.06$).

Discussion

Common neural circuitry for WM and interference resolution

This is the first brain imaging study to examine directly the relationship between WM and interference resolution. In the present study, increased demands on WM (through an increase in load) and on behavioural inhibition (through an increase in interference) were associated with slowed response times and activation of a common set of brain regions, including bilateral middle frontal gyrus, left inferior

Table 2 *Group activations for the interference contrast (Load 4 High Recency > Load 4)*

Region of activation	Brodmann area	Talairach coordinates			*Z*-score	Volume (mm^3)
		x	*y*	*z*		
Middle frontal	R9	44	16	36	3.31	224
Anterior cingulate	R24	6	2	32	3.25	160

Regions that were less active in Load 4 than Load 1 are not shown. Clusters of five or more continguous voxels whose maxima meet a *Z*-score threshold of 3.09 are reported.

frontal gyrus, bilateral anterior insula, caudal anterior cingulate gyrus, bilateral parietal cortex and anterior cerebellum. Each of these regions has been implicated previously in verbal WM tasks (Petrides *et al*., 1993; Cohen *et al*., 1994; Awh *et al*., 1996; Fiez *et al*., 1996; Braver *et al*., 1997; Rypma *et al*., 1999). These regions were activated more extensively and more strongly in the Load manipulation, which taxed behavioural performance more heavily than the

Table 3 *Regions exhibiting a linear relationship between load-related activation and load susceptibility*

Region of activation	Brodmann area	Talairach coordinates			*Z*-score	Volume (mm^3)	Correlation coefficient	
		x	*y*	*z*			Load	Interference
Positive relationship								
Anterior cingulate	R32/24	2	24	28	4.65	5472	+0.78	–0.02
Medial frontal gyrus	R6	4	4	48	3.57	384	+0.48	+0.06
Inferior frontal gyrus	L45/46	−34	30	8	3.14	400	+0.30	–0.34
Middle temporal gyrus	L22	−52	−40	4	3.97	416	+0.43	–0.06
Thalamus	R, L	6	−10	8	3.27	1840	+0.56	–0.10
Posterior cerebellum		10	−72	−16	3.21	96	+0.43	+0.21
Negative relationship								
Superior temporal gyrus	L22	−46	8	−12	3.16	160	−0.21	+0.16

Note: Regions that were less active in Load 4 than Load 1 are not shown. Clusters of five or more contiguous voxels whose maxima meet a *Z*-score threshold of 3.09 are reported. 'Local' indicates a local maximum. ROIs exhibiting linear relationships between magnitude of Load-related activation and Load-related reaction time increases (averaged over positive and negative trials) were identified on the basis of linear regression analyses in SPM. Regression statistics were then computed for each ROI to examine the relationship between adjusted mean signal intensity and performance in each manipulation.

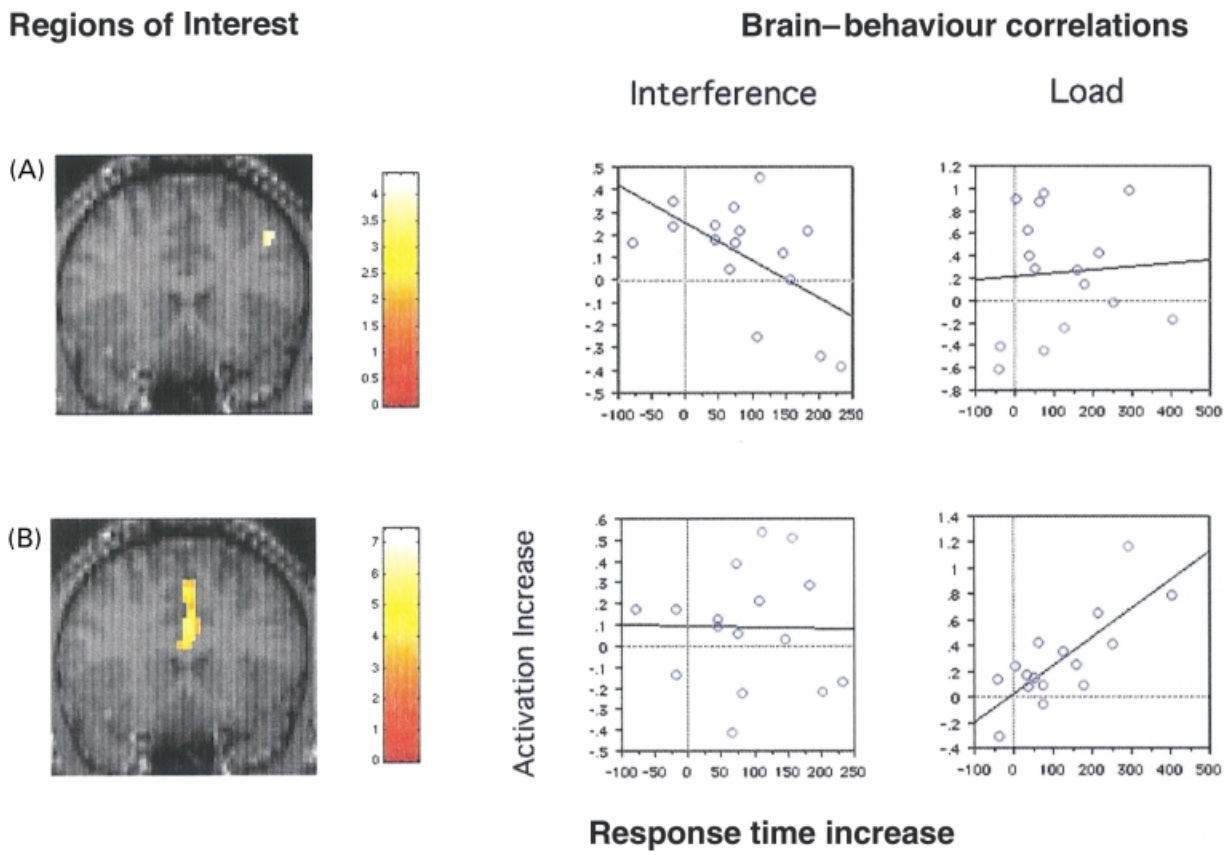

Fig. 4 Brain–behaviour correlations: (**A**) right middle frontal gyrus (BA 9); (**B**) anterior cingulate gyrus (BA 32). Individual differences analyses showing correlations between behavioural performance [increase in response times (ms)] and activation (increase in signal intensity) across subjects for the Interference and Load manipulations. Response time increases were calculated for the negative trials only for the Interference manipulation and were averaged over positive and negative trials for the Load manipulation (see Results).

Table 4 *Regions exhibiting a linear relationship between interference-related activation and interference susceptibility*

Region of activation	Brodmann area	Talairach coordinates			*Z*-score	Volume (mm^3)	Correlation coefficient	
		x	*y*	*z*			Load	Interference
Negative relationship								
Middle frontal gyrus	R9	42	20	36	3.88	128	+0.07	−0.58
Superior temporal gyrus	R22	52	−52	16	3.41	112	+0.42	−0.48

Regions that were less active in Load 4 than Load 1 are not shown. Clusters of five or more contiguous voxels whose maxima meet a *Z*-score threshold of 3.09 are reported. ROIs exhibiting linear relationships between magnitude of interference-related activation and interference-related reaction time increases (averaged over positive and negative trials) were identified on the basis of linear regression analyses in SPM. Regression statistics were then computed for each ROI to examine the relationship between adjusted mean signal intensity and performance in each manipulation.

Interference manipulation. Critically, every region activated by the Interference manipulation was also activated by the Load manipulation. Regions activated by prior-trial interference were a subset of the regions activated by current-trial WM. Thus, a common neural network was activated when either WM or inhibitory demands increased.

The interpretation that a common neural circuitry is implicated by increased WM or inhibitory demands rests on the finding that the same brain areas were activated by both manipulations. The spatial resolution of fMRI, however, is limited. Activation of the same area by two manipulations may arise from recruitment of different pools of neurones in the same region, or even from small, adjacent regions. Nonetheless, single-unit recordings in non-human primates suggest that individual prefrontal neurones have properties that are consistent with a role in both WM and interference suppression. These neurones exhibit delay-period activity which is selective to information that must be kept in mind and, unlike neurones in a higher association visual area (inferotemporal cortex), this delay-period activity is not disrupted by irrelevant distractors (Miller *et al*., 1996).

Although a common neural circuitry was identified for WM and interference resolution, individuals differed in the extent to which they recruited different brain regions within the circuitry. Several regions in PFC exhibited correlations between brain activation and task performance, such that subjects who recruited these regions more strongly were less susceptible to interference. These brain–behaviour correlations provide empirical support for the idea that adult-individual differences in interference control are related to individual differences in prefrontal function (e.g. Dempster, 1991; Engle *et al*., 1995; Kane and Engle, 2000). These data fit into a larger framework in which the rise and fall of the ability to control interference across the lifespan are related to the maturation of PFC in childhood and subsequent decline in old age (Hasher and Zacks, 1988; Dempster, 1992).

Right dorsolateral PFC

Despite the verbal nature of the task, the most robust activations related to interference were in the right hemisphere. Left-sided activations were identified in the Interference manipulation at a liberal statistical threshold ($P < 0.025$), but interference-related activations significant at a more stringent threshold ($P < 0.005$) were all right-lateralized. The most statistically significant interference-related activation in lateral PFC was in right middle frontal gyrus (BA 9). Across subjects, this region exhibited a negative correlation between interference susceptibility and activation, suggesting that neural activity in right dorsolateral PFC contributes significantly to an individual's ability to resolve interference in this verbal WM task. This finding is consistent with a number of studies proposing that the right lateral PFC plays a role in behavioural inhibition across many tasks (Konishi *et al*., 1999*a*). Left prefrontal regions have been implicated in interference tasks involving verbal stimuli (Taylor *et al.*, 1994; Thompson-Schill *et al*., 1997, 1998; Desmond *et al*., 1998; Jonides *et al*., 1998; D'Esposito *et al*., 1999; Leung *et al*., 2000; Macdonald *et al*., 2000), but right lateral prefrontal regions have been activated under interference conditions across a number of tasks involving both non-verbal and verbal stimuli (Konishi *et al*., 1998*a*, 1998*b*, 1999; Garavan *et al*., 1999; Hazeltine *et al*., 2000; E. Hazeltine, S. A. Bunge and J. D. E. Gabrieli, unpublished results).

As in the case of the Interference manipulation, the Load manipulation was associated with more robust right-lateralized than left-lateralized prefrontal activation. Right dorsolateral PFC was activated by an increase in WM load from 4 to 6, but not from 1 to 4 items. The current findings are consistent with other findings (Rypma *et al*., 1999) showing that left ventrolateral regions are recruited for low WM loads (e.g. 1–4 items), but that right dorsolateral PFC is additionally recruited for higher loads (e.g. 6 items). Dorsolateral PFC may mediate strategic mnemonic processes which become important when the load exceeds the verbal short-term memory capacity of left ventrolateral PFC (Rypma *et al*., 1999). Activation of right BA 9 across individuals was not correlated with susceptibility to load.

Left ventrolateral PFC

The region in left inferior frontal gyrus which has been activated previously by the Interference manipulation in this

paradigm (Jonides *et al*., 1998; D'Esposito, *et al*., 1999*a*) was not significantly activated in this study. This discrepancy may be related to the large inter-individual variability in interference susceptibility in the present study, which may have reduced the ability to detect interference-related activation at the group level. The extent to which left inferior frontal gyrus (BA 45) was activated by interference was correlated with an individual's ability to resolve interference efficiently, such that the subjects who were least susceptible to interference exhibited the greatest activation in this region. This is consistent with a study showing that older subjects were both more susceptible to interference than younger subjects, and failed to exhibit interference-related activation in this region (Jonides *et al*., 2000). Together, these results suggest that the level of activation of left BA 45 predicts the extent to which an individual, young or old, is susceptible to interference in this task. However, this region may not be specifically involved in resolving conflict on negative High Recency trials, because activation of this region was correlated with response time differences for positive trials to the same extent as for negative trials. Activation of this region in the Interference manipulation may be related to the activation of the long-term memory representation of an item from the prior trial, which would be expected to occur on both positive and negative High Recency trials. Left BA 45 is more active in negative High Recency trials than load-matched low recency trials (D'Esposito *et al*., 1999), but further testing of the long-term memory account would require examination of whether this finding holds for positive trials as well.

Dorsolateral and ventrolateral prefrontal contributions to interference resolution

A number of imaging studies have emphasized the role of ventrolateral, rather than dorsolateral, PFC in behavioural inhibition (e.g. Konishi *et al*., 1999). However, the present study and others (Garavan *et al*., 1999; Leung *et al*., 2000; S. A. Bunge, E. Hazeltine and J. D. E. Gabrieli, unpublished results) have found interference-related activations of equal or greater extent in dorsolateral as compared with ventrolateral regions. This finding, in conjunction with lesion studies in non-human primates demonstrating that lesions to different regions within PFC cause different types of inhibitory deficits (Dias *et al*., 1997; Roberts and Wallis, 2000), supports the emerging view that different regions within PFC may provide distinct contributions to behavioural inhibition (Miller and Cohen, 2001). There is substantial evidence for at least a partial functional dissociation between ventrolateral and dorsolateral PFC (Petrides, 1994; Owen, 1997; Smith *et al*., 1998; D'Esposito *et al*., 1998). Ventrolateral PFC may play a relatively greater role in filtering out irrelevant information and selecting among competing stimuli or responses (Konishi *et al*., 1998*a*, 1998*b*, 1999; Hazeltine *et al*., 2000; Leung *et al*., 2000) or memories or associations (Thompson-Schill *et al*., 1997; Jonides *et al*., 1998). In contrast, dorsolateral PFC may be more involved in maintaining a representation of the context (goals, rules, sequence of events, etc.) necessary to perform a task accurately (Cohen and Servan-Schreiber, 1992) and in manipulating and updating information that has been determined to be task-relevant (Petrides, 1994; D'Esposito *et al*., 1999*b*). Further studies are needed to examine the ways in which different prefrontal regions contribute to behavioural inhibition.

Anterior cingulate cortex

The anterior cingulate was activated by the Interference and Load manipulations in the present study. Activation of this region is thought to be related to detecting cognitive conflict and signalling the need for greater allocation of attention for the purpose of resolving conflict (Carter *et al*., 1998; Botvinick *et al*., 1999; Macdonald *et al*., 2000; Ochsner *et al*., 2001). Thus, this region would be expected to be recruited on negative High Recency trials, when there is a need to resolve conflict between the fact that the probe letter is irrelevant yet familiar. The anterior cingulate was not activated in a previous PET experiment, which employed a similar interference manipulation (Jonides *et al*., 1998). Jonides and colleagues' result was taken to suggest that the anterior cingulate might mediate the inhibition of pre-programmed responses, as in the Stroop paradigm, but not under conditions in which the response is not overlearned, as in the Interference Sternberg paradigm (Smith and Jonides, 1999). The present study employed a 3 T MRI scanner and included a greater number of subjects than the prior study, and therefore may have had greater power to detect anterior cingulate activation. The present findings suggest that the anterior cingulate was involved in detecting the conflict engendered by interference from the prior trial.

Although the anterior cingulate was significantly activated by the Interference manipulation in the present study, it was activated to a greater extent by the Load manipulation. Additionally, activation in this region was correlated with behavioural performance for the Load manipulation, but not the Interference manipulation. There are at least three plausible reasons for the stronger influence of load than interference on activation of the anterior cingulate. First, the load effect on response times was stronger than the interference effect. Secondly, the Load manipulation led to slowing on both positive and negative trials, whereas the Interference manipulation slowed only the negative trials. It is therefore possible that twice as many trials elicited cingulate activation in the Load manipulation relative to the Interference manipulation. An event-related fMRI design would be needed to explore this possibility. However, it should be noted that neither of these factors precluded the identification of a prefrontal region for which activation was more closely tied to interference than load. A third, more intriguing, reason relates to differences in awareness of conflict between the

two manipulations. After being scanned, all subjects reported being aware of the Load manipulation. However, the majority (14 out of 16) were unaware of the Interference manipulation. Although the anterior cingulate is active under conditions in which subjects are unaware of the need for greater attentional allocation (e.g. the Interference manipulation of the present study; Berns *et al*., 1997), it is possible that this region is more extensively involved when subjects are aware of the increased attentional demands of a task (Ochsner and Feldman Barrett, 2001).

Double-dissociation between prefrontal and anterior cingulate cortices

The present findings constitute a double-dissociation in brain–behaviour correlations between PFC and the anterior cingulate. On one hand, activation of the right middle frontal gyrus was negatively correlated with interference susceptibility, but was not correlated with susceptibility to increased load. On the other hand, activation within a region of anterior cingulate gyrus was positively correlated with load-related performance decrements, but was not correlated with interference susceptibility. A similar pattern of results was found in a study in which activation of dorsolateral PFC was negatively correlated with interference susceptibility on a modified Stroop task, whereas activation of the anterior cingulate gyrus was positively, though non-significantly, correlated with this measure (MacDonald *et al*., 2000). Taken together, these findings suggest that the anterior cingulate is involved in detecting conflict and that lateral PFC is involved in resolving it.

Implications for models of prefrontal function

The present data suggest that a common network of brain regions is involved in suppressing interference from items represented in long-term memory and maintaining additional items in WM. However, the brain–behaviour correlations suggested that regions within this network were more closely tied to the management of interference or WM load demands. On the surface, these observations seem paradoxical. One plausible reconciliation is that the regions in the common network do not have load- or interference-management functions *per se*, but rather have functions that are tapped by both manipulations, to a greater extent by one or the other. Another possibility is that the two manipulations tax the common network in different ways because of the way in which these two manipulations were implemented in this task. For example, these manipulations might be expected to tax WM circuitry at different points in the trial. Logically, the Load manipulation influences the encoding, maintenance and retrieval stages of each trial. The Interference manipulation influences only the retrieval stage, since interference occurs when a target item from the prior trial appears as the probe in the current trial.

Consistent with the idea that the two manipulations tax the WM circuitry at different stages in the trial, the effect of load on prefrontal activity has been shown to occur during encoding of the target set (Rypma and D'Esposito, 1999), and is likely to continue during maintenance and retrieval. In contrast, an event-related study showed that the effect of interference on prefrontal activity occurs specifically while subjects are evaluating the probe (D'Esposito *et al*., 1999*a*). Because the Load manipulation taxes the WM system at an earlier stage than the Interference manipulation, it may affect a greater number of processes. On one hand, this may account for the stronger performance decrements and more robust brain activation associated with the Load but not the Interference manipulation. On the other hand, the fact that the Interference manipulation affects fewer processes may account for the finding that the activation of several prefrontal regions was closely related to the ability to resolve interference but not load. The ability to manage an increase in load may depend on different components of the WM system at different points in the trial, such that the magnitude of activation in any one region does not predict the efficiency of the final behavioural outcome. Therefore, it is plausible that, rather than interference affecting processes distinct from WM, the manipulations used to increase load and interference tax WM in different ways.

There are several prevailing models of the role of PFC in WM and behavioural inhibition. One model holds that dorsal regions of PFC are important for WM whereas ventral (in particular orbitofrontal) regions are important for inhibition (for summary, see Fuster, 1997). In contrast, several models suggest that PFC competitively biases information processing in posterior association regions by enhancing the association of task-relevant associations relative to task-irrelevant ones (Kimberg and Farah, 1993; Miller and Cohen, 2001). According to one model, PFC enhances task-relevant representations, which in turn leads to the suppression of task-irrelevant associations through local inhibitory connections between associations in posterior cortices (Miller and Cohen, 2001). According to another model, PFC enhances task-relevant representations relative to irrelevant representations without relying on inhibitory interactions between neurones (Kimberg and Farah, 1993). A natural prediction of both of these latter models is that the prefrontal regions that are involved in maintaining relevant information in mind should also be involved in keeping irrelevant information out of mind.

Contrary to the model of prefrontal function positing that separate prefrontal regions are important for WM and behavioural inhibition, the present data suggest that interference resolution in this task is mediated by the same regions—both within and outside of PFC—that are involved in maintaining information in WM. These data provide empirical support for computational models which suggest that the same neural systems underlie both WM and interference resolution functions (Kimberg and Farah, 1993; Cohen *et al*., 1996; Houghton and Tipper, 1996; Miller and Cohen, 2001). The striking dissociations between deficits related to lesions of dorsolateral versus ventral prefrontal regions (e.g. deficits in memory and attention versus deficits

in the ability to inhibit inappropriate responses in a social situation) may be related more to a difference in the type of information processed in these regions (more cognitive versus more emotionally or socially relevant information) than to a difference in the types of processes carried out in these regions (Dias *et al*., 1997; Roberts and Wallis, 2000; Miller and Cohen, 2001).

Nothing in the present study provides evidence that PFC plays a role in suppressing interference, rather than simply enhancing the representation of task-relevant relative to task-irrelevant information. However, other findings appear to support this view. De Fockert and colleagues asked subjects to perform a selective attention task that required them to ignore distractor faces (de Fockert *et al*., 2001). Subjects performed this task while maintaining a low or high verbal WM load. Maintenance of a higher WM load resulted in greater interference from distractor faces on the selective attention task, and was associated with greater activation of prefrontal regions as well as in visual areas involved in face processing. These data suggest that when PFC is otherwise occupied, behavioural interference susceptibility and brain activation related to the processing of irrelevant stimuli are both increased. If PFC were to act simply by enhancing the activation of task-relevant representations without at least indirectly suppressing task-irrelevant representations, one would not expect increased activation of face areas with an increase in verbal WM load.

Conclusion

Working memory and behavioural inhibition are broad concepts that are applied to a wide variety of tasks. The present study examined verbal short-term memory, and tasks involving other knowledge domains (e.g. spatial location, object identity, word meaning and emotional salience) would be expected to invoke at least partially different neural systems. The present results suggest that, in a given domain of knowledge and performance, inhibitory processes are a subset of WM processes. Further studies will be needed to determine whether keeping information in mind and out of mind always depends upon common brain circuitry.

Acknowledgements

We wish to thank Kalina Christoff, Anne Sawyer-Glover, Yoon Kyung Jung and Chandan Vaidya for their assistance or helpful comments. We would additionally like to thank two anonymous reviewers for their comments. This research was supported by NIH grants AG12995, RR09784 and MH60234. S.A.B. was supported by a fellowship from the Baxter Foundation.

References

Awh E, Jonides J, Smith EE, Schumacher E, Koeppe RA. Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. Psychol Sci 1996; 7: 25–31.

Baddeley AD. Working memory. Oxford: Clarendon Press; 1986.

Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science 1997; 276: 1272–5.

Bjork RA. Retrieval inhibition as an adaptive mechanism in human memory. In: Roediger HL, Craik FIM, editors. Varieties of memory and consciousness. Hillsdale (NJ): Erlbaum; 1989. p. 309–30.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 1999; 402: 179–81.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 1997; 5: 49–62.

Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, et al. Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci USA 1996; 93: 8016–21.

Carter CS, Braver TS, Barch D. M, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex error detection and the online monitoring of performance. Science 1998; 280: 747–9.

Cohen J, Servan-Schreiber D. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. [Review]. Psychol Rev 1992; 99: 45–77.

Cohen J, MacWhinney B, Flatt M, Provost J. Psyscope: an interactive graphical system for designing and controlling experiments in the Psychology laboratory using Macintosh computers. Behav Res Meth Instrum Comput 1993; 25: 257–71.

Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC. Activation of the prefrontal cortex in a non-spatial working memory task with functional MRI. Hum Brain Mapp 1994; 1: 293–304.

Cohen JD, Braver TS, O'Reilly RC. A computational approach to prefrontal cortex, cognitive control and schizophrenia: recent developments and current challenges. [Review]. Philos Trans R Soc Lond B Biol Sci 1996; 351: 1515–27.

Conway AR, Tuholski SW, Shisler RJ, Engle RW. The effect of memory load on negative priming: an individual differences investigation. Mem Cognit 1999; 27: 1042–50.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 1998; 7: 1–13.

D'Esposito M, Postle BR, Jonides J, Smith EE. The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. Proc Natl Acad Sci USA 1999a 96: 7514–19.

D'Esposito M, Postle BR, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn 1999b; 41: 66–86.

de Fockert JW, Rees G, Frith CD, Lavie N. The role of working memory in visual selective attention. Science 2001; 291: 1803–6.

Dempster FN. Inhibitory processes: a neglected dimension of intelligence. Intelligence 1991; 15: 157–73.

Dempster FN. The rise and fall of the inhibitory mechanism: toward a unified theory of cognitive development and aging. Dev Rev 1992; 12: 45–75.

Desimone R, Duncan J. Neural mechanisms of selective visual attention. [Review]. Ann Rev Neurosci 1995; 18: 193–222.

Desmond JE, Gabrieli JD, Glover, GH. Dissociation of frontal and cerebellar activity in a cognitive task: Evidence for a distinction between selection and search. Neuroimage 1998; 7: 368–76.

Diamond A. Abilities and neural mechanisms underlying AB performance. Child Dev 1988; 59: 523–7.

Dias R, Robbins TW, Roberts AC. Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from 'on-line' processing. J Neurosci 1997; 17: 9285–97.

Drewe EA. Go-no-go learning after frontal lobe lesions in humans. Cortex 1975; 11: 8–16.

Engle RW, Conway ARA, Tuholski SW, Shisler RJ. A resource account of inhibition. Psychol Sci 1995; 6:122–5.

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci 1996; 16: 808–22.

Friston KJ Jezzard P, Turner R. Analysis of functional MRI time-series. Hum Brain Mapp 1994; 1: 153–71.

Fuster JM. The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe. 3rd ed. New York: Lippincott-Raven; 1997.

Fuster JM, Alexander GE. Delayed response deficit by cryogenic depression of frontal cortex. Brain Res 1970; 20: 85–90.

Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: An event-related functional MRI study. Proc Natl Acad Sci USA 1999; 96: 8301–6.

Glover GH, Lai S. Self-navigated spiral fMRI: interleaved versus single-shot. Magn Reson Med 1998; 39: 361–8.

Goldman-Rakic PS. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Mountcastle VB, Plum F, editors. Handbook of physiology. Sect. 1, Vol. 5, Pt 1. Bethesda (MD): American Physiological Society; 1987. p. 373–417.

Hasher L, Zacks RT. Working memory, comprehension, and aging: a review and a new view. In: Bower GH, editor. The psychology of learning and motivation, Vol. 22. San Diego (CA): Academic Press; 1988. p. 193–225.

Hazeltine, E, Poldrack, R, Gabrieli JDE. Neural activation during response competition. J Cogn Neurosci 2000; 12 Suppl 2: 118–29.

Holmes AP and Friston KJ. Generalisability, random effects and population inference. Neuroimage 1998; 4 (4 Pt 2): S754.

Houghton G, Tipper SP. Inhibitory mechanisms of neural and cognitive control: applications to selective attention and sequential action. [Review]. Brain Cogn 1996; 30: 20–43.

Jacobsen CF. Studies of cerebral function in primates. I. The functions of the frontal association areas in monkeys. Comp Psychol Monogr 1936; 13: 1–60.

Jonides J, Smith EE, Marshuetz C, Koeppe RA, Reuter-Lorenz PA. Inhibition in verbal working memory revealed by brain activation. Proc Natl Acad Sci USA 1998; 95: 8410–13.

Jonides J, Marshuetz C, Smith EE, Reuter-Lorenz PA, Koeppe RA, Hartley RA. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. J Cogn Neurosci 2000; 12: 188–96.

Kane MJ, Engle RW. Working memory capacity, proactive interference, and divided attention: limits on long-term memory retrieval. J Exp Psychol Learn Mem Cogn 2000; 26: 336–58.

Kimberg DY, Farah MJ. A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex organized behavior. [Review]. J Exp Psychol Gen 1993; 122: 411–28.

Knight RT, Hillyard SA, Woods DL, Neville HJ. The effects of frontal cortex lesions on event-related potentials during auditory selective attention. Electroencephalogr Clin Neurophysiol 1981; 52: 571–82.

Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, et al. Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat Neurosci 1998a; 1: 80–4.

Konishi S, Nakajima K, Uchida I, Sekihara, K Miyashita, Y. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. Eur J Neurosci 1998b; 3: 1209–13.

Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain 1999; 122: 981–91.

Lumia AR. Higher cortical functions in man. New York: Basic Books; 1966.

Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the Stroop color word interference task. Cereb Cortex 2000; 10: 552–60.

MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000; 288: 1835–8.

Malmo RB. Interference factors in delayed response in monkeys after removal of frontal lobes. J Neurophysiol 1942; 5: 295–308.

May CP, Hasher L, Kane MJ. The role of interference in memory span. Mem Cognit 1999; 27: 759–67.

Miller EK, Cohen, JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001; 24: 167–202.

Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci 1996; 16: 5154–67.

Monsell S. Recency, immediate recognition memory, and reaction time. Cogn Psychol 1978; 10: 465–501.

Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E. Activation of medial temporal structures during episodic memory retrieval. Nature 1996; 380: 715–17.

Ochsner KN, Feldman Barrett L. A multi-process perspective on the neuroscience of emotion. In: Mayne TJ, Bonnano G, editors. Emotion: current issues and future directions. New York: Guilford Press; 2001. p. 38–81.

Ochsner KN, Kosslyn SM, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, et al. Deficits in visual cognition and attention following bilateral anterior cingulotomy. Neuropsychologia 2001; 39: 219–30.

Owen AM. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. [Review]. Eur J Neurosci 1997; 9: 1329–39.

Perret E. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. Neuropsychologia 1974; 12: 323–30.

Petrides M. Frontal lobes and behaviour. [Review]. Curr Opin Neurobiol 1994; 4: 207–11.

Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 1993; 90: 878–82.

Roberts AC, Wallis JD. Inhibitory control and affective processing in the prefrontal cortex: neuropsychological studies in the common marmoset. [Review]. Cereb Cortex 2000; 10: 252–62.

Roberts RJ Jr, Hager LD, Heron C. Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. J Exp Psychol Gen 1994; 123: 374–93.

Rosen VM, Engle RW. Working memory capacity and suppression. J Mem Lang 1998; 39: 418–36.

Rypma B, D'Esposito M. The roles of prefrontal brain regions in components of working memory: effects of working memory load and individual differences. Proc Natl Acad Sci USA 1999; 96: 6558–63.

Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JDE. Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 1999; 9: 216–26.

Smith E, Jonides J. Storage and executive processes in the frontal lobes. [Review]. Science 1999; 283: 1657–61.

Smith EE, Jonides J, Marshuetz C, Koeppe RA. Components of verbal working memory: evidence from neuroimaging. [Review]. Proc Natl Acad Sci USA 1998; 95: 876–82.

Sternberg S. High speed scanning in human memory. Science 1966; 153: 652–4.

Taylor SF, Kornblum S, Minoshima S, Oliver LM, Koeppe RA. Changes in medial cortical blood flow with a stimulus-response compatibility task. Neuropsychologia 1994; 32: 249–55.

Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of the left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci USA 1997; 94: 14792–7.

Thompson-Schill SL, Swick D, Farah MJ, D'Esposito M, Kan IP, Knight RT. Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. Proc Natl Acad Sci USA 1998; 95: 15855–60.

Received December 31, 2000. Revised May 8, 2001.
Accepted June 11, 2001