Active maintenance in prefrontal area 46 creates distractor-resistant memory

Katsuyuki Sakai¹, James B. Rowe¹ and Richard E. Passingham^{1,2}

¹ Wellcome Department of Cognitive Neurology, Institute of Neurology, 12 Queeen Square, London WC1N 3BG, UK

² Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, UK

Correspondence should be addressed to K.S. (ksakai@fil.ion.ucl.ac.uk)

Published online: 15 April 2002, DOI: 10.1038/nn846

How does the brain maintain information in working memory while challenged by incoming distractions? Using functional magnetic resonance imaging (fMRI), we measured human brain activity during the memory delay of a spatial working memory task with distraction. We found that, in the prefrontal cortex (PFC), the magnitude of activity sustained throughout the memory delay was significantly higher on correct trials than it was on error trials. By contrast, the magnitude of sustained activity in posterior areas did not differ between correct and error trials. The correlation of activity between posterior areas was, however, associated with correct memory performance after distraction. On the basis of these findings, we propose that memory representations gain resistance against distraction during a period of active maintenance within working memory. This may be mediated by interactions between prefrontal and posterior areas.

Patients with prefrontal lesions show particularly impaired performance on working memory tasks that include distractors¹. This is consistent with the view that a function of the PFC is to protect memories from distraction². In monkeys, sustained neural activity during the memory delay of a working memory task is taken as the neural correlate of actively maintained information, and such activity is seen in the PFC^{3–6} as well as in the posterior association areas^{5,7,8}. When distractors intervene during the memory delay, the PFC sustains stimulus-selective activity², whereas the posterior association areas do not^{2,7,8}.

These observations indicate that the PFC protects memory against distraction, but how? One possibility is that a local neural circuit within the PFC itself maintains information against distraction. Modeling studies show that this can be achieved by recurrent interaction of excitatory and inhibitory circuits⁹. Such a system would provide distraction resistance within the maintenance component of working memory. Here, we propose another mechanism—interaction between the PFC and posterior association areas—that creates resistance against distraction. According to our model, the PFC plays an executive role in transforming the maintained information into a representation that can survive distraction.

Normal human subjects performed a spatial working memory task in which they viewed, and tried to memorize, a sequence of five spatial positions indicated by red squares on a screen (Fig. 1). After a memory delay (during which no stimuli were presented), the subjects performed a distractor task in which they viewed, and tried to remember, a sequence of five blue dots. The distractor task required subjects to shift spatial attention to the positions of distractors, which made it impossible to mentally rehearse the first sequence^{10,11}. After making a recognition judgment about the blue dots, participants were tested on their memory for the spatial order of the red squares. These 'distractor-plus' trials were intermixed with 'distractor-minus' trials, in which the memory delay was immediately followed by a memory test for the spatial sequence of red squares. In control trials, there was no spatial order to remember (see Methods). We used event-related fMRI to identify activity sustained during the memory delay. Long and variable lengths for the memory-delay period (8–16 s) allowed us to distinguish sustained activity from the phasic activity time-locked to viewing stimuli (red squares), viewing distractors (blue dots) and performing a memory test. We compared fMRI data collected during the distractor-plus and distractorminus conditions with data collected during control conditions.

RESULTS

Behavioral results

Accuracy on the distractor task was 98% for both memory and control conditions. On the memory test for the spatial order of the red squares, the accuracy was 68% in the distractor-plus condition (with 22% 'forgotten' responses, see Methods) and 97% in the distractor-minus condition. Accuracy was not correlated with the length of the memory delay (P > 0.1).

Participants were instructed not to move their eyes during the memory delay (a rehearsal strategy that can aid in remembering the locations). The extent and tracking distance of subjects' eye movements were minimal as compared to the extent of the array of the five red squares ($24^{\circ} \times 18^{\circ}$ of visual angle), and did not differ significantly between the distractor-plus, distractor-minus and control conditions (P > 0.1; mean extent of eye movements, 0.58°, 0.52° and 0.61° of visual angle; mean tracking distance, 1.74°, 1.97° and 1.55° of visual angle, respectively). During the memory delay,

saccadic eye movements occurred in only 2.2% and 2.5% of the distractor-plus and -minus trials, respectively, and in 3.0% of control trials. Upon presentation of distractors, eye movements naturally followed the order of the distractor locations.

Sustained activity on distractor-plus trials

We found sustained activity in two prefrontal regions during the memory delay of correct trials in the distractor-plus condition (P < 0.05 corrected, compared to control condition). One region was the mid-part of the middle frontal gyrus (area 46 [ref. 12]; Fig. 2a), and the other was the posterior part of the superior frontal sulcus just anterior to the precentral sulcus (area 8; Fig. 2b). There was also sustained activity in the posterior part of the intraparietal sulcus (IPS, Fig. 2c left) as well as in other areas (Table 1).

Time course of sustained activity

On correct trials, the activity in area 46, area 8 and the IPS was sustained throughout the memory delay, and expanded according to the length of memory delay (Fig. 2, center panels). This finding is consistent with previous unit recording studies in monkeys^{3,4,13}. On error trials, however, the activity in area 46 was not sustained during the memory delay (Fig. 2a, right). The activity on error trials was not significantly different from that on control trials (P > 0.1) and was significantly less than that on correct trials (P < 0.05). This finding is in accord with previous unit recording studies^{4,6,14}, although there was no distraction in those studies. By contrast, the activity in area 8 and the IPS was sustained during the memory delay even on error trials (Fig. 2b and c, right) and did not differ significantly between correct and error trials (P > 0.1).

Differential activity for correct and error trials

We investigated the times at which activity on correct and error trials diverged. Trials with different lengths of the memory delay were collapsed together and the time-series of BOLD signals (see Methods) was realigned at the onset (x = 0 on the left panels in Fig. 3) and offset (x = 0 on the right panels in Fig. 3) of the memory delay. For area 46, the activity on correct trials (blue) differed significantly from that on error trials (red) during the period between 6 s after onset and 6 s after offset of the memory delay (P < 0.05, Fig. 3a, see also Fig. 2a). Given the delayed timing of the BOLD signal compared with electrical activity, this period functionally corresponds to the memory delay. On error

Table I. Sustain	ed activation during the memory delay o	эf
'distractor-plus'	trials.	

Area	Side	Coordinates			t- value
		x	у	z	
Prefrontal area 46	Right	40	46	22	6.49
Prefrontal area 46	Left	-44	54	22	6.38
Prefrontal area 8	Right	32	6	62	8.25
IPS/SPL	Right	18	-62	48	13.5
IPS/SPL	Left	-18	-62	64	9.66
IPS	Right	34	-50	36	9.83
IPS	Left	-52	-40	40	11.23
Premotor cortex	Right	52	16	36	9.88
SMA	Right	4	4	58	14.67
Inferior temporal cortex	Right	62	-44	-22	9.63
Cerebellum	Left	-24	-62	-32	9.56

IPS, cortex in the intraparietal sulcus; SPL, superior parietal lobule; SMA, supplementary motor area.



Fig. 1. Schematic diagram of a distractor-plus trial. Subjects remembered a sequence of five spatial positions that were indicated by red squares (reproduced here as orange, but red in the scanner). After an unfilled memory delay of 8-16 s (varied in steps of 2 s), they performed a distractor task in which they remembered positions of five blue dots and then judged whether the position of a blue asterisk matched one of the positions of the blue dots. Immediately after the distractor judgment, subjects saw an array of five boxes and an arrow and were asked to judge whether the arrow replicated the spatial order of the red squares. Bottom, the timing of the task epochs relative to the onset of memory delay at time '0'.

trials, area 46 showed a biphasic response: the first response peaked at 4 s after the onset of the memory delay, that is, 8.75 s after the presentation of the first stimulus, whereas the second response peaked at 8 s after the offset of memory delay, that is, 8 s after the presentation of the first distractor (**Fig. 3a**, red). At these peaks, the activity in area 46 did not differ significantly between the correct and error trials (P > 0.1). In contrast, the activity in area 8 and the IPS did not differ between the correct and error trials at any time throughout the task epoch (P > 0.1, **Fig. 3b** and c). A three-way ANOVA with factors of area, accuracy and time-bin confirmed the existence of a significant difference between the pattern of sustained activation in area 46 and that in area 8 and the IPS (P < 0.05).

Tight signal coupling on correct trials

Prefrontal areas 46 and 8 and the IPS are heavily interconnected^{15,16}. To see how they interact, we first examined the correlation (by calculating the correlation coefficient, r) of activity between area 8 and the IPS (Fig. 4a). This correlation was significantly higher for correct trials (blue) than for error trials (red). Data were pooled from all the subjects (correct, r = 0.766, n = 312; error, r = 0.562, n = 156; P < 0.01). The slope and intercept of the regression lines did not differ: IPS = $0.690 \times \text{area } 8 + 0.305$ for correct trials and IPS = $0.672 \times \text{area } 8 + 0.316$ for error trials. We further calculated the correlation coefficient for each subject. Paired *t*-tests across subjects showed that the correlation was significantly higher on correct trials than on error trials (P < 0.01), indicating that it applies to the general population.

The tighter signal coupling between area 8 and the IPS on correct trials may be due to common inputs from area 46. The correlation of activity between area 46, area 8 and the IPS supports the idea. We found that when the signal in area 46 was high, the signals in area 8 and IPS were tightly clustered (Fig. 4b), and this was true even when data for correct trials (blue in Fig. 4b) were considered alone. We divided the data for area 46 into two halves—higher and lower activity. The correlation of signals in area 8 and the IPS was significantly higher (P < 0.01) for the higher-activity half in area 46 (r = 0.909, n = 156) than for the lower-



activity half in area 46 (r = 0.638, n = 156). This finding supports the idea of a common input from area 46 to area 8 and IPS.

To what extent did the activation in area 46 predict the memory performance? We plotted the accuracy of memory performance as a function of the BOLD signal changes in area 46 (Fig. 5). For distractor-plus trials (filled circles), the accuracy of performance fell to chance when activity in area 46 was low, and improved with an increase in activity.

Sustained activity on distractor-minus trials

We also examined sustained activity in the distractor-minus condition. For all brain regions, the activity in the distractor-minus condition did not differ significantly from that in the distractorplus conditions when correct and error trials were taken together (P > 0.1). This was expected, because the subjects were unable to predict whether or not there would be distractors. The correlation of the BOLD signals between area 8 and the IPS did not differ between the distractor-minus and distractor-plus conditions when correct and error trials were taken together (Fig. 4c, r = 0.684, n = 492 for distractor-minus condition and r = 0.677, n = 468 for distractor-plus condition, P > 0.1). Moreover, the distribution of Fig. 2. Sustained activation during the memory delay. (a) Prefrontal area 46 (x, y, z coordinates: 40, 46, 22). (b) Prefrontal area 8 (32, 6, 62). (c) Intraparietal sulcus region (IPS; 18, -62, 48). The left side of the images (or top in b) corresponds to the left side of the brain. Data for correct and error trials are shown separately in the center and right panels, respectively (a–c). The adjusted BOLD signal data from the activation peaks (blue cross-hairs) were temporally realigned at the onset of the memory delay and are shown as relative increase of BOLD signals (y-axis) over time (x-axis) for each length of memory delay (z-axis). Time '0' on the x-axis corresponds to the onset of memory delay.

the signals in area 46 on correct trials in the distractor-minus condition (blue in Fig. 4d) was similar to that on all the trials in the distractor-plus condition (blue and red in Fig. 4b). Our subjects were almost always successful at recall in the distractor-minus condition (accuracy 97%) and this high accuracy was maintained regardless of the amount of activity in area 46 (Fig. 5). Note again that, even in the dist-

tractor-minus condition, higher activation in area 46 was associated with tighter coupling of area 8 and the IPS (**Fig. 4d**). Thus inter-regional interactions during the memory delay predicted successful memory recall with distraction, but had no correlation with performance on trials without distraction.

DISCUSSION

Our results support the view that the PFC is centrally involved in protecting working memory representations against distraction^{1,2,17}. In the condition with distractors, we found significant activation in prefrontal area 46 during the memory delay on correct trials but not on error trials. Notably, it was the sustained prefrontal activity before, not after², presentation of the distractors that corresponded with resistance to distraction. Whereas activity after distraction is taken to reflect on-line maintenance of information that survives distraction, activity before distraction may reflect executive processes that transform the maintained information into distraction-resistant representations.

Prefrontal mechanisms to protect memory against distractors could operate at various stages during memory tasks. Upon presentation of distractors, the PFC might be involved in filtering



Fig. 3. Time course of activation for correct and error trials. (**a**) In prefrontal area 46, correct and error trials have divergent time courses of activation. (**b**, **c**) In prefrontal area 8 and the intraparietal sulcus region (IPS), activation is similar for correct and error trials. The time series of the adjusted BOLD signal data were collapsed across different lengths of memory delay and were realigned at the onset (time '0' on the left panel) and offset (time '0' on the right panel) of memory delay. For each 2-s bin, the mean and 95% confidence interval of the signals are shown separately for correct (blue) and error (orange) trials. The red and blue shaded horizontal bars at the bottom of each graph indicate the time epoch for presentation of stimuli and distractors (see **Fig. 1**).

Fig. 4. Correlation of activation. (**a**, **b**) On the distractorplus trials, higher correlation was associated with correct performance. (**c**, **d**) On the distractor-minus trials, correct performance was achieved regardless of correlation. The data for correct (blue circle) and error (orange cross) trials are shown separately. For visualization purposes, the number of data points for correct trials is matched to that for error trials in the distractor-plus condition (n = 152 for each).

out irrelevant information^{18,19}. At retrieval of memory items, the PFC might be involved in selecting relevant information to overcome interference effects from the preceding trials^{20,21}. In the present study, we have shown that the PFC starts to operate before presentation of the distractors.

As participants knew that there might be distractors after the memory delay, they may have been preparing to switch tasks^{22–24}; it has been shown previously that the PFC is involved task switching^{25,26}. In this case, one would expect to see a rise in PFC activity at the time subjects would begin to anticipate the new task. Our data show, however, that activity in prefrontal area 46 remained high immediately after the presentation of the spatial stimuli. We think it unlikely that subjects started to prepare for the task switch this early as they knew it would be at least 8 s before

switch this early, as they knew it would be at least 8 s before onset of the distractor task.

It is also unlikely that the activity in area 46 reflected simple maintenance of information because subjects were successful in the distractor-minus condition irrespective of the level of activation in this area. Sustained activity in area 46 may not be necessary for simple maintenance in the absence distraction. This view is consistent with previous imaging results that did not show sustained activation in area 46 when subjects simply maintained spatial information without distraction^{27,28}. By contrast, studies in monkeys have shown that sustained activity in area 46 is associated with correct performance even when there is no explicit distraction^{4,6,14}. It is possible that monkeys are more prone to distraction even without distractors presented as such. Monkeys with prefrontal lesions performed at 97% accuracy on a delayed response task in complete darkness, whereas they performed at chance when the task was administered in light conditions²⁹. Furthermore, the number of stimulus locations used in monkey studies is relatively small (two to eight) and many trials are given in one session; thus there could be high interference in memory across trials.

On error trials, prefrontal area 46 showed a normal phasic response to the stimuli, but did not show sustained activity during the memory delay. The phasic response to the stimuli is associated





with registration of the spatial information¹³. As subjects were almost always successful on distractor-minus trials, it is clear that they successfully registered or encoded the spatial order. In this respect, our finding differs from previous studies^{30,31} in which phasic prefrontal activity at incidental encoding was associated with subsequent performance on a recognition test given 30 minutes later. Our study has shown that sustained prefrontal activation during the memory delay of intentional remembering was associated with success on a recall test given after 4.5 s of a distractor task. Both studies suggest that PFC activity enhances the strength of memory.

In addition to area 46, we also found sustained activation in the more posterior prefrontal area 8 and the IPS. These areas have been consistently found to show sustained activity during a memory delay in imaging as well as in unit recording studies^{5,27,28,32}. Sustained activity in these areas may reflect simple maintenance of information in working memory, without additional executive processing. Unlike area 46, the activity in area 8 and the IPS did not differ between correct and error trials in the distractor-plus condition. Both prefrontal area 8 and the IPS have been shown to be involved in covert shifts of attention^{33–35}. Therefore, this finding weakens the possibility that the subjects made errors simply because they did not pay attention to the remembered positions.

We found that the correlation of the sustained activity between area 8 and the IPS was associated with resistance against distraction. The degree of coupling between these areas was associated with correct memory retrieval after distraction. This indicates that the correlation of neural activity can be controlled independently of neural firing rates³⁶. Increased correlation is thought to strengthen information representations^{36,37}. In the present study, the tight coupling of area 8 and the IPS may reflect the robustness of a memory representation in the face of distraction. Our results also point to the possibility that area 46 controls the coupling between area 8 and the IPS. Although activity in area 46 was

Fig. 5. Increased accuracy of memory performance as a function of activity in prefrontal area 46 for distractor-plus trials (filled circles). On distractor-minus trials (open circles), memory performance was maintained at a high level regardless of the magnitude of prefrontal activation. Note that 50% accuracy is chance performance.

not significantly correlated with activity in either area 8 or the IPS alone (r = 0.281 and 0.279, respectively), it was associated with tighter coupling between area 8 and IPS. This higher-order correlation might indicate a modulatory role of area 46 rather than a transmissive one¹⁷. Because our data are correlational, only an intervention study could settle the direction of the causality.

What processes could underlie the memory maintenance seen here? One possibility is that during the memory delay, participants engaged in a process of active rehearsal, covertly shifting spatial attention to the remembered target positions¹¹. This would be equivalent to repeatedly selecting representations for the appropriate spatial locations. Selection may be achieved by a top-down signal from prefrontal area 46 to posterior association areas where the memory representations are stored^{17,27,38,39}. Repeated inputs from area 46 may cause reverberation of activity within area 8 and the IPS, thereby enhancing the memory representation during distraction⁴⁰. Alternatively, representations of spatial order may have been re-organized or elaborated during the memory delay: the sharpness of the spatial tuning of prefrontal neurons increases during the memory delay⁶. It has also been shown that prefrontal area 46 is involved in the elaboration of maintained information, which subsequently leads to better memory performance⁴¹.

Our findings support a marked difference between the nature of the sustained activity in prefrontal area 46 and that of other areas. We suggest the term 'active maintenance'¹⁷ to distinguish activity in area 46 from activity in other areas that may be associated with 'simple maintenance'. We propose that active maintenance makes demands on executive processes, consistent with claims that prefrontal area 46 has an executive role in memory^{42–44}. We further propose that the mechanism by which these executive processes are carried out involves higher-order interactions between prefrontal and posterior association areas⁴⁵. In the face of distraction, these interactions are essential for correct memory performance.

METHODS

Subjects. Fourteen normal right-handed volunteers (age range 20–40 years, seven males, seven females) gave written informed consent to participate in the study. The study was approved by the joint ethics committee of the Institute of Neurology and University College London Hospital, London, UK.

Behavioral task. Participants were asked to remember the spatial positions of a sequence of five red squares, which were presented on a screen for 750 ms each with an inter-stimulus interval of 250 ms. The array of the five squares subtended a visual angle of $24^{\circ} \times 18^{\circ}$ (Fig. 1). This was followed by an unfilled memory delay, lasting 8–16 s (varied in steps of 2 s), during which subjects were instructed not to rehearse the remembered locations by moving their eyes. On 'distractor-plus' trials, a spatial distractor task followed the delay: five blue dots were presented successively for 500 ms each with an interstimulus interval of 250 ms. Then, after 500 ms, participants were shown an asterisk for 500 ms and made a button press with the right index or middle finger to report whether or not a blue circle had appeared at the position of the asterisk. Subjects were explicitly instructed to perform the distractor task as accurately as possible.

One second after the distractor task, participants were tested on their memory for the spatial order of the red squares. We presented an array of five boxes that matched the positions of the five red squares, with an arrow pointing from one box to another (Fig. 1). Participants responded with a button press (again using the right index or middle finger) to report whether or not the arrow indicated the correct spatial order of the red squares. They pressed a button with the right ring finger if they had forgotten the order. The distractor task was demanding enough to prevent people from mentally rehearsing the spatial order of red squares. This was confirmed by a pilot experiment in which three subjects were asked to continue the rehearsal of red squares while performing the distractor task. With an accuracy of 95% on the memory task, performance on the distractor task deteriorated nearly to chance (56%). Intermixed with these distractor-plus trials were memory trials without distractors ('distractor-minus' trials). On these trials, the unfilled memory delay was followed immediately by a memory test for the spatial order of red squares. The conditions were otherwise identical to those in 'distractor-plus' trials. We also presented control trials in which five red squares appeared in the same position at the center of the screen. After a delay, subjects were shown an array of five squares, one at the center and the others at the four corners of the screen. They pressed a button with their index finger if the square at the center was indicated by an arrow. In half of the control trials, a distractor task came after the delay, as in 'distractor-plus' trials.

After participants had practiced the task for 15 min, imaging began. Eighteen distractor-plus trials, 18 distractor-minus trials and 36 control trials (18 with distractors and 18 without distractors) were randomly presented with inter-trial intervals of 8–16 s, which were varied in steps of 2 s. For each trial we used different arrays of five boxes. Throughout the task, the subjects' eye movements were recorded using an infrared eye-tracking system (Model 504LRO, Applied Science Laboratories, Bedford, Massachusetts) that detected eye movements larger than 0.25° of visual angle at a sampling rate of 240 Hz. We measured the extent of eye movements during the memory delay by calculating the diameter of the minimum circle that covered all eye-traces. We also measured the eye-tracking distance, or the total distance of eye movements, and the frequency of saccadic eye-movements (velocity > 30°/s)⁴⁶ during the memory delay.

fMRI imaging. Imaging was performed using a 2-Tesla scanner (Siemens Vision, Erlagen, Germany). The functional images sensitive to blood oxygenation level–dependent (BOLD) contrasts were acquired by T2*-weighted echo planar imaging (TR = 4.5 s, TE = 40 ms, 540 sequential whole brain volume acquisitions, $64 \times 64 \times 48$ voxels at 3 mm isotropic resolution). The onset of each task trial relative to the preceding image acquisition was jittered in steps of 0.75 s within 1 TR (4.5 s). High-resolution structural T1-weighted MPRAGE images (TR = 9.5 s, TE = 4 ms, TI = 600 ms, voxel size $1 \times 1 \times 1.5$ mm, 108 axial slices) were also acquired on all subjects.

Data analysis. We used SPM99 software (http://www.fil.ion.ucl.ac.uk/ spm) for image processing and analysis. The first five volumes of images were discarded to allow for T1 equilibration. The remaining 535 image volumes were realigned to the first image, sinc-interpolated over time to correct for phase advance during volume acquisition, and normalized to the Montreal Neurological Institute (Montreal, Canada) reference brain. The data were spatially smoothed with a Gaussian kernel (10 mm, fullwidth at half-maximum). Statistical parametric maps of t-statistics were calculated for condition-specific effects within a general linear model. Sustained activity was modeled as an epoch time-locked to the start of the memory delay, with duration matched to the length of the memory delay. We created separate models for correct and error trials for each of the distractor-plus, distractor-minus and control conditions. Error trials were those for which subjects gave an incorrect response or reported that they could not remember. The trials in which subjects made errors in the distractor task were also modeled separately. The model included separate covariates for transient activation in response to the presentation of each stimulus, distractor and memory test. All events were convolved with a canonical hemodynamic response function. The data were high-pass filtered with a frequency cutoff at 100 s.

We performed a random effects analysis. Images of parameter estimates for the contrast of interest were created for each subject (first-level analysis), and were then entered into a second-level analysis using a onesample *t*-test across the subjects. To equate the weighting of each subject contributing to the second-level analysis, we selected 12 subjects who made at least 10 correct responses and at least 5 error responses in the distractor-plus condition. For each subject, 10 correct trials and 5 error trials were randomly chosen for the statistical comparisons; thus, approximately 120-s memory-delay epochs for correct trials and 60-s memory-delay epochs for error trials were chosen for each subject.

Identification of activation foci. First, we identified areas that showed sustained activity during the memory delay. We made comparisons between the memory delay of the correct trials in the distractor-plus condition and the delay of the control condition (P < 0.05 corrected; $t_{11} > 8.95$). Because

of our prior hypothesis regarding the role of the PFC, we also corrected for a reduced search volume within the lateral PFC ($t_{11} > 5.50$). Then we used this activation map as an inclusive mask. Within this mask, we made comparisons between correct and error trials in the distractor-plus condition, and also between the error trials in this condition and all trials in the control condition. The contrasts were thresholded at P < 0.05, corrected for a 10mm-radius spherical search volume centered at the peaks of activation foci shown in Table 1 (t_{11} > 3.55). We also compared the memory delay of correct trials in the distractor-minus condition and the memory delay of all the trials in the distractor-plus condition (P < 0.05 corrected).

Time course of activation. The time course of the BOLD signals was realigned at the onset and offset of the memory delay and was re-sampled in 2-s time bins. The signals within each bin were then averaged across the trials for the 12 subjects (120 correct trials and 60 error trials). The signals for the correct and error trials were compared for each bin using an unpaired *t*-test.

Correlation of activation. The signals during the period of sustained activation, that is, between 6 s after the onset and 6 s after the offset of the memory delay, were collected from the 10 correct and 5 error trials for each of the 12 subjects. We obtained 312 and 156 data points for correct and error trials, respectively, in the distractor-plus condition and 492 data points for correct trials in the distractor-minus condition. We calculated Pearson's product-moment correlation coefficients (r) to estimate the linear correlation of the signals. The difference in the strength of correlation between the correct and error trials was tested by transforming the correlation coefficients into z-scores (Fisher's z-transformation) and comparing them using a χ^2 -test.

Acknowlegments

We are grateful to C. Frith, M. Rugg and R. Frackowiak for comments. This study was supported by the Wellcome Trust. K.S. was supported by the Human Frontier Science Program.

Competing interests statement

The authors declare that they have no competing financial interests.

RECEIVED 2 JANUARY; ACCEPTED 4 MARCH 2002

- D'Esposito, M. & Postle, B. R. The dependence of span and delayed-response 1. performance on prefrontal cortex. *Neuropsychologia* 37, 1303–1315 (1999). Miller, E. K., Erickson, C. A. & Desimone, R. Neural mechanisms of visual
- working memory in prefrontal cortex of the macaque. J. Neurosci. 16, 5154-5167 (1996).
- Fuster, J. M. Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. J. Neurophysiol. 36, 1-78 (1973).
- Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. 61, 331-349 (1989).
- Chafee, M. V. & Goldman-Rakic, P. S. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J. Neurophysiol. **79**, 2919–2940 (1998).
- 6. Sawaguchi, T. & Yamane, I. Properties of delay-period neuronal activity in the monkey dorsolateral prefrontal cortex during a spatial delayed matching-tosample task. J. Neurophysiol. 82, 2070–2080 (1999).
- 7. Miller, E. K., Li, L. & Desimone, R. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. J. Neurophysiol. 13, 1460-1478 (1993)
- Constantinidis, C. & Steinmetz, M. A. Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. J. Neurophysiol. 76, 1352-1355 (1996).
- Compte, A., Brunel, N., Goldman-Rakic, P.S. & Wang, X. J. Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. Cereb. Cortex 10, 910-923 (2000).
- Smyth, M. M. Interference with rehearsal in spatial working memory in the absence of eye movements. Q. J. Exp. Psychol. A 49, 940–949 (1996).
- Awh, E. & Jonides, J. Overlapping mechanisms of attention and spatial working memory. *Trends Cogn. Sci.* 5, 119–126 (2001).
- 12. Rajkowska, G. & Goldman-Rakic, P. S. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. Cereb. Cortex 5, 323-337 (1995)
- 13. Kojima, S. & Goldman-Rakic, P. S. Delay-related activity of prefrontal

neurons in rhesus monkeys performing delayed response. Brain Res. 248, 43-49 (1982)

- 14. Funahashi, Ś., Inoue, M. & Kubota, K. Delay-period activity in the primate prefrontal cortex encoding multiple spatial positions and their order of resentation. Behav. Brain Res. 84, 203-223 (1997)
- 15. Petrides, M. & Pandya, D. N. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. J. Comp. Neurol. 228, 105-116 (1984)
- Cavada, C. & Goldman-Rakic, P. S. Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. J. Comp. Neurol. 287, 422-445 (1989).
- 17. Miller, E. K. & Cohen, J. D. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167-202 (2001).
- 18. Chao, L. L. & Knight, R. T. Human prefrontal lesions increase distractibility
- to irrelevant sensory inputs. *Neuroreport* 6, 1605–1610 (1995).
 19. Guillery, R. W., Feig, S. L., & Lozsadi, D. A. Paying attention to the thalamic reticular nucleus. *Trends Neurosci.* 21, 28–32 (1998).
- 20. D'Esposito, M., Postle, B. R., Jonides, J. & Smith, E. E. The neural substrate and temporal dynamic of interference effects in working memory as revealed by event-related functional MRI. Proc. Natl. Acad. Sci. USA 96, 7514-7519 (1999).
- 21. Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H. & Gabrieli, J. D. E. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074-2086 (2001).
- 22. Rogers, R. D. & Monsell, S. Costs of a predictable switch between simple cognitive tasks. J. Exp. Psychol. Gen. 124, 207–231 (1995). 23. Gopher, D., Armony, L. & Greenshpan, Y. Switching tasks and attention
- olicies. J. Exp. Psychol. Gen. 129, 308-339 (2000).
- 24. Rubinstein, J. S., Meyer, D. E. & Evans, J. E. Executive control of cognitive processes in task switching. J. Exp. Psychol. Hum. Percept. Perform. 27, 763–797 (2001).
- D'Esposito, M. et al. The neural basis of the central executive system of working memory. Nature 378, 279–281 (1995).
- 26. Sohn, M-H., Ursu, S., Anderson, J. R., Stenger, V. A. & Carter, C. S. The role of prefrontal cortex and posterior parietal cortex in task switching. Proc. Natl. Acad. Sci. USA 97, 13448–13453 (2000).
- 27. Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S. J. & Passingham, R. E. The prefrontal cortex: response selection or maintenance within working memory? Science 288, 1656-1660 (2000).
- 28. Rowe, J. B. & Passingham, R. E. Working memory for location and time: activity in prefrontal area 46 relates to selection rather than maintenance in memory. Neuroimage 14, 77-86 (2001). 29. Malmo, R. B. Interference factors in delayed response in monkeys after
- removal of frontal lobes. J. Neurophysiol. 5, 295-308 (1942).
- 30. Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H. & Gabrieli, J. D. E. Making memories: brain activity that predicts how well visual experience will be remembered. Science 281, 1185-1187 (1998).
- 31. Wagner, A. D. et al. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281, 1188-1191 (1998).
- 32. Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G. & Haxby, J. V. An area specialized for spatial working memory in human frontal cortex. Science 279, 1347-1351 (1998).
- 33. Rosen, A. C. et al. Neural basis of endogenous and exogenous spatial orienting: a functional MRI study. J. Cognit. Neurosci. 11, 135-152 (1999)
- 34. Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P. & Shulman, G. L. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3, 292-297 (2000).
- 35. Perry, R. J. & Zeki, S. The neurology of saccades and covert shifts in spatial attention. An event-related fMRI study. Brain 123, 2273-2288 (2000).
- 36. Salinas, E. & Sejnowski, T. Correlated neuronal activity and the flow of neural information. Nat. Rev. Neurosci. 2, 539-550 (2001).
- 37. Varela, F., Lachaux, J. -P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229-239 (2001)
- 38. Frith, C. in Control of Cognitive Processes: Attention and Performance XVIII (eds. Monsell, S. & Driver, J.) 549-565 (MIT Press, Cambridge, Massachusetts, 2000).
- Miyashita, Y. & Hayashi, T. Neural representation of visual objects: encoding and top-down activation. *Curr. Opin. Neurobiol.* 10, 187–194 (2000).
- 40. Wang, X. J. Synaptic reverberation underlying mnemonic persistent activity. Trends Neurosci. 24, 455–463 (2001).
- Wagner, A. D., Maril, A., Bjork, R. A. & Schacter, D. L. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage* 14, 1337–1347 (2001). 42. Petrides, M. in *The Prefrontal Cortex* (eds. Roberts, A. C., Robins T. W. &
- Weiskrantz, L.) 103–116 (Oxford Univ. Press, Oxford, UK, 1998).
- 43. Owen, A. M. et al. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur. J. Neurosci. 11, 567–574 (1999).
- 44. D'Esposito, M., Postle, B. R., Ballard, D. & Lease, J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn. 41, 66-86 (1999).
- Engel, A. K., Fries, P. & Singer, W. Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* 2, 704–716 (2001).
- 46. Kato, M. et al. Eye movements in monkeys with local dopamine depletion in the caudate nucleus. I. Deficits in spontaneous saccades. J. Neurosci. 15, 912-927 (1995).

484