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## Transient and sustained activity in a distributed neural system for human working memory

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Working memory involves the short-term maintenance of an active representation of information so that it is available for further processing. Visual working memory tasks, in which subjects retain the memory of a stimulus over brief delays, require both the perceptual encoding of the stimulus and the subsequent maintenance of its representation after the stimulus is removed from view. Such tasks activate multiple areas in visual and prefrontal cortices<sup>1–9</sup>. To delineate the roles these areas play in perception and working memory maintenance, we used functional magnetic resonance imaging (fMRI) to obtain dynamic measures of neural activity related to different components of a face working memory task—non-selective transient responses to visual stimuli, selective transient responses to faces, and sustained responses over memory delays. Three occipitotemporal areas in the ventral object vision pathway had mostly transient responses to stimuli, indicating their predominant role in perceptual processing, whereas three prefrontal areas demonstrated sustained activity over memory delays, indicating their predominant role in working memory. This distinction, however, was not absolute. Additionally, the visual areas demonstrated different degrees of selectivity, and the prefrontal areas demonstrated different strengths of sustained activity, revealing a continuum of functional specialization, from occipital through multiple prefrontal areas, regarding each area's relative contribution to perceptual and mnemonic processing.

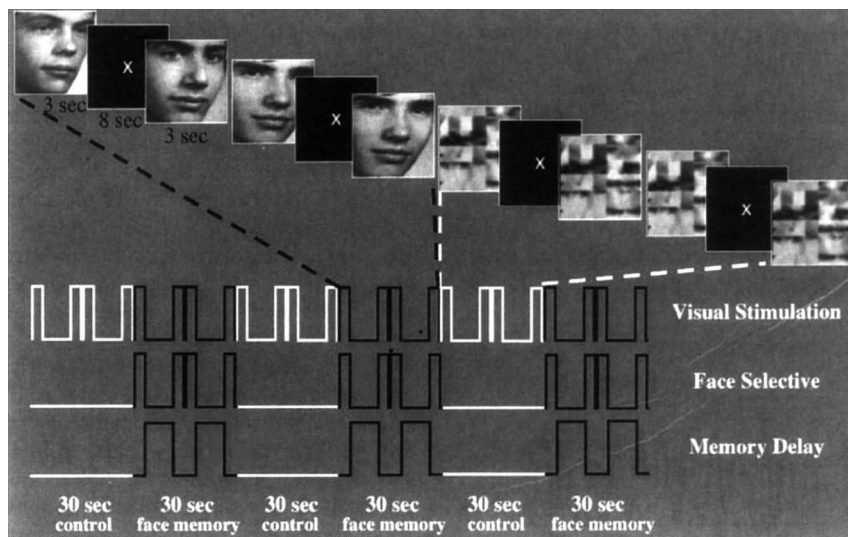
Imaging studies in humans have shown that both visual and prefrontal cortices are active during visual working memory tasks, but these studies did not have sufficient temporal resolution to distinguish transient activity during stimulus presentation from sustained activity after the stimulus is removed from view<sup>1–9</sup>. Increases in activity in visual and prefrontal cortices could therefore be attributed either to attentional enhancement of responses to stimuli, or to working memory, or to both. By contrast, electrophysiological studies in humans, which do have sufficient temporal resolution to distinguish transient from sustained activity, have not had sufficient spatial resolution to attribute the sources of these signals to specific anatomical locations<sup>10,11</sup>. We used fMRI to measure changes in neural activity over the course of a working memory task in order to distinguish the perceptual and mnemonic roles played by the cortical regions that participate in visual working memory (see also ref. 12).

Functional MRI scans were obtained while eight subjects alternately performed working memory and sensorimotor control tasks (Fig. 1; and see Methods). Six bilateral regions were identified that were consistently activated across subjects (Tables 1 and 2). The temporal responses of these regions were analysed using multiple regression with regressors related to three different cognitive components of the task: (1) a transient, non-selective response to visual stimulation that was equivalent for faces and scrambled faces; (2) a transient, selective response to faces; and (3) a sustained response over memory delays (Figs 1–3; and see Methods). Because complex objects other than faces were not used as stimuli, the transient, selective response to faces could indicate either face-selectivity *per se* or selectivity for any meaningful visual stimulus. Similarly, a sustained response over memory delays could indicate either a working memory system that is specific to faces, or a generic visual object working memory system.

All subjects showed activity in ventral occipitotemporal extrastriate visual areas that was correlated with stimulus presentation. A region in the posterior lingual and fusiform gyri, Brodmann area (BA) 18, showed a transient, mostly non-selective response to stimuli (Fig. 2a). In half of the subjects, the response to faces in this region was significantly greater than the response to scrambled faces, but the magnitude of this difference was small. Rostral to this relatively non-selective area, a ventral temporal region in the mid-to-anterior fusiform gyrus (BA 37) showed a transient, more face-selective response with a small, but significant, level of sustained activity during the memory delay. This pattern of activation indicates that the anterior fusiform gyrus is involved to a greater extent in the perceptual processing of faces than is the more posterior region and may also be involved in the maintenance of an active representation of the face during the memory delay (Fig. 2b). Face-selective responses, similar to the responses in the anterior fusiform gyrus, were also seen in the inferior occipital sulcus (BA 18/19), an area more lateral and more posterior than the fusiform face-selective area. The activity in the inferior occipital sulcus was more sustained during the memory delay than was the activity in the anterior fusiform gyrus, but the regression weights for non-selective and face-selective responses to stimuli in these regions were approximately the same.

Three distinct prefrontal areas were identified that all showed sustained activity during the memory delay interval: one in the posterior middle and inferior frontal gyri (BA 9/44), a second in the inferior frontal gyrus near the anterior end of the insula (BA 45/47), and a third in the anterior middle frontal gyrus (BA 46) (Table 2; Figs 2c–e and 3). The contribution of the memory delay regressor was significant for all three of these areas, but the relative magnitudes of the regression weights were different, indicating that the functional responses for these regions differed. The posterior middle frontal gyrus area had the most non-selective visual stimulation activity and the least memory delay activity, whereas the anterior middle frontal area had the least non-selective visual stimulation activity and the most memory delay activity. Regression weights for the posterior middle frontal gyrus differed significantly from those for the other two prefrontal areas ( $F(1, 111) = 27.91$ ,  $P < 0.0001$ ). Although the difference between the weights for the inferior frontal and anterior middle frontal areas did not reach significance ( $P = 0.054$ ), their anatomical segregation clearly identified them as distinct regions.

There was a systematic progression in the relative strengths of perception- and memory-related activity from posterior extrastriate through prefrontal areas, indicating that this distributed neural system for working memory is hierarchically organized (Fig. 3). In the extrastriate visual areas, the progression from mainly non-selective perceptual to face-selective perceptual activity is consistent with the well established hierarchical organization of visual cortex<sup>13</sup>. Progressive changes in perception- and memory-related activity in the prefrontal areas suggest that these areas, like those in extrastriate



**Figure 1** For each series of scans, subjects performed three baseline-activation task cycles, each consisting of 30 s of a sensorimotor control task, followed by 30 s of a working-memory task. Each task period consisted of two items for that task. Three time series are shown which represent the different cognitive components of the task: a transient, non-selective response to visual stimuli; a

transient, selective response to faces; and sustained activity during memory delays. These time series (smoothed and delayed by convolution with a model of the haemodynamic response) were used as regressors in a multiple regression analysis of the time course of activation in each area (see Methods).

**Table 1 Areas showing statistically significant activation in at least half of the subjects**

Area of activation	Subjects							
	S1	S2	S3	S4	S5	S6	S7	S8
Posterior lingual and fusiform gyri (BA 18)	B	B	B	B	B	B	B	B
Mid-to-anterior fusiform gyrus (BA 37)	B	B	L	R	B	B	B	-
Inferior occipital sulcus (BA 18/19)	B	B	B	-	B	B	-	B
Posterior mid-frontal/inferior-frontal gyrus (BA9/44)	L	R	-	-	R	B	L*	L*
Anterior insula/inferior frontal gyrus (BA 45/47)	B	B	B	-	L	B	-	-
Anterior mid-frontal gyrus (BA 46)	L	B	-	-	B	B	L*	-

Numbers in parentheses are the probable Brodmann areas  
L, left hemisphere only; R, right hemisphere only; B, bilateral.

\* Voxels in these regions reached the threshold of  $Z > 3.09$ , but the region of activation was not of sufficient spatial extent to pass the correction for multiple comparisons.

**Table 2 Group analysis of areas of activation**

Area of activation	Talairach coordinates			Multiple regression coefficients			$R^2$
	x	y	z				
				stimul†	face†	delay†	
Posterior lingual and fusiform gyri (BA 18)	19 -24	-90 -90	-11 -6	0.78*** 0.72***	0.17* 0.21*	0.05 0.07	0.763 0.771
Mid-to-anterior fusiform gyrus (BA 37)	31 -32	-60 -60	-20 -16	0.32* 0.40**	0.52*** 0.40**	0.16* 0.20**	0.587 0.682
Inferior occipital sulcus (BA 18/19)	34 -28	-85 -82	1 -1	0.27** 0.50*	0.45** 0.28*	0.28*** 0.22*	0.583 0.442
Posterior mid-frontal/inferior frontal gyrus (BA 9/44)	42 -38	13 15	26 25	0.19 0.15*	0.55*** 0.37*	0.26* 0.47***	0.550 0.489
Anterior insula/inferior frontal gyrus (BA 45/47)	30 -31	21 20	0 3	0.17* 0.04	0.33*** 0.46*	0.51*** 0.50***	0.496 0.465
Anterior mid-frontal gyrus (BA 46)	28 -20	43 40	16 11	0.11 -0.17	0.34*** 0.50***	0.55*** 0.67***	0.503 0.505

Numbers in parentheses are the probable Brodmann areas (BA)<sup>30</sup>. A positive x Talairach coordinate<sup>30</sup> indicates an area in the right hemisphere; a negative x coordinate indicates an area in the left hemisphere. There were no significant hemispheric effects ( $P > 0.1$  for main effect and all interactions). Asterisks, contribution of regressor is significant in  $\geq 50$ ,  $\geq 75$  or 100% of active regions for one, two or three asterisks, respectively.

† Each regression coefficient is divided by the sum of all three coefficients.

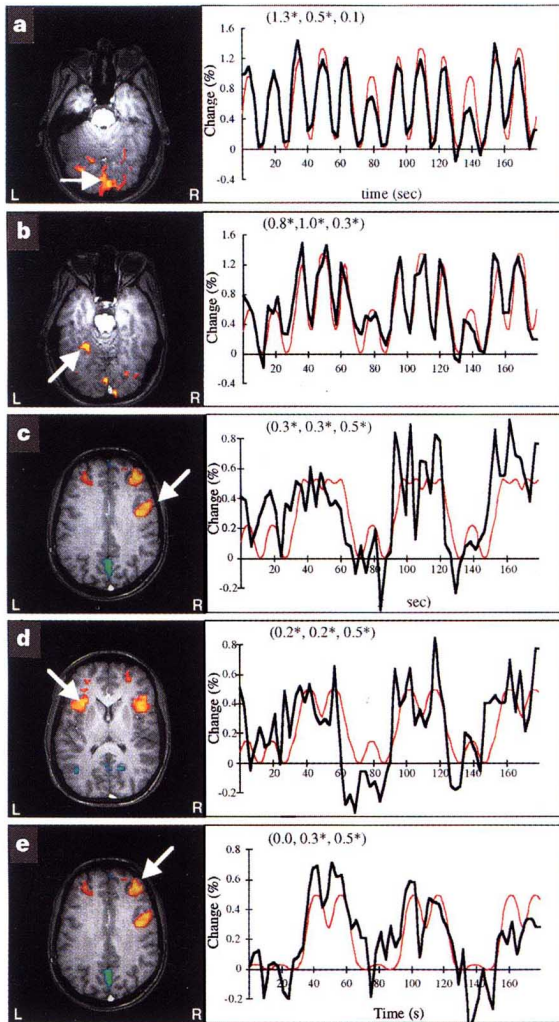
$R^2$ , fraction of variance accounted for by all 3 regressors.

visual cortex, may also be hierarchically organized for working memory, although corroborating evidence about interregional connectivity and functional dependencies does not yet exist.

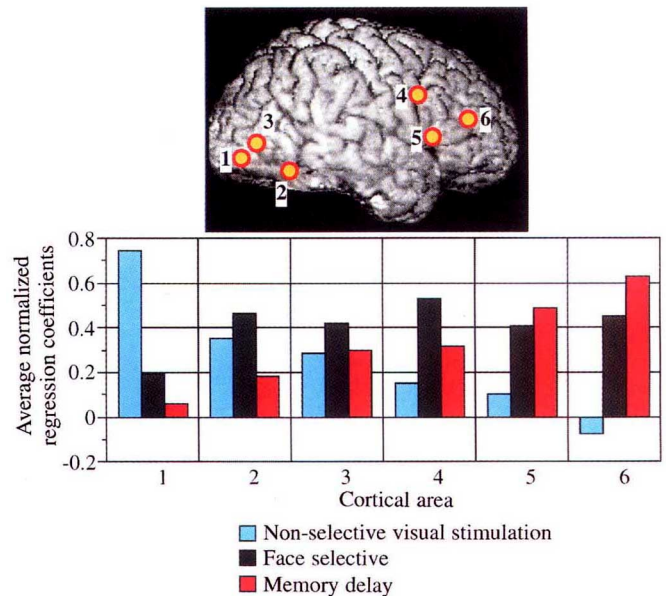
The precise roles played by the prefrontal regions in working memory remain to be specified. Previous imaging studies have reported activation in regions with similar locations during verbal and visual working memory tasks<sup>1-9</sup>, as well as during long-term memory retrieval<sup>14,15</sup>. Activation of the same areas by both long-term retrieval and working memory is consistent with the idea that retrieval produces an active representation of the recalled material much like the active representation of material held during a

working memory delay. Functional differences among several regions in prefrontal cortex have been studied<sup>7,8</sup>. Our inferior prefrontal area (BA 45/47) is close to a ventrolateral prefrontal area previously identified<sup>7</sup> which has been proposed to be involved in the encoding and retrieval of information held in posterior cortical areas. Verbal semantic functions have also been associated with this inferior frontal region<sup>16,17</sup>, suggesting that its activation in our study may also reflect verbal processing of the face stimuli. Our anterior midfrontal area (BA 46) appears to be inferior and anterior to a cluster of regions in BA 9/46 that Petrides and colleagues<sup>7,8</sup> have associated with monitoring mnemonic performance. Our posterior middle and inferior prefrontal region is inferior and anterior both to a region in BA 8 reported by Petrides<sup>8</sup> and to the human frontal eye field<sup>18</sup>, suggesting that our result is related to neither conditional associative memory nor oculomotor control.

The reliability of results from this new method of fMRI time series analysis is corroborated by results from a subsequent face working memory study using different subjects and a different experimental protocol<sup>19</sup>. In the new study, subjects were required to remember a set of three faces instead of a single face, and a longer intertrial interval (6 s instead of 1 s) followed the test stimulus. This new study showed activation in the same three prefrontal areas that were identified in the current study and confirmed their relative participation in perceptual and mnemonic processing. The new study



**Figure 2** Results from a single subject, S2, overlaid onto that subject's anatomical MR images, collected in the same session and in the same planes as the functional MR images. Red and yellow indicate areas with significant positive correlations with either visual stimulation, memory task, or both. Areas shown in blue and green have significant negative correlations. Per cent changes in signal over time, averaged over all voxels in the activated region, are shown by the thick black line to the right of each MRI image. Time series were analysed with the multiple regression model described for Fig. 1. The thin red line shows the sum of the regressors, multiplied by their corresponding coefficients, shown in parentheses above each graph (non-selective perceptual, face-selective perceptual, memory delay). Asterisks indicate regressors whose contribution was statistically significant ( $P < 0.05$ ). **a**, Posterior lingual and fusiform gyri (BA 18). **b**, Mid-to-anterior fusiform gyrus (BA 37). **c**, Posterior mid- and inferior frontal gyri (BA 9/44). **d**, Inferior frontal gyrus and anterior insula (BA 45/47). **e**, Anterior mid-frontal gyrus (BA 46).



**Figure 3** Average locations across subjects of the regions of activation listed in Tables 1 and 2 are shown in lateral projection onto a brain that has been stereotactically normalized into Talairach space<sup>20</sup>. Locations shown are the mean locations for the right and left hemispheres. The areas, numbered in order of decreasing relative contribution from non-selective visual stimulation and increasing contribution from the memory delay, are: (1) posterior lingual and fusiform gyri (BA 18), (2) mid-to-anterior fusiform gyrus (BA 37), (3) inferior occipital sulcus (BA 18/19), (4) posterior mid- and inferior frontal gyri (BA 9/44), (5) inferior frontal gyrus and anterior insula (BA 45/47), and (6) anterior mid-frontal gyrus (BA 46). The graph shows the three normalized regression coefficients for each area, averaged across subjects and across hemispheres, demonstrating the gradual shift in the relative contributions of each task component to the activity within this distributed neural system.

also confirmed that the sustained activity during the memory delay was related to working memory and not simply to a more prolonged response to faces than to control stimuli. Because the new study had a much longer intertrial interval following the test stimulus, prolonged activity during this interval, related solely to the perceptual processing of faces, could be distinguished from sustained activity during the working memory delay interval. Activity during the working memory delay was significantly higher than activity following the test face in the posterior middle frontal area (increases of 0.42 versus 0.03% relative to control item intervals,  $P < 0.001$ ) and the anterior middle frontal area (increases of 0.57 versus 0.09%,  $P < 0.001$ ). The effect in the inferior frontal area was in the expected direction but failed to reach statistical significance (increases of 0.34 versus 0.21%,  $P > 0.1$ ).

These fMRI results demonstrate the existence of areas in human cortex with response properties that are analogous to those described in single-cell recording experiments in non-human primates: (1) early extrastriate visual areas demonstrate transient, relatively non-selective responses to complex visual stimuli<sup>20</sup>; (2) later extrastriate visual areas demonstrate transient, selective responses to faces, indicating a more specialized role in the processing of meaningful images<sup>21,22</sup>; and (3) both extrastriate visual<sup>23,24</sup> and prefrontal<sup>25,26</sup> cortical areas demonstrate sustained activity during memory delays, indicating a role in maintaining an active representation of the face in working memory. In non-human primates, delay activity in temporal cortex, unlike that in prefrontal cortex, is disrupted by intervening stimuli<sup>27</sup>. These results, supported by our results in humans, suggest that the dominant function of temporal cortex is perceptual but that this region also participates in maintaining a working memory as long as it is not recruited for the perception of new stimuli. Our results extend findings from non-human primates both by quantifying the relative strengths of sustained activity during delays in later extrastriate visual as compared to prefrontal areas and by demonstrating that in human cortex, multiple, functionally distinct, prefrontal regions participate in working memory. □

**Methods**

**Task.** Each memory item began with a 3-s presentation of a single sample face, followed by an 8-s fixation delay, and then a 3-s presentation of a test face. Subjects were instructed to keep an image of the sample face in mind during the delay, and to respond by pressing a right button to indicate that the test face matched the immediately preceding face and a left button if it did not. For the control task, which controlled for visual stimulation, motor response, and anticipation of response, subjects saw a scrambled face, a fixation delay, and then the same scrambled face, after which they responded by pressing both buttons. The control task used the same timing as the memory task. Subjects did not attempt to remember or match the scrambled faces. Scrambled faces were filtered to remove the high-frequency edges created by scrambling.

**Imaging.** 12 contiguous, axial, 6-mm-thick slices were obtained in 8 series of 64 scans each (repeat time, 3 s), beginning at the most ventral extent of the occipital lobe in 8 healthy volunteers (3 male, 5 female; age  $24 \pm 2.1$  yr, education  $16.6 \pm 1.1$  yr). Gradient echo, echo planar imaging was used (TE 40 ms, flip angle  $90^\circ$ ) on a GE Signa 1.5 Tesla magnet. A significant increase in the MRI signal is referred to in the text as 'activation'. All subjects gave written informed consent.

**Statistics.** Voxels that were activated during the working memory task were identified by calculating correlations between the time series of MRI intensities in a single voxel and two idealized response functions<sup>28</sup>, reflecting contrasts between (1) non-selective visual stimulation versus no stimulation, and (2) the memory task versus the control task (face selective + memory-delay regressors; Fig. 1). To increase statistical power, all 8 series of scans in each subject were analysed together using an ANCOVA to factor out the series variance. All statistical results have a single voxel Z threshold of 3.09 (degrees of freedom corrected for correlation between adjacent time points). Statistical significance ( $P < 0.05$ ) of a region of activation was determined using an analysis based on the spatial extent of each region to correct for multiple comparisons<sup>29</sup>. The time

course of activation in each of these regions was analysed using multiple regression<sup>28</sup>. Each regressor was tested to see whether it could account for a significant portion of the variance, independent of the variance attributable to the other regressors. A weighting coefficient for each regressor was obtained by simultaneously finding the best fit to the data for the sum of the three regressors multiplied by their weighting coefficients. The weights produced by multiple regression provide measures of the relative strengths of (1) perceptually non-selective, (2) perceptually selective, and (3) memory-related responses.

Because of variability in the magnitude of responses, both across subjects and across regions, regression coefficients were normalized by dividing each coefficient by the sum of all three. These normalized regression coefficients express the relative strength of three types of responses in a single region. Regional differences in normalized regression weights were tested by treating each significantly activated region as an independent observation in a 3-way ANOVA (region  $\times$  hemisphere  $\times$  regressor).

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