

Distinguishing the Functional Roles of Multiple Regions in Distributed Neural Systems for Visual Working Memory

James V. Haxby,* Laurent Petit,† Leslie G. Ungerleider,* and Susan M. Courtney‡

*Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, Maryland 20892-1366; †Groupe d'Imagerie Neurofonctionnelle, 14074 Caen, France; and ‡Department of Psychology, Johns Hopkins University, Baltimore, Maryland 21218

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We have investigated the human neural systems for visual working memory using functional magnetic resonance imaging to distinguish sustained activity during memory delays from transient responses related to perceptual and motor operations. These studies have identified six distinct frontal regions that demonstrate sustained activity during memory delays. These regions could be distinguished from brain regions in extrastriate cortex that participate more in perception and from brain regions in medial and lateral frontal cortex that participate more in motor control. Moreover, the working memory regions could be distinguished from each other based on the relative strength of their participation in spatial and face working memory and on the relative strength of sustained activity during memory delays versus transient activity related to stimulus presentation. These results demonstrate that visual working memory performance involves the concerted activity of multiple regions in a widely distributed system. Distinctions between functions, such as perception versus memory maintenance, or spatial versus face working memory, are a matter of the degree of participation of different regions, not the discrete parcellation of different functions to different modules. © 2000 Academic Press

INTRODUCTION

Working memory refers to processes that maintain an active representation of information over a brief period so that it is available for recall or further processing (Baddeley, 1986). Sustained neural activity over memory retention intervals in delayed response, delayed alternation, and delayed match-to-sample tasks is generally interpreted as the neural basis of working memory. With functional magnetic resonance imaging (fMRI) it is now possible to detect such sustained activity and distinguish it from activity related to the perceptual and motor events that precede and follow memory delays (Courtney *et al.*, 1997, 1998; Cohen *et al.*, 1997; Petit *et al.*, 1998). Moreover, fMRI simultaneously

measures activity in the entire brain, making it well suited to the study of large-scale, distributed neural systems for higher order cognitive processes like working memory.

In this paper we review our fMRI investigations of the human neural systems for visual working memory. Our goals have been to identify all of the brain regions that participate in visual working memory task performance and to distinguish the functional contributions of different regions. Specifically, we have attempted to distinguish participation in the perceptual and motor operations associated with stimulus encoding and recognition testing from participation in the operations associated with maintaining an active representation of a visual stimulus after it is removed from view. To make these distinctions, we have exploited the temporal resolution of fMRI to distinguish between neural responses that are separated in time.

Our results show that visual working memory task performance is associated with the activation of multiple, widely distributed regions in posterior visual cortices, motor cortices, and prefrontal cortex. These studies have identified the visual and motor regions that participate primarily in perceptual and motor operations. These results also clearly show that sustained activity during memory delays is not restricted to a single prefrontal working memory area but, rather, is a broadly distributed function. Sustained activity during memory delays is observed in temporal and parietal extrastriate cortices as well as in frontal regions. Within the frontal lobe, we have identified six distinct regions that demonstrate sustained activity during memory delays. These regions can be further distinguished functionally based on the relative strength of sustained activity during memory delays versus transient activity associated with nonmnemonic components of working memory tasks. They can also be distinguished based on the relative strength of sustained activity during working memory tasks for different kinds of visual information (working memory for faces versus spatial locations). Modulation of sustained activity by information type indicates that this activity

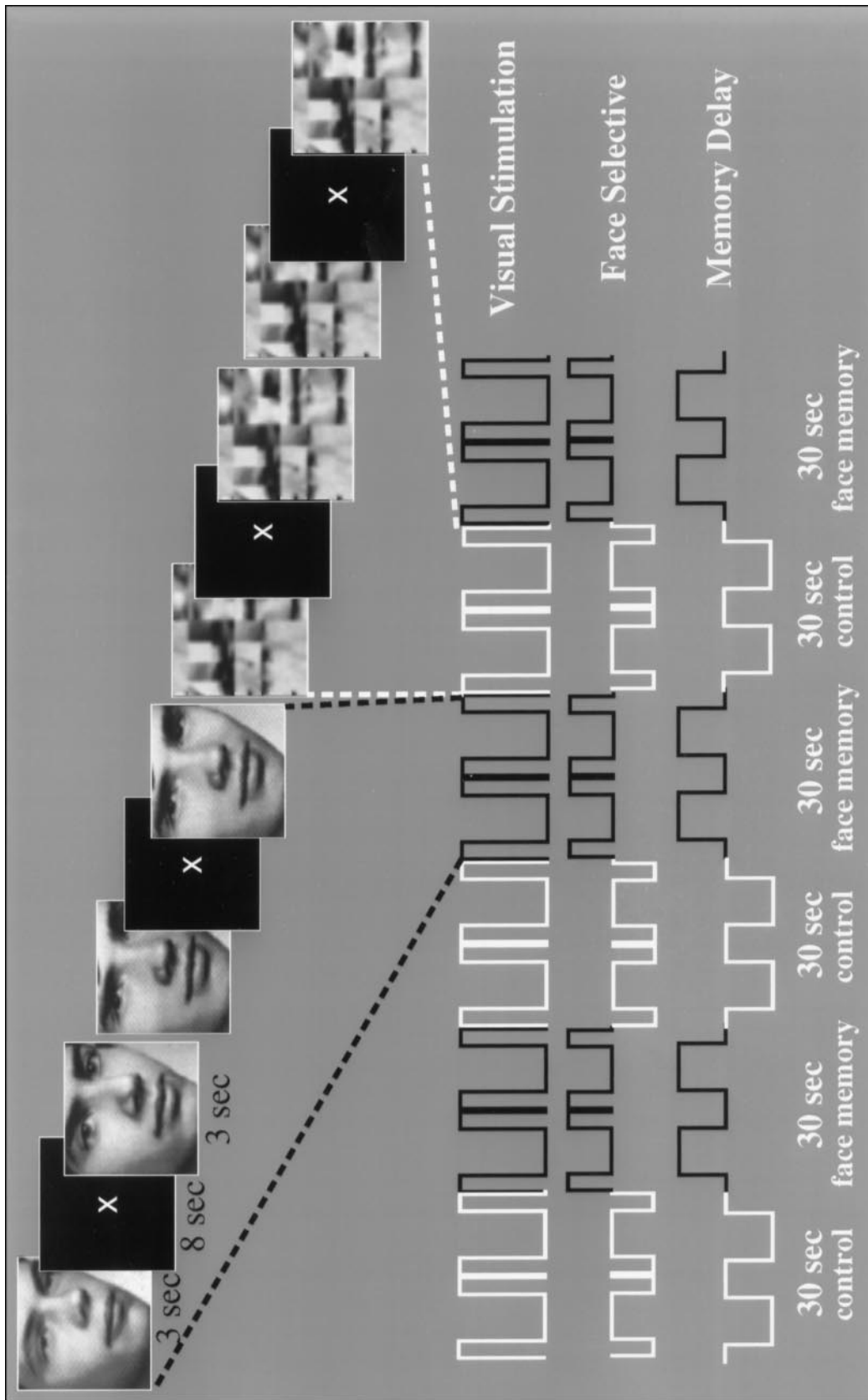


FIG. 1. Task design for a fMRI study of working memory for faces (Courtney et al., 1997) and the square-wave input functions used to derive regressors for a multiple regression analysis. The square-wave input functions shown here are orthogonal to each other, whereas the regressors used for the original report were not. Analysis with the orthogonal and nonorthogonal regressors give identical estimates for the strengths of stimulus-related and memory-related activity (reproduced from Haxby et al., 2000).

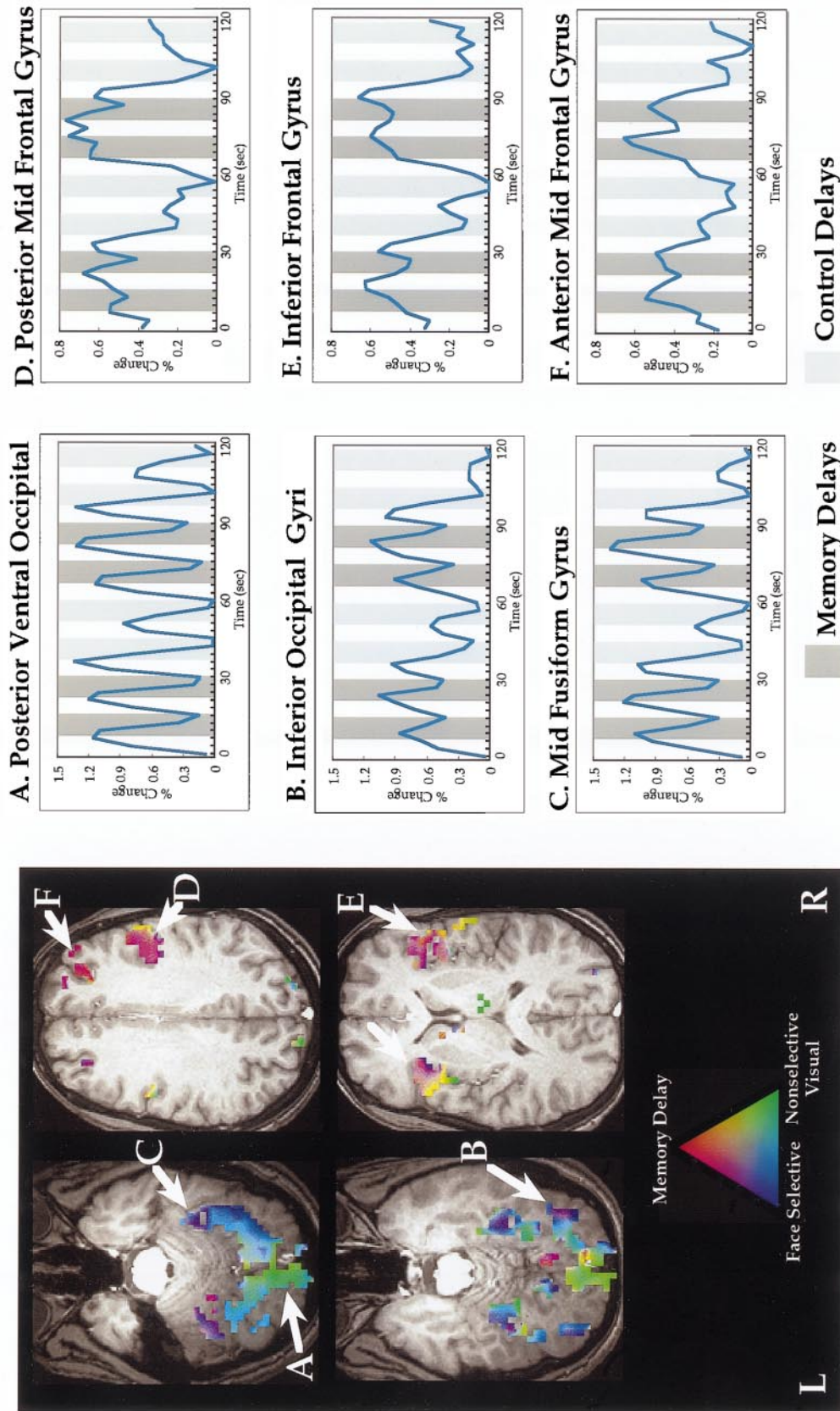


FIG. 2. Left: Regions activated during a face working memory task in an individual subject ($Z > 3.33$) shown in colors that indicate the relative dominance of nonselective transient responses to stimuli (green), selective transient responses to faces (blue), and sustained activity over memory delays (red). Regions shown in color demonstrated a significant experimental effect ($Z > 3.33$). Right: Graphs show the region mean fMRI time series for each region, averaged over subjects and voxels. The locations of the regions are illustrated in a single subject on the left. Gray bars indicate the times of delays in memory and control items (see Fig. 1). Each delay was preceded and followed by the presentation of a stimulus (face or scrambled picture) during the epochs depicted as white bars. Responses are delayed by the hemodynamic response function, resulting in transient responses to stimuli during the early part of item delays and sustained activity extending into the times of stimulus presentations (data from Courtney et al., 1997).

reflects direct participation in the representation of the contents of working memory and does not simply reflect heightened attention or preparation to make a motor response at the end of the delay.

DISTINGUISHING SUSTAINED ACTIVITY FROM TRANSIENT RESPONSES TO PERCEPTUAL AND MOTOR EVENTS

Working memory performance involves perceptual events associated with memory encoding and retrieval, motor events associated with responses, and memory operations for maintaining an active representation of information. Working memory operates over brief intervals, and in most laboratory working memory tasks these events all occur over a period measured in seconds or tens of seconds. These events can be temporally segregated, at least in part, making it possible to distinguish them directly with methods that have sufficient temporal resolution, such as fMRI.

Prior to fMRI, brain-imaging studies of working memory using positron emission tomography (PET), with its coarser temporal resolution, attempted to isolate the activity related to active memory maintenance indirectly. Some studies tried to subtract out activity related to perceptual and motor events by designing baseline and memory tasks with equivalent perceptuomotor components (e.g., Jonides *et al.*, 1993). Others used a parametric design that varied memory and perceptuomotor components independent of each other (e.g., Haxby *et al.*, 1995). Another method extended the memory maintenance interval so that it filled the period of measurement (e.g., Fiez *et al.*, 1996). All of these methods successfully identified prefrontal cortical regions that appeared to be activated by the memory component of working memory tasks, but the inferential nature of these demonstrations left doubt as to whether the experimental manipulations inadvertently altered the cognitive operations that were supposedly held constant. For example, the mnemonic demands of a memory task might also increase the activation due to perceptual encoding, because of increased attention, compared to a nonmnemonic baseline task. The use of unusually long memory intervals might alter the nature of memory maintenance operations and, therefore, not be representative of the operations used for the more typical, briefer intervals.

With the temporal resolution of fMRI it is possible to measure the sustained activity during memory delays directly and thus avoid any inadvertent alteration of nonmnemonic operations by task manipulation. In order to take advantage of this potential, we developed methods for using multiple regression analysis to obtain separate measures of sustained activity associated with memory maintenance and transient activity associated with perception and motor responses (Haxby *et*

al., 2000; Friston *et al.*, 1995). We modeled the changes in neural activity associated with different epochs during a working memory task as square-wave step functions. For each experiment we developed a set of orthogonal square-wave functions that tested contrasts of interest between different epochs. These square-wave functions are then convolved with a model of the hemodynamic response function to derive the regressors for multiple regression analysis.

In our first experiment, we investigated working memory for a single face (Courtney *et al.*, 1997) (Fig. 1). Three regressors were used to model the changes in neural activity associated with performance of face working memory and sensorimotor control items. The first input function tested the contrast between activity during presentation of visual stimuli, making no distinction between control and face stimuli, compared to blank intervals. This regressor probed for nonselective, transient responses to visual stimuli, presumably associated with early stages of perceptual processing. The second input function tested the contrast between the transient response to faces compared to the transient response to control stimuli. This regressor probed for perceptual processing that was more selective for faces or meaningful stimuli. The third input function tested the contrast between activity during memory delays compared to control item delays and, thus, was a probe for sustained activity associated with maintaining an active representation of a face in working memory.

The results of this experiment revealed six cortical regions that responded to some aspect of the face working memory task. Figure 2 illustrates the locations of these regions in one subject and presents the mean time series, averaged over subjects and item repetitions. Three of these regions were in ventral occipitotemporal cortex. The most posterior of these regions demonstrated large transient responses to both control and face stimuli but did not demonstrate significant sustained activity over memory delays, indicating that it participates primarily in the earlier stages of perceptual processing. More anterior regions in the inferior occipital and mid-fusiform gyri also demonstrated primarily transient responses to stimuli, but these responses were much greater for faces than for control stimuli, suggesting that they participate in face-selective perceptual processing. These more anterior regions also demonstrated some significant sustained activity over memory delays, suggesting a role in working memory maintenance. Three prefrontal regions were also identified by this study. These regions were in the inferior frontal gyrus near the anterior end of the insula, in the posterior middle frontal gyrus, and in the anterior middle frontal gyrus. All of these regions demonstrated sustained activity over the memory delays and significant transient responses to face stimuli. The relative strength of sustained activity compared to

the transient response to control stimuli varied systematically by region, suggesting that these frontal regions have a hierarchical organization analogous to that seen in posterior extrastriate cortex. The posterior middle frontal region had the greatest transient response to visual stimuli and the smallest amount of sustained activity during the memory delay. The inferior frontal region had intermediate amounts of perception- and memory-related activity. The anterior middle frontal region had the the greatest amount of sustained delay activity and did not respond at all to control stimuli.

These results demonstrated that performance of a working memory task involves the concerted participation of multiple regions in a widely distributed neural system. The functional contribution of the regions in this system could be distinguished, but no function, such as face perception or working memory maintenance, was restricted to a single region. Rather, multiple regions demonstrated activity related to each function. Thus, maintenance of a working memory for a face appears to involve the concerted participation of anterior extrastriate and three distinct prefrontal regions. Overall, this neural system for working memory appears to be hierarchically organized. The difference between posterior and anterior extrastriate cortices demonstrated a progression toward a more selective transient response to faces and greater participation in working memory maintenance. The hierarchical progression appears to continue in the frontal lobe, as suggested by the differences between the response profiles for the three prefrontal regions.

DISTINGUISHING LATERAL FRONTAL AREAS BASED ON INFORMATION SPECIFICITY

In the monkey, prefrontal neurons show different amounts of sustained activity over memory delays depending on the type of information held in working memory, indicating further that this activity is related to the maintenance of an active representation of information and not to a heightened state of awareness or a state of preparedness to respond at the end of the delay (Funahashi *et al.*, 1989; Goldman-Rakic, 1990; Fuster, 1990; Rainer *et al.*, 1998). This specificity exists at two levels. First, individual cells respond selectively to different types of stimuli. For example, cells may respond selectively to some objects and not others (*what* cells), others respond selectively to stimuli presented in a particular part of the visual field (*where* cells), and others are tuned to both preferred objects and preferred locations (*what and where* cells) (Rainer *et al.*, 1998). Some cells respond selectively to faces and not other objects (O'Scalaidhe *et al.*, 1997). Second, cells that are tuned to spatial and object information are distributed differently in prefrontal cortex (Wilson *et al.*, 1993). Cells that respond selectively to faces are

found exclusively in the inferior convexity and orbito-frontal cortex, never in the principal sulcus (O'Scalaidhe *et al.*, 1997). Most cells around the principal sulcus show sustained activity tuned only to spatial location (*where* cells) or to both spatial location and object identity (*what and where* cells), but only rarely to only object identity (*what* cells) (Rao *et al.*, 1997; Rainer *et al.*, 1998). A region at the caudal end of the principal sulcus, just anterior to the frontal eye field, contains only cells that are tuned to spatial location (*where* cells) (Rainer *et al.*, 1998).

Functional brain imaging cannot measure single-cell responses, but can assess whether the cells that are tuned to different types of information are differentially distributed in prefrontal cortex. The demonstration of such a dissociation would provide further evidence that sustained activity in prefrontal cortical regions is associated with maintenance of an active representation of stimulus information.

In an earlier PET-rCBF study of spatial and face working memory, we identified prefrontal areas that were differentially activated by spatial and face working memory tasks (Courtney *et al.*, 1996). The regions activated more by face than by spatial working memory were in locations similar to those that showed sustained activity in our fMRI study of face working memory. The region activated more by spatial than by face working memory, however, was in a problematical location. Rather than being in Brodmann area 46/9, the presumed human homologue for the region around the principal sulcus in the monkey brain that has been associated with spatial working memory, this region had a more posterior and superior location in the superior frontal sulcus. Although many functional imaging studies of spatial working memory have shown activation of this region (Jonides *et al.*, 1993; Baker *et al.*, 1996; Courtney *et al.*, 1996, 1998; Mellet *et al.*, 1996; Owen *et al.*, 1996; Petit *et al.*, 1996; Smith *et al.*, 1996), it has generally been dismissed because it was assumed to be located within the premotor cortex or the frontal eye field and thus related to either hand or eye movements (but see Courtney *et al.*, 1996, 1998; Mellet *et al.*, 1996; Petit *et al.*, 1996). However, even without explicit dissociation of hand movement-, eye movement-, and working memory-related activations, there was still a suggestion from several PET studies that the superior frontal sulcus activation could not be solely attributable to motor control. For example, spatial working memory studies conducted by Jonides, Smith, and colleagues (Jonides *et al.*, 1993; Smith *et al.*, 1995) required fixation and the same motor response for both the memory and the control tasks, yet memory-related activation was still observed near the superior frontal sulcus. A spatial imagery task by Mellet *et al.* (1996) also activated this region in the complete absence of eye and hand movements. In our study (Courtney *et al.*,

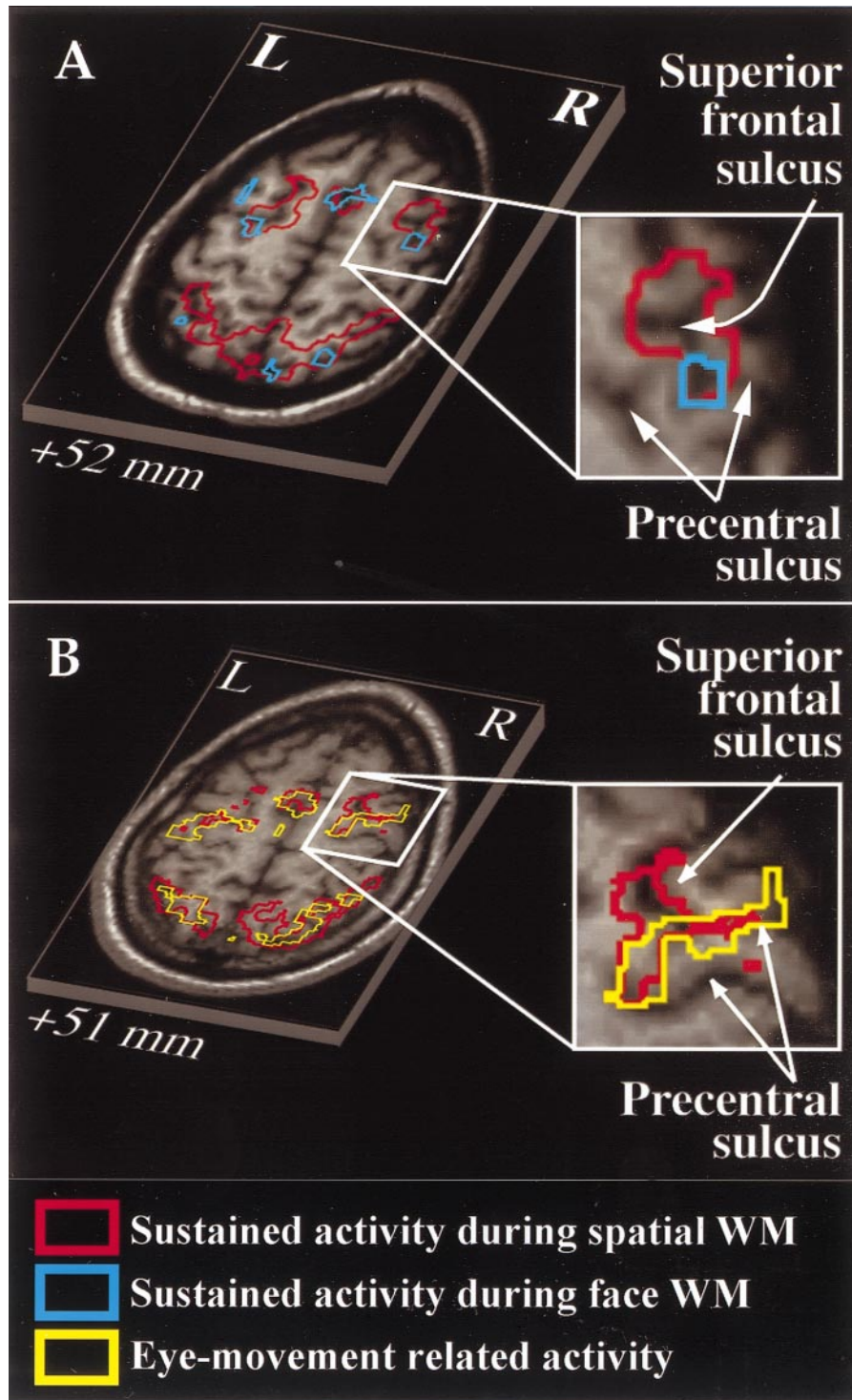


FIG. 3. (A) Regions with significant sustained activity in a single subject during the working memory delay for spatial locations (red outline) and faces (blue outline) overlaid on the subject's Talairach normalized MR image (axial image, $z = +52$ mm), illustrating the dissociation between spatial and face working memory in the superior frontal sulcus. (B) Regions in a single subject demonstrating significant sustained activity during the working memory delay for spatial locations (red outline) and significant eye movement-related activity during a visually guided saccade task (yellow outline), overlaid on the subject's Talairach normalized MR image (axial image, $z = +51$ mm). Note the dissociation between spatial working memory-related activity in the superior frontal sulcus and eye movement-related activity in the immediately adjacent frontal eye field in the precentral sulcus (reproduced from Courtney *et al.*, 1998).

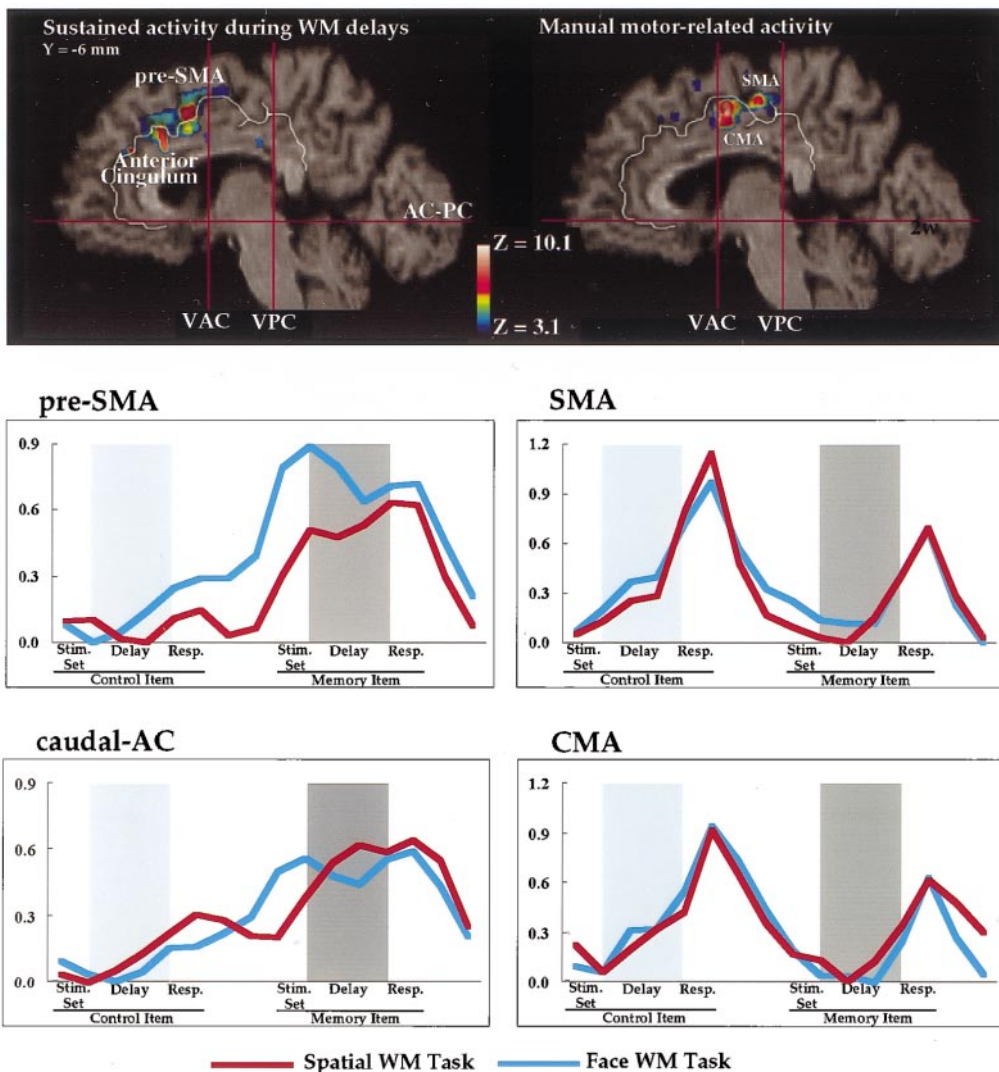


FIG. 4. Top: Medial wall regions in a single subject demonstrating significant sustained activity during working memory delays (left) and significant manual motor-related activity (right). Bottom: Mean time series, averaged over voxels and subjects, in regions showing sustained activity during spatial and face working memory (pre-supplementary motor area—pre-SMA and caudal anterior cingulate—caudal-AC) and in regions showing significant transient responses related to manual movements at the end of control and memory items (supplementary motor area—SMA and cingulate motor area—CMA). Gray bars indicate the times of delays in memory and control items. Each delay was preceded by the sequential presentation of three stimuli and followed by the presentation of a single test stimulus (reproduced from Petit *et al.*, 1998).

1996) the superior frontal sulcus was activated more by spatial than by face working memory, even though the tasks used identical stimuli and were designed to have identical hand and eye movements. Moreover, although the region with a greater response during spatial working memory was not in Brodmann area 46/9, it did have the same topological relationship with the human frontal eye field that the monkey region with a preponderance of *where* working memory cells has with the monkey frontal eye field. The region around the principal sulcus in the monkey is immediately anterior to the monkey frontal eye field, which lies on the anterior bank of the arcuate sulcus. The region activated more

by spatial working memory in the human superior frontal sulcus is immediately anterior to the human frontal eye field, which lies in the precentral sulcus (Paus, 1996; Sweeney *et al.*, 1996; Petit *et al.*, 1997; Luna *et al.*, 1998).

We decided to use the temporal resolution of fMRI to examine directly whether the activation in the superior frontal sulcus was specific to spatial working memory and not attributable to spatial perception, hand movements, or eye movements (Courtney *et al.*, 1998). Face and spatial working memory tasks used equivalent stimulus sequences and required identical motor responses. They differed only in terms of the information

that subjects were instructed to retain selectively over memory delays, namely the identity or the location of three faces presented sequentially as a memory set before a 9-s delay. By distinguishing sustained activity from transient responses to stimuli, we could determine whether the response in the superior frontal sulcus was related to spatial perception or spatial memory maintenance. By distinguishing between the amount of sustained activity seen during face and spatial memory, we could determine if the activity in the superior frontal sulcus, compared to activity in the mid- and inferior frontal gyri, was related to the type of information held in working memory. Moreover, differential sustained activity during face and spatial memory delays would indicate that that activity was not due to the preparation to make a motor response, as the motor requirements of the two working memory tasks were matched. Finally, the location of the frontal eye fields was determined in five subjects, using a visually guided saccade task, to determine whether the region demonstrating sustained activity in the superior frontal sulcus could be distinguished from the frontal eye field.

The results supported the hypothesis. A region was identified in the superior frontal sulcus that showed more sustained activity during spatial memory than during face memory and that was distinct from and anterior to the frontal eye field (Fig. 3). Similarly, left inferior and midfrontal cortex both showed more sustained activity during face memory than during spatial memory. The location of the frontal eye field was identified in the precentral sulcus in each subject. Whereas sustained activity over spatial memory delays was predominantly in the superior frontal sulcus compared to the precentral sulcus, transient activity during stimulus presentation was predominantly in the precentral sulcus. These transient responses may be related to eye movements that subjects were instructed to make to each stimulus as it appeared on the screen.

These results indicate that the lateral prefrontal regions show different levels of sustained activity associated with maintaining different types of visual information in working memory. The activity in the superior frontal sulcus during spatial working memory could be distinguished from activity related to spatial perception and eye movements. Because it also differed from the sustained activity seen during the face working memory task, which had identical motor components, sustained activity during spatial memory delays also cannot be attributed to the preparation to make a manual motor response.

The dissociation between regions showing sustained activity during spatial and face working memory tasks was not absolute. In the superior frontal sulcus, cortex showing significant sustained activity during face working memory delays was observed, but its volume was 43% of that showing sustained activity during spatial

working memory delays. In ventral frontal regions, the overlap between the face and the spatial tasks was even greater. In the left inferior and midfrontal gyri, the volume of cortex showing sustained activity during spatial memory delays was 55 and 65% of that showing sustained activity during face memory delays, respectively. In the right inferior and midfrontal gyri, differences between tasks were not significant. This overlap may indicate that subjects maintained active representations of task-irrelevant spatial information over face memory delays and vice versa. Alternatively, the overlap may indicate that the working memory representations of spatial and face identity information are distributed across these lateral frontal regions and that the dissociation between these regions is a matter of the level of participation in these representations, not the presence or absence of participation. Similarly, the distributions of cells in monkey prefrontal cortex that participate in spatial working memory, object working memory, or both spatial and object working memory overlap, and the degree of dissociation between these distributions is currently a matter of controversy (Wilson *et al.*, 1993; O'Scalaidhe *et al.*, 1997; Rao *et al.*, 1997; Rainer *et al.*, 1998).

MEDIAL FRONTAL AREAS SHOW SUSTAINED ACTIVITY BUT NOT INFORMATION SPECIFICITY

The dissociation that we find between lateral frontal areas in the extent to which they show sustained activity over face and spatial memory delays indicates that that activity is related to the type of information held in working memory. This result provides further evidence that these regions participate in maintaining an active representation of information in working memory.

We also consistently observed sustained activity during memory delays in medial frontal cortex, but these regions showed no dissociation between face and spatial working memory (Fig. 4). We noted that many previous neuroimaging studies of working memory had also reported activations in the same vicinity. We were able to distinguish two medial frontal regions that showed sustained activity, one in the pre-supplementary motor area (pre-SMA), located in the superior frontal gyrus anterior to the vertical plane through the anterior commissure, and the other in the caudal portion of the anterior cingulate. These could be distinguished from more posterior medial motor regions. By identifying the regions that demonstrate a transient response associated with the manual response in both the control and the memory items, the locations of the supplementary motor area (SMA) and the cingulate motor area (CMA) could be determined in each subject. The visually guided saccadic eye movement task identified the location of the supplementary eye field (SEF).

It has been suggested that the pre-SMA and the caudal portion of the anterior cingulate play a role in more complex aspects of motor behavior and response selection (Picard and Strick, 1996). We found that both the strength of sustained activity and the volume of cortex demonstrating that activity in these regions were equivalent for the spatial and face working memory tasks. This result suggests that sustained activity in the pre-SMA and anterior cingulate may not be related to the type of information held in working memory. Instead, this activity may reflect participation in motor behavior that is common to the face and spatial memory tasks but different from the control task. In the control task, the subject makes the same response to the test stimulus at the end of every item, namely pressing buttons simultaneously with the right and left thumbs. In the memory tasks, by contrast, the subject does not know which response to make before seeing the test stimulus. The sustained activity over memory delays, therefore, may be related to a state of preparedness to select a response based on the information that is currently held in working memory.

SUMMARY AND COMMENT

Using fMRI, we have identified six distinct regions in frontal cortex that show sustained activity during retention delays in visual working memory tasks (Fig. 5 and Table 1). These regions were in the inferior frontal cortex near the anterior insula, in the posterior middle frontal gyrus, in the anterior middle frontal gyrus, in the superior frontal sulcus, in the caudal part of the anterior cingulate, and in the medial superior

TABLE 1

Locations of Six Bilateral Frontal Regions That Demonstrate Sustained Activity during Visual Working Memory for Faces and/or Spatial Locations

Region	Hemisphere	Coordinates		
		<i>x</i>	<i>y</i>	<i>z</i>
Ventral lateral frontal				
Posterior middle frontal gyrus	Left	-38	15	25
	Right	42	13	26
Inferior frontal gyrus/anterior insula	Left	-31	20	3
	Right	30	21	0
Anterior middle frontal gyrus	Left	28	43	16
	Right	-20	40	11
Dorsal lateral frontal				
Superior frontal sulcus	Left	-31	-7	46
	Right	27	-5	49
Medial wall				
Pre-supplementary motor area		-1	7	52
Cingulate motor area		0	13	35

Note. Coordinates are in the space of the Talairach and Tournoux brain atlas (1988).

frontal cortex (pre-SMA). By examining the responses in these regions to different components of face and spatial working memory tasks, their function could be distinguished from that of other brain regions that participate more in perceptual and motor operations and the working memory regions could be distinguished from each other.

Relative to the lateral frontal working memory regions, regions in ventral visual extrastriate cortex had stronger transient responses to visual stimuli, indicating the predominant role of these posterior regions in perceptual processing of stimuli during encoding and recognition. The frontal working memory regions could also be distinguished from nearby frontal regions that were involved in oculomotor and manual motor control. The region in the superior frontal sulcus could be distinguished from the frontal eye field in the adjacent precentral sulcus. In the medial wall the anterior cingulate and pre-SMA regions could be distinguished from the SEF, the CMA, and the SMA.

Some of these frontal regions also showed differential involvement in spatial and face working memory. The more ventral lateral regions showed more sustained activity during face working memory delays than during spatial working memory delays, whereas the region in the superior frontal sulcus showed more sustained activity during spatial working memory delays. In contrast, the regions in the medial wall showed equivalent levels of sustained activity during both kinds of visual working memory delays.

The demonstration that sustained activity during memory delays is modulated by the type of information held in working memory, as we have shown for the lateral frontal regions, suggests that the neurons in those regions have memory fields that encode stimulus information. The absence of information selectivity, as we found in the medial frontal regions, suggests that those regions may be involved in maintaining a state of heightened attention or of preparedness to respond. Because these regions have been associated with more complex aspects of motor preparation in other studies, it is likely that they are playing a similar role in working memory tasks. Their role, however, is probably not simply preparation to make a response but, rather, preparation to select a response based on the information held in working memory.

It is unclear if the information selectivity we have demonstrated indicates a general dissociation between object and spatial working memory or is more specific to face versus spatial working memory. The information selectivity we found in lateral frontal cortex was a matter of the level of sustained activity, not a matter of the presence or absence of sustained activity, during face and spatial working memory delays. It is possible that memory for other types of objects may evoke responses that differ less from spatial memory. In the

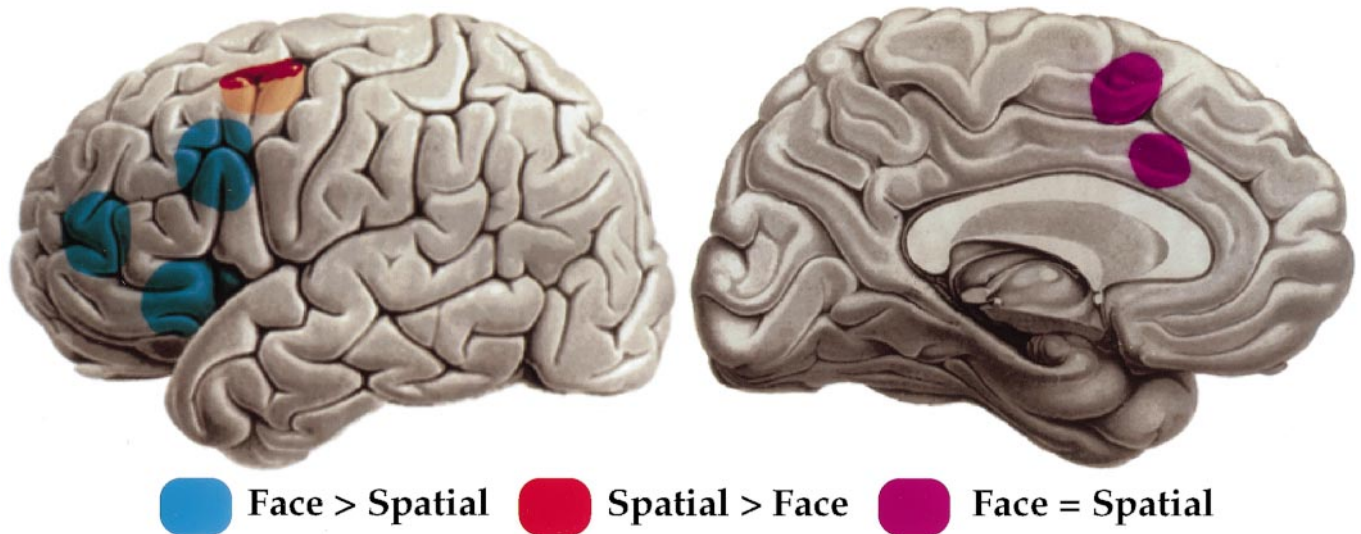


FIG. 5. Illustration of the location of six frontal regions that demonstrated significant sustained activity during spatial and face working memory delays. Regions showing more sustained activity during face than during spatial working memory were in the posterior middle frontal gyrus, the inferior frontal gyrus, and the anterior middle frontal gyrus. The region showing more sustained activity during spatial than during face working memory was in the superior frontal sulcus. Medial wall regions showing equivalent amounts of sustained activity during face and spatial working memory were in the pre-supplementary motor area and the cingulate motor area. See Table 1 for Talairach coordinates.

monkey, prefrontal neurons that respond selectively to faces are restricted to the inferior convexity and orbito-frontal cortex and are never found in the principal sulcus (O'Scalaidhe *et al.*, 1997), whereas neurons that respond selectively to nonface objects may have a broader distribution (Rao *et al.*, 1997). In fMRI studies of differential patterns of response to faces and different categories of objects in posterior extrastriate cortex, we have found that the response to faces has a more restricted distribution in ventral occipitotemporal cortex than does the response to other meaningful objects, such as houses and chairs (Haxby *et al.*, 1999a; Ishai *et al.*, 1999). Moreover, we have found that the response to these other objects extends into regions in dorsal occipital cortex that respond only very weakly to faces. Face perception may be the most developed and practiced human perceptual skill, perhaps accounting for the restricted representation of faces. Face perception may also be more holistic than the perception of other objects. If nonface object perception is more parts based, it may require more participation of spatial perception to represent the spatial configuration of the parts. Such a processing difference could underlie the greater activation of dorsal extrastriate areas by non-face objects and might blur the dissociation between activations related to object and spatial working memory. Presumably, perception of artificial, highly geometric objects, such as irregular polygons or wire-frame structures, would cause even more participation of spatial perception (e.g., Postle *et al.*, 1999). Further working memory studies that directly contrast the

responses caused by these different kinds of object stimuli are required to clarify these issues.

The processing demands of a task may also affect the degree of segregation between sustained activity related to spatial and object working memory. For example, tasks that require both spatial and object working memory but in different parts of the same trial may induce more overlap in the degree to which neurons or regions represent spatial and object information (Rao *et al.*, 1997; Rainer *et al.*, 1998; Postle *et al.*, 1999).

The three ventral frontal regions that responded preferentially during face working memory could also be distinguished functionally from each other based on the relative strength of sustained activity during face working memory delays compared to transient responses to visual stimuli. These differences in response profile suggest that these regions may play different roles in face working memory maintenance. "Working memory maintenance" is a general concept that necessarily involves a diverse array of operations. The contents of working memory can be simply refreshed by rehearsal, or scanned during retrieval, or augmented by integration with new information from the environment or from long-term memory. The contents of working memory may be discarded, or displaced by new information, or protected from displacement by distracting stimuli. Our studies do not attempt to dissociate these operations with experimental manipulations, but the differences in response profile that we do find suggest that the orchestration of operations that comprise working memory maintenance involves the partici-

pation of multiple prefrontal regions. Others have suggested that operations for simple memory maintenance and operations that involve manipulation of the contents of memory may be differentially represented in the ventral and dorsal lateral prefrontal cortices, respectively, which correspond to the inferior and middle frontal regions in our studies (Petrides, 1994; D'Esposito *et al.*, 1998).

As in single-unit studies in monkeys, it is now possible with fMRI to examine the temporal dynamics of local neural activity during working memory task performance in humans. Unlike single unit studies, fMRI studies make it possible to examine the temporal dynamics of neural activity in all brain regions simultaneously. Results from fMRI studies highlight that working memory performance involves the concerted activity of multiple regions in a widely distributed network. Single functions, like working memory maintenance, involve the participation of multiple regions in extrastriate and prefrontal cortex. Distinctions between functions, like perception versus memory maintenance, or spatial versus object working memory, are a matter of degree of participation, not the discrete parcellation of different functions to different modules. It is possible that we simply have not yet identified the more elementary operations that are performed by single regions. It is equally likely, however, that even elementary perceptual and mnemonic functions are represented by the pattern of activity across multiple regions.

REFERENCES

- Baddeley, A. D. 1986. *Working Memory*. Clarendon, Oxford.
- Baker, S. C., Frith, C. D., Frackowiak, R. S. J., and Dolan, R. J. 1996. Active representation of shape and spatial location in man. *Cereb. Cortex* **6**:612–619.
- Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., and Smith, E. E. 1997. Temporal dynamics of brain activation during a working memory task. *Nature* **386**:604–608.
- Courtney, S. M., Ungerleider, L. G., Keil, K., and Haxby, J. V. 1996. Object and spatial visual working memory activate separate neural systems in human cortex. *Cereb. Cortex* **6**:39–49.
- Courtney, S. M., Ungerleider, L. G., Keil, K., and Haxby, J. V. 1997. Transient and sustained activity in a distributed neural system for human working memory. *Nature* **386**:608–611.
- Courtney, S. M., Petit, L., Maisog, J., Ungerleider, L. G., and Haxby, J. V. 1998. An area specialized for spatial working memory in human frontal cortex. *Science* **279**:1347–1351.
- D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., Lease, J. 1998. Functional MRI studies of spatial and non-spatial working memory. *Cognit. Brain Res.* **7**:1–13.
- Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., and Petersen, S. E. 1996. A positron emission tomography study of the short-term maintenance of verbal information. *J. Neurosci.* **16**:808–822.
- Friston, K. J., Holmes, A. P., Poline, J.-B., Grasby, P. J., Williams, C. R., and Frackowiak, R. S. J. 1995. Analysis of fMRI time-series revisited. *NeuroImage* **2**:45–53.
- Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* **61**:331–349.
- Fuster, J. M. 1990. Behavioral electrophysiology of the prefrontal cortex of the primate. In *Progress in Brain Research* (H. B. M. Uylings, J. P. C. Van Eden, M. A. De Bruin, M. A. Corner, and M. G. P. Feenstra, Eds.), pp. 313–323. Elsevier, Amsterdam.
- Goldman-Rakic, P. S. 1990. Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In *Progress in Brain Research* (H. B. M. Uylings, J. P. C. Van Eden, M. A. De Bruin, M. A. Corner, and M. G. P. Feenstra, Eds.), pp. 325–336. Elsevier, Amsterdam.
- Haxby, J. V., Ungerleider, L. G., Horwitz, B., Rapoport, S. I., and Grady, C. L. 1995. Hemispheric differences in neural systems for face working memory: A PET-rCBF study. *Hum. Brain Mapp.* **3**:68–82.
- Haxby, J. V., Ungerleider, L. G., Clark, V. P., Schouten, J. L., Hoffman, E. A., and Martin, A. 1999. The effect of face inversion on activity in human neural systems for face and object perception. *Neuron* **22**:189–199.
- Haxby, J. V., Maisog, L. M., and Courtney, S. M. 2000. Multiple regression analysis of effects of interest in fMRI time series. In *Mapping and Modeling the Human Brain* (J. Lancaster, P. Fox, and K. Friston, Eds.). Wiley, New York, in press.
- Ishai, A., Ungerleider, L. G., Martin, A., Schouten, J. L., and Haxby, J. V. 1999. Distributed representation of objects in the human ventral visual pathway. *Proc. Natl. Acad. Sci. USA* **96**:9379–9384.
- Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., and Mintun, M. A. 1993. Spatial working memory in humans as revealed by PET. *Nature* **363**:623–625.
- Luna, B., Thulborn, K. R., Strojwas, M. H., McCurtain, B. J., Berman, R. A., Genovese, C. R., and Sweeney, J. A. 1998. Dorsal cortical regions subserving visually guided saccades in humans: An fMRI study. *Cereb. Cortex* **8**:40–47.
- Mellet, E., Tzourio, N., Crivello, F., Joliot, M., Denis, M., and Mazoyer, B. 1996. Functional anatomy of spatial mental imagery generated from verbal instructions. *J. Neurosci.* **16**:6504–6512.
- O'Scalaidhe, S. P., Wilson, F. A. W., and Goldman-Rakic, P. S. 1997. Areal segregation of face-processing neurons in prefrontal cortex. *Science* **278**:1135–1138.
- Owen, A. M., Evans, A. C., and Petrides, M. 1996. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study. *Cereb. Cortex* **6**:31–38.
- Paus, T. 1996. Location and function of the human frontal eye-field: A selective review. *Neuropsychologia* **34**:475–483.
- Petit, L., Orssaud, C., Tzourio, N., Crivello, F., Berthoz, A., and Mazoyer, B. 1996. Functional anatomy of a prelearned sequence of horizontal saccades in humans. *J. Neurosci.* **16**:3714–3726.
- Petit, L., Clark, V. P., Ingeholm, J., and Haxby, J. V. 1997. Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *J. Neurophysiol.* **77**:3386–3390.
- Petit, L., Courtney, S. M., Ungerleider, L. G., and Haxby, J. V. 1998. Sustained activity in the medial wall during working memory delays. *J. Neurosci.* **18**:9429–9437.
- Petrides, M. 1994. Frontal lobes and behavior. *Curr. Opin. Neurobiol.* **4**:201–211.
- Picard, N., and Strick, P. L. 1996. Motor areas of the medial wall: A review of their location and functional activation. *Cereb. Cortex* **6**:342–353.

- Postle, B. R., and D'Esposito, M. 1999. "What"—then—"where" in visual working memory: An event-related fMRI study. *J. Cognit. Neurosci.*, in press.
- Rainer, G., Asaad, W. F., and Miller, E. K. 1998. Memory fields of neurons in primate prefrontal cortex. *Proc. Natl. Acad. Sci. USA* **95**:15008–15013.
- Rao, S. C., Rainer, G., and Miller, E. K. 1997. Integration of what and where in the primate prefrontal cortex. *Science* **276**:821–824.
- Smith, E. E., Jonides, J. J., Koepp, R. A., Awh, E., Schumacher, E. H., and Minoshima, S. 1995. Spatial versus object working memory: PET investigations. *J. Cognit. Neurosci.* **7**:337–356.
- Smith, E. E., Jonides, J., and Koepp, R. A. 1996. Dissociating verbal and spatial working memory using PET. *Cereb. Cortex* **6**:11–20.
- Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenber, D. R., and Carl, J. R. 1996. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J. Neurophysiol.* **75**:454–468.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.
- Wilson, F. A., O'Scalaidhe, S. P., and Goldman-Rakic, P. S. 1993. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* **260**:1955–1958.