



Organization of working memory within the human prefrontal cortex: a PET study of self-ordered object working memory

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Abstract

The prefrontal cortex plays a critical role in working memory, the active maintenance of information for brief periods of time for guiding future motor and cognitive processes. Two competing models have emerged to account for the growing human and non-human primate literature examining the functional neuroanatomy of working memory. One theory holds that the lateral frontal cortex plays a domain-specific role in working memory with the dorsolateral and ventrolateral cortical regions supporting working memory for spatial and non-spatial material, respectively. Alternatively, the lateral frontal cortex may play a process-specific role with the more dorsal regions becoming recruited whenever active manipulation or monitoring of information in working memory becomes necessary. Many working memory tasks do not allow for direct tests of these competing models. The present study used a novel self-ordered working memory task and positron emission tomography to identify whether dorsal or ventral lateral cortical areas are recruited during a working memory task that required extensive monitoring of non-spatial information held within working memory. We observed increased blood flow in the right dorsolateral, but not ventrolateral, prefrontal cortex. Increases in blood flow in the dorsolateral region correlated strongly with task performance. Thus, the results support the process-specific hypothesis. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Dorsolateral prefrontal cortex; Ventrolateral prefrontal cortex; Positron emission tomography; Self-ordered task; Working memory

1. Introduction

Ample evidence from human and non-human primate studies indicates that the prefrontal cortex (PFC) plays a critical role in working memory, the active maintenance and manipulation of information for brief periods of time for guiding future motor and cognitive processes [1]. However, how working memory processes are organized or distributed within the PFC remains unclear.

Two competing models have emerged to account for the growing human and non-human primate literature

examining the functional neuroanatomy of working memory. Support for both models exists [4,21,41,44]. One theory holds that the role of the lateral frontal cortex within working memory is domain-specific, and the dorsolateral and ventrolateral cortical regions support working memory for spatial and non-spatial material, respectively [9]. This model is theoretically appealing because it suggests that the segregated dorsal “where” and ventral “what” streams of visual processing originating in the posterior visual cortex extend into the PFC [43]. Alternatively, it has been suggested that the organization of working memory within the PFC is not domain-specific, but instead, is process-specific in that the dorsolateral area tends to be recruited when active manipulation or monitoring of information in working memory is necessary [29]. This model suggests an organization less dependent upon

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the type of information held in working memory. Rather, the organization of working memory within the PFC is a function of the degree of manipulation and monitoring of material within working memory buffers.

Damage to the dorsolateral PFC impairs performance on self-ordered working memory tasks in human [32] and non-human primates [14,28]. In such tasks, subjects are required to monitor within working memory an array of self-generated responses. Thus, self-ordered tasks require both storage and executive working memory functions.

One difficulty in differentiating between these models is that both models predict the same localization of activity under many working memory conditions (Fig. 1). For instance, both models predict dorsolateral activity in the case of a working memory task that is spatial and requires a high degree of monitoring. Similarly, both models predict ventrolateral activity in the case of a working memory task that is non-spatial and requires little monitoring. In order to test the process- and domain-specific models, we examined the neural correlates of a task for which the two models make different predictions. Specifically, we used a non-spatial, self-ordered object working memory task that requires extensive monitoring of information held within working memory. The self-ordered task required subjects to select a different object each trial from an array of the same 11 objects. After each selection, the objects rearranged themselves in space. Thus, subjects had to store in working memory all objects selected on previous trials, monitor these objects in working memory, and use active mnemonic representations to guide their next response. Because the task requires maintenance of non-spatial material in working memory and extensive monitoring, the process- and domain-specific models make different predictions

		MODALITY	
		SPATIAL	OBJECT
MONITORING	HIGH	SAME (DLPFC)	DIFFERENT
	LOW	DIFFERENT	SAME (VLPFC)

Fig. 1. Under different working memory task conditions, the domain and process-specific models predict the same or different activation within the lateral prefrontal cortex. In the case of a spatial working memory task that requires a substantial amount of monitoring, both models predict activation of the dorsolateral prefrontal cortex (DLPFC). Similarly, both models predict activation of the ventrolateral prefrontal cortex (VLPFC) in the case of a non-spatial (e.g., object) working memory task that does not require monitoring or manipulation of information. Taking advantage of the differential prediction of the models, the current study used a non-spatial working memory task that required a substantial amount of monitoring (highlighted cell).

regarding the location of processing within the lateral frontal cortex. Specifically, finding activity in the dorsolateral PFC would support the process-specific model while activity in the ventral PFC would support the domain-specific model.

2. Materials and methods

2.1. Subjects

Eight healthy, right-handed (average laterality quotient = +75; R.50th percentile [20]) subjects (four females and four males) with an average age of 22 years (range 19–26 years) and an average of 15.4 years of education (range 13–18) participated in the object self-ordered working memory study. All subjects gave written informed consent as approved by the VAMC Human Subjects Committee.

2.2. Object self-ordered working memory task

All stimuli were presented on a 15" computer monitor positioned approximately 50 cm from the subject's eyes. Subjects made responses with a stylus and touch-

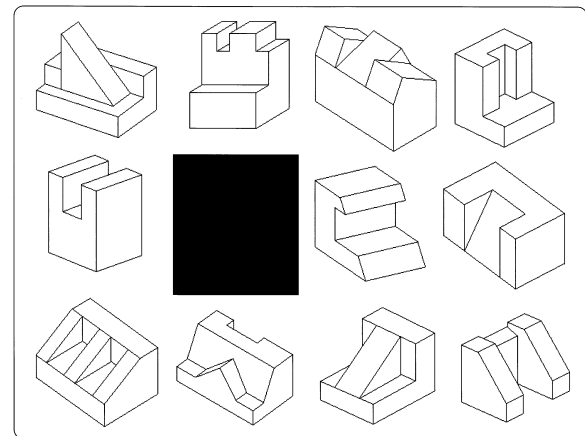


Fig. 2. Schematic diagram of the self-ordered object working memory task. The subject was presented with an array of 11, black and white, 3D line drawings arranged in a hidden 3 × 4 grid. Subjects were instructed that the goal of the task was to select each object once and only once, in any order. They were told that since the objects rearranged themselves after each selection, they would have to remember which objects had been chosen so as not to choose the same object more than once. Each time an object was selected, it was briefly encircled with a line, and then all of the objects were randomly reordered in the matrix. Since spatial cues were irrelevant, the task was non-spatial in nature. To prevent a strategy of responding to the same location on the each trial, a black square that did not accept a response was presented in the position where the last selected object had appeared. This prevented subjects from taking advantage of the randomization of the objects. The objects were carefully chosen to prevent verbal mediation, rank-ordering, and grouping based on object features.

pad using their dominant hand. All subjects practiced extensively with the response device before scanning. The self-ordered task was modeled after that used by Petrides and Milner [32]. Subjects viewed 11 3D line drawings of objects in an invisible 3×4 matrix (Fig. 2). These objects have been used in various other perceptual and memory studies [38,39]. Subjects received the following instructions: “On this task, you will see a grid of different objects. Your job is to choose each one of the objects only once, in any order. After you have made a choice, the objects will rearrange themselves. Thus, you will have to remember which ones you have already selected, so you can choose each object only once.”

Each time an object was selected, it was briefly encircled with a line, and then all of the objects randomly rearranged themselves in the matrix. All subjects practiced the task prior to scanning with a 2×3 grid of only four objects that were not included in the other set of 11.

A few features of this self-ordered task warrant comment. First, given that the objects reordered in space randomly, it is non-spatial in nature. After a subject made a response, a black muted square that did not accept a response was presented in the place of the chosen object. This prevented the strategy of responding to the same location to take advantage of the randomization of the objects. Second, verbal mediation was limited by using objects that are not readily nameable. The objects were chosen to prevent the use of strategies such as rank-ordering or grouping based on object features. Finally, the large number of objects places a high demand upon one's ability to store and monitor objects in working memory. Taken together, these features helped to highlight the object working memory demands of the task, while limiting the use of alternative strategies.

The subjects also completed a control task which required them to scan a 3×4 matrix of another 11 objects, all different from the other scan condition, and to select the object that had a small (10-point font) asterisk embedded on top of the figure. This condition provided a control for the perceptual and motor demands of the experimental task. The order of the control and experimental task was completely counter-balanced across subjects. Thus, each subject's data consisted of a single experimental–control scan pair.

2.3. PET imaging and analysis

Regional cerebral blood flow (rCBF) was estimated from normalized (1000 counts) tissue radioactivity using an ECAT 935B camera (Siemens, Knoxville, TN) with septa retracted; a slow-bolus injection of H_2^{15}O (0.25 mCi/kg) infused at a constant rate over 30 s [40], and a 90-s scan acquisition beginning upon

radiotracer arrival into the brain. Images were reconstructed using a 3D reconstruction algorithm [12] with a Hanning filter of 0.5 cycles/pixel and measured (2D transmission scan) attenuation correction. Normalization for global activity, intra-subject coregistration, and nonlinear warping to a reference stereotactic atlas [42] were accomplished with automated software [16–18]. Images were smoothed with a 6.75 mm, 3D Gaussian filter producing a final image resolution of approximately 9.8 mm full-width at half-maximum. Statistical analyses utilized the global variance of all intracerebral pixels [45]. We employed a significance threshold of $P < 0.0005$ (equivalent to a Z -score = 3.3) based on previous bootstrapping studies of the rate of false positive foci emerging due to chance [46]. Because the field of view emphasized inferior brain regions, we note that very superior activations, Talairach coordinates of $z > 50$ mm, are subject to interpolation and sampling artifacts; these should be considered cautiously. To examine the relation between rCBF changes and performance, we performed a pixel-wise correlation analysis using in-house software. Pearson correlations were computed between task performance and frontal regions demonstrating significant rCBF increases in the subtraction analysis. This technique provides a map of the regions correlated with task performance and avoids the arbitrary nature of placing regions of interests.

3. Results

Table 1 lists the behavioral performance data for the eight subjects. Since the task increased in difficulty as more objects had been selected, it is important to note that all of the subjects had selected at least nine of the 11 objects by the end of the scan. This assures us that we imaged our subjects actively engaged in monitoring many objects within working memory.

Tables 2 and 3 list the areas that demonstrated significant increases in rCBF during performance of the self-ordered task over that of the control condition. The object working memory task activated the right dorsolateral PFC (BA 46 and 9/46) (Fig. 3a). No significant increases in the ventrolateral PFC were noted. Examining individual subtracted scans indicated that seven of the eight subjects had rCBF increases in the right dorsolateral PFC (all $> 6\%$; $M = 11\%$; $SD = 9\%$). The one female subject (laterality quotient = +63; R.30th percentile) that did not show an increase in the right dorsolateral PFC, demonstrated robust activation in the left dorsolateral PFC ($x = -24$, $y = 39$, $z = 29$). Thus, all subjects demonstrated increased rCBF in the dorsolateral PFC while performing the non-spatial working memory task.

In addition, pixel-wise Pearson correlations com-

Table 1
Behavioral performance data for the eight subjects performing the self-ordered object working memory task

Subject	Trial response time in seconds, mean (SD)	Time until completion in seconds	Trials to completion	Number of objects selected by the end of the scan (90 s)
1	7.54 (4.46)	93.40	13	10
2	7.08 (3.11)	120.04	18	10
3	6.88 (3.65)	185.87	28	9
4	4.82 (2.53)	101.24	22	10
5	6.94 (2.38)	178.89	26	9
6	5.59 (3.01)	61.91 ^a	11	11
7	4.58 (0.76)	51.76 ^b	11	11
8	8.35 (6.45)	283.88	35 ^c	10
Mean total	6.47 (1.66)	134.62	20.5	10.0

^a Task restarted automatically and subject was given the following instructions, “let’s try it again”. Only two additional trials were performed before the scan ended.

^b Same as above, but five additional trials were performed.

^c Subject had selected 10 of the 11 objects by trial 14 (49 s into scan), but had difficulty with the remaining object.

puted between rCBF increases and number of trials and time to completion revealed a relationship between the amount of blood flow to the right dorsolateral prefrontal cortex and performance on the self-ordered task. Although each subject’s peak activation varied slightly within BA 9/46 (peak maxima extended posterior as far as $y = 28$ mm), the peak correlation between rCBF and task performance was found to be within 2 mm of the group peak activation ($x = 39$, $y = 44$, $z = 27$ mm). Increased blood flow was related to better performance in a linear manner [r (trials to completion) = -0.71 , $P < 0.03$; r (time to completion) = -0.63 , $P < 0.05$, $df = 6$; Fig. 3b]. Nonetheless, these statistically significant correlations are based on a small number of subjects and requires replication.

Strong activations also emerged bilaterally in the ventral frontopolar/frontomarginal gyrus region (BA 10/11) (Fig. 3a). Other areas of activation included the right frontal eye fields [26], left caudal anterior cingulate, right fusiform gyrus, and precuneus. Widespread activation also localized to posterior visual processing

cortices including striate and extrastriate areas of the occipito-temporal cortex (BA 17/18/19). The increased activation in posterior visual areas most likely reflects additional perceptual processing in the experimental compared to control task.

4. Discussion

The present study utilized a non-spatial, self-ordered, working memory task that required extensive monitoring of information within working memory. The domain [9] and process [29] specific models make divergent predictions regarding the recruitment of lateral PFC areas during performance. The domain-specific model emphasizes the *type* of information being held in memory. Since the working memory task used was non-spatial in nature, it predicts ventrolateral activation. The process-specific model emphasizes not what is held in memory, but what *executive* operations are performed on the information in memory. Since

Table 2
Stereotactic coordinates and Z-scores of anterior brain areas showing significant activation foci during performance of the self-ordered object working memory task

Brain area	Coordinates			Z-score	$P < ^a$
	x	y	z		
Right dorsolateral PFC (BA 9/46)	39	44	27	3.30	5.0×10^{-4}
Frontomarginal gyrus (BA 10/11)					
Right	28	50	-9	3.91	4.6×10^{-5}
Left	-26	55	-11	4.21	1.3×10^{-5}
Right middle frontal gyrus (BA 6)	26	1	47	4.64	1.8×10^{-6}
Left premotor area (BA 6)	-33	-19	63	3.49	2.4×10^{-4}
Left caudal anterior cingulate (BA 24/32)	-8	3	47	4.04	2.7×10^{-5}

^a Uncorrected for multiple comparisons.

the self-ordered working memory task required substantial monitoring of information within working memory, it predicts dorsolateral activation.

The findings from the current study provide support for the process-specific model of the organization of working memory within the human prefrontal cortex. We observed significant increases in rCBF in the dorsolateral PFC during performance of a non-spatial working memory task. No activity was noted in the ventrolateral PFC. Moreover, differences in performance on the working memory task were positively correlated with increases in the amount of blood flow to the dorsolateral PFC. Subjects who performed better on the self-ordered task showed a greater amount of blood flow to the right dorsolateral PFC.

The current study makes two important contributions to our understanding of how working memory may be organized within the lateral prefrontal cortex. First, our data converge with the findings from other neuroimaging studies of self-ordered working memory to indicate that the dorsolateral PFC is activated by the performance of self-ordered tasks, irregardless of the type of information being manipulated. The peak maximum reported here in the right dorsolateral PFC ($x = 39, y = 44, z = 27$) is very similar to those reported within the same region in other PET studies of self-ordered tasks using verbal ($x = 38, y = 39, z =$

26 and $x = 40, y = 34, z = 29$) [31], abstract design ($x = 31, y = 42, z = 24$ and $x = 35, y = 32, z = 21$) [30], and spatial ($x = 39, y = 37, z = 20$ and $x = 31, y = 37, z = 23$) [23] information. In addition, they are in agreement with a recent fMRI study that found that both spatial and non-spatial working memory tasks activate the dorsolateral PFC when the tasks required manipulation and monitoring of information within working memory buffers [25].

Second, the correlation reported here links activation in the right dorsolateral PFC to successful task performance. Thus, it appears that the dorsolateral PFC supports working memory operations when executive processing of material is required for optimal performance irregardless of the nature of the material. Visual information is segregated in posterior brain regions into ventral “what” and dorsal “where” streams and these two pathways independently project to the ventrolateral and dorsolateral PFC, respectively [43]. Nonetheless, our results converge with other data [24,25,30,31,34] and suggest that both spatial and non-spatial object feature information is represented in the dorsolateral PFC. Indeed, a distinction between spatial and non-spatial processing may exist *within* dorsal or ventral PFC [41] but it seems unlikely that such a gross segregation exists *between* dorsal and ventral regions.

The role of the frontopolar cortex, which in humans is considerably more developed compared to other primates [33], is not well understood. Activation in frontopolar regions has been a consistent finding across neuroimaging studies of episodic memory [3,6,15]. It is thought that the frontal lobes make important contributions to learning and memory by organizing the material to be remembered [11]. Investigators have suggested that activity in the frontopolar cortex during studies of episodic memory reflects the establishment of a retrieval set [5,19], the degree of retrieval effort [36], the organizing of information to be remembered [7,8] and the verification of information that has been retrieved [35,37].

Other studies indicate that slightly more ventral frontopolar regions, more similar to the coordinates reported here, are intricately involved in planning and problem solving [2,22]. A recent fMRI study addressing how memory and attentional allocation becomes integrated found activity in the frontopolar region specifically when subjects had to keep in mind the overall task goal, while attentional resources are poised upon sub-goals [13]. They did not find increased signal in the frontopolar region when only working memory or attentional resource allocation was required. These investigators suggested that the diverse experimental conditions under which the frontopolar cortex has been activated could be explained by this role. For example, in the current study using the self-ordered

Table 3
Stereotactic coordinates and Z-scores of posterior brain areas showing significant activation foci during performance of the self-ordered object working memory task

Brain area	Coordinates			Z-score	$P <^a$
	x	y	z		
Cuneus (BA 17/18/19)					
Right	12	-80	29	3.50	2.4×10^{-4}
Left	-1	-87	7	6.81	5.0×10^{-12}
Left	-30	-78	0	5.30	6.0×10^{-8}
Occipital cortex (BA 18/19)					
Right	15	-89	11	6.72	9.0×10^{-12}
Right	46	-62	-7	4.73	1.2×10^{-6}
Right	39	-76	2	4.43	4.7×10^{-6}
Left	-26	-87	11	6.32	1.3×10^{-10}
Left	-42	-64	-7	5.54	1.6×10^{-8}
Lingual gyrus (BA 19)					
Right	24	-71	-4	4.94	4.0×10^{-7}
Right	12	-67	-9	4.76	9.7×10^{-7}
Precuneus (BA 7)					
Right	30	-73	22	3.81	7.1×10^{-5}
Left	-17	-46	54	4.17	1.5×10^{-5}
Right fusiform gyrus (BA 37)	28	-44	-9	4.11	2.0×10^{-5}
Cerebellum					
Right	3	-64	-27	3.49	2.5×10^{-4}
Right	28	-40	-36	3.40	3.4×10^{-4}
Left	-30	-51	-43	3.54	2.0×10^{-4}
Left	-30	-55	-20	3.52	2.2×10^{-4}

^a Uncorrected for multiple comparisons.

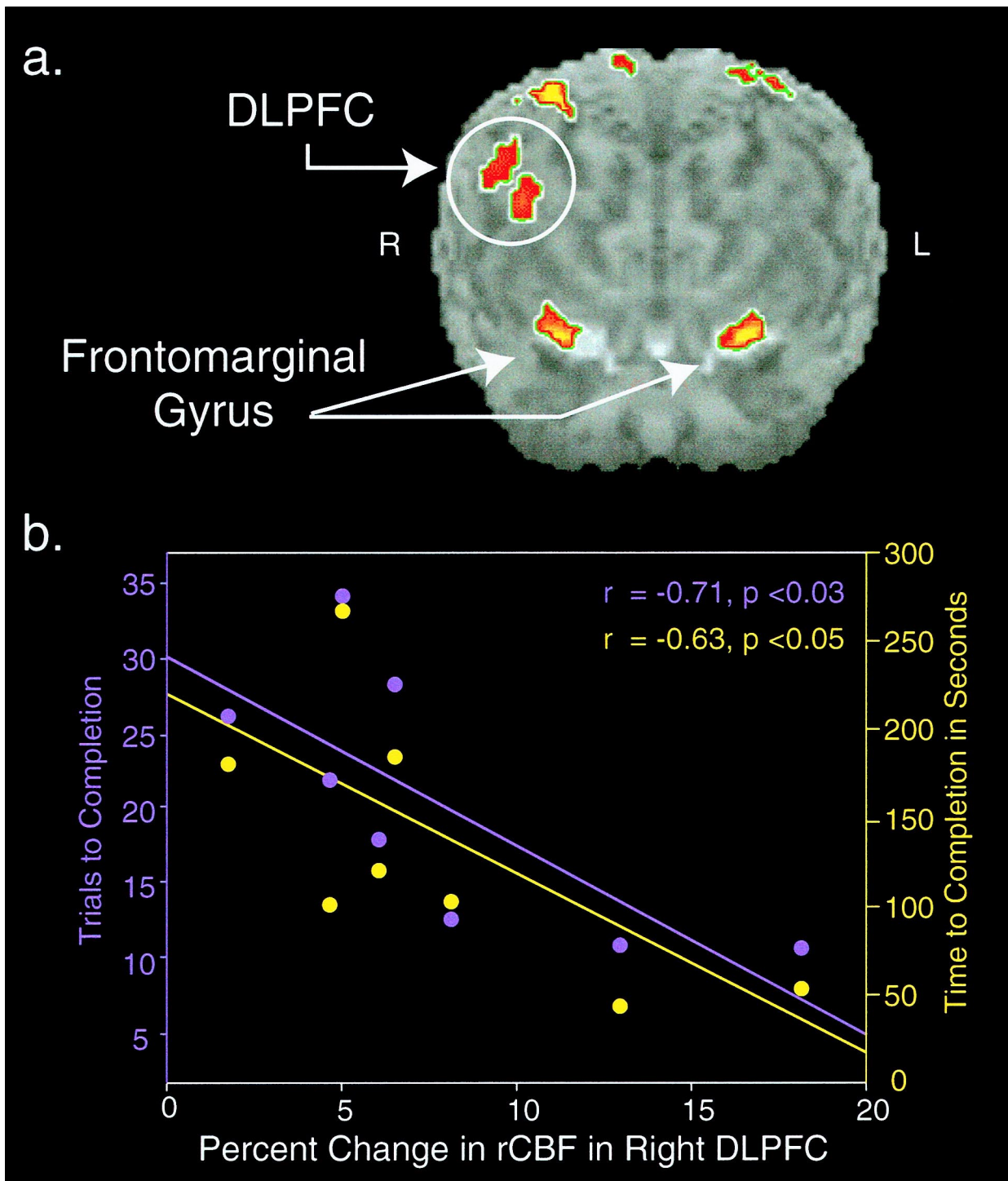


Fig. 3. Right dorsolateral prefrontal cortical activation is associated with performance of self-ordered object working memory task. (a) Average rCBF increases of the eight subjects superimposed on a rendering of the anterior surface of a standard MRI. Activations are thresholded to only show rCBF increases with $P < 0.005$. Significant activations include the right dorsolateral prefrontal cortex (DLPFC) and the ventral frontopolar region/ frontomarginal gyrus, bilaterally. Although two foci emerge in the right DLPFC, only the more anterior focus is statistically significant ($P < 0.0005$). (b) Scatter-plot showing the relationship between the number of trials (left axis) and number of seconds (right axis) to completion of the self-ordered working memory task and the individual pattern of rCBF in the right DLPFC (x, y, z coordinates = 39, 42, 27; r (trials) = $-0.71, P < 0.03$; and r (time) = $-0.63, P < 0.05, df = 6$). The graph shows the scatter-plot at one pixel, but multiple contiguous pixels in the right DLPFC demonstrated a similar pattern of correlation.

task, subjects had to keep in mind the overall task goal of selecting each object in the array. While maintaining the task goal in mind, the sub-goal was to scan the array for an object that they had not yet selected and make a response based upon this information. Within this framework, the dorsolateral PFC accomplished the sub-goals with the use of working memory processes (maintenance and monitoring). The ventral frontopolar regions maintained the task goal with the use of strategy and planning. Thus, the activity noted bilaterally in the ventral frontopolar region (BA 10/11) most likely reflects strategic, or organizational processes utilized not only by working memory, but more long-term memory as well. Such processes were surely necessary to perform the task because the number of objects to be remembered was supraspan. Indeed, Grasby et al. [10] demonstrated bilateral activity in the ventral frontopolar cortex when rCBF related to the recall of subspan was subtracted from that of supraspan; this suggests involvement in strategic or organizational processes that facilitate memory.

We also report that the caudal portion of the left anterior cingulate showed robust activity during the working memory task. A recent study demonstrated reliable, sustained activity during working memory delays in this area regardless of whether face or space information was being maintained [27]. This activity likely reflects either the holding on-line of material or more likely the preparation of a motor response based upon the information stored in working memory. In this sense, the caudal anterior cingulate may generally support the integration of information stored in working memory buffers with computations that prepare one for a motor response.

Our findings strongly suggest that when executive processes, such as monitoring, influence the utilization of material within working memory, the dorsolateral prefrontal cortex is recruited. Indeed, the extent of recruitment of the dorsolateral area directly relates to successful working memory task performance. This is the case even if the material held on-line in working memory is non-spatial in nature.

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