

The neural basis of the central executive system of working memory

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WORKING memory refers to a system for temporary storage and manipulation of information in the brain, a function critical for a wide range of cognitive operations. It has been proposed that working memory includes a central executive system (CES) to control attention and information flow to and from verbal and spatial short-term memory buffers¹. Although the prefrontal cortex is activated during both verbal and spatial passive working memory tasks²⁻⁸, the brain regions involved in the CES component of working memory have not been identified. We have used functional magnetic resonance imaging (fMRI) to examine brain activation during the concurrent performance of two tasks, which is expected to engage the CES. Activation of the prefrontal cortex was observed when both tasks are performed together, but not when they are performed separately. These results support the view that the prefrontal cortex is involved in human working memory.

Cerebral activation was measured in six normal, right-handed subjects (3 men, 3 women, aged 22–28 years) with fMRI using blood oxygen level-dependent contrast⁹. The experimental working-memory paradigm consisted of a comparison between dual-task and single-task performance. To test the hypothesis that dorsolateral prefrontal cortex is involved in dual-task performance, we chose two non-working-memory single tasks, a semantic-judgement task and a spatial-rotation task, which predominantly activated posterior brain regions in previous functional neuroimaging studies^{10,11}. The semantic-judgement task required the subject to identify exemplars of a target category ('vegetable') in a series of aurally presented words. The spatial-rotation task required subjects to indicate which of two squares had a dot in the same location, relative to a double line, as a spatially rotated target square¹¹. The dual-task condition required subjects to perform the semantic-judgement task and spatial rotation task concurrently. During the single-task condi-

tion, the mean accuracy of performance on the spatial-location task was 93% and on the semantic-judgement task was 95%. The decrement in performance during the dual-task condition ranged from 0 to 5% for the semantic-judgement task and from 4 to 11% for the spatial task. The protocol for each experimental condition is illustrated in Fig. 1.

When compared to the resting baseline (Fig. 2), the spatial-rotation task produced significantly increased activation in bilateral superior parietal regions (Brodmann's area (BA) 7) and

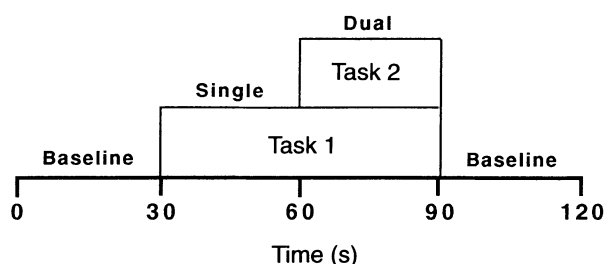


FIG. 1 Illustration of task design. Each activation run began with a 30-s resting baseline, followed by 30 s of either the semantic task or the visuospatial task performed alone (task 1), then 30 s of both tasks performed simultaneously (tasks 1 and 2), and concluded with another 30 s of resting baseline. Each subject performed multiple runs in which the order of task presentation was varied so that task 1 and task 2 alternated between the semantic and spatial task. Subjects were trained on the tasks before the fMRI study. Auditory stimuli were presented over the MRI intercom system at a rate of one word every 2 s. The visual stimuli were presented every 3 s on a rear projection screen by a computer using a LCD panel and an overhead projector. Subjects visualized images on the screen by looking through a mirror attached to the top of the MRI head coil. Subjects responded in the affirmative to each stimulus by dorsiflexion of their toes.

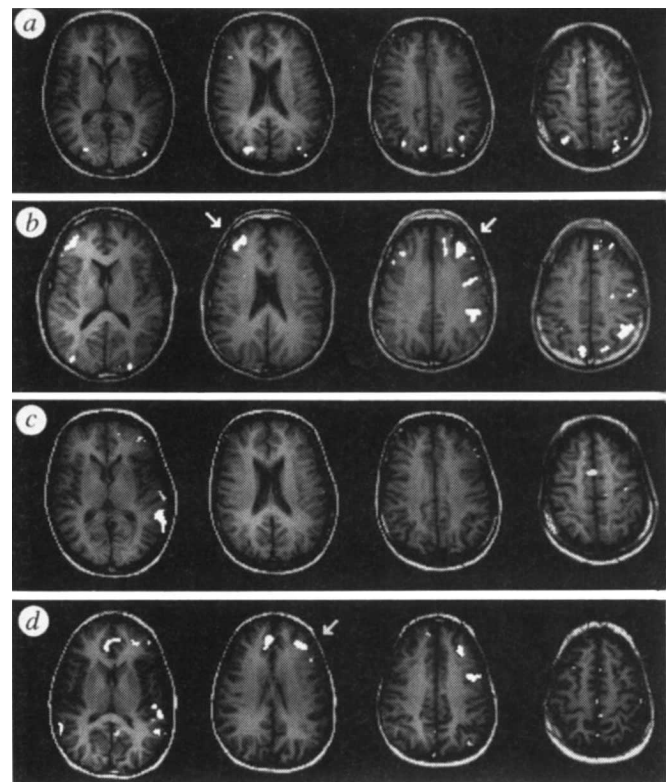


FIG. 2 Regions significantly activated in the single- and dual-task conditions in individual subjects are shown in a–d. Single-task activations are from the same subject; dual-task activations are from two different subjects. Comparison of the single-task versus baseline conditions show activation in the bilateral parieto-occipital regions for the dot-location task (a) and the left temporal region for the semantic-judgement task (c). Regions significantly activated during the dual-task versus single-task conditions are shown in b and d. In the first comparison (dual task minus semantic task), activation is seen in prefrontal cortex, anterior cingulate and premotor cortex (b). In addition, activation is seen in bilateral parieto-occipital regions, which represents activation during the dot-location task. In the second comparison (dual task minus spatial task), activation again is seen in prefrontal cortex and anterior cingulate (d). In addition, activation is seen in bilateral superior temporal gyri, which represents activation during the semantic-judgement task. The fMRI was performed at 1.5 T (G.E. Signa) using a prototype fast gradient system. Four axial slices through dorsolateral prefrontal cortex were chosen from sagittal images. Each activation run consisted of 60 gradient-echo echo-planar images (TR = 2 s, TE = 50 ms, 64 × 64 matrix, 24-cm field of view, 5-mm slices with 5-mm gaps). In-plane motion correction was performed and an upper threshold of 2 s.d. above typical changes in signal intensity with task activation was set to eliminate large signal changes representing residual motion. Activation maps were determined using a pixel-wise *t*-test for significant signal intensity changes in task versus baseline conditions, including a 4-s delay for vascular transit²⁰. Pixels exceeding a lower threshold for significance were overlaid on axial T1 weighted images; *P* < 0.005, grey; *P* < 0.001, white; negative signal changes not displayed. A 3 × 3 pixel median filter was used to eliminate isolated pixels exceeding these thresholds, resulting in increased significance for the displayed activation. Anatomical location of activated regions was determined using a computer-based stereotaxic coordinate system²¹.

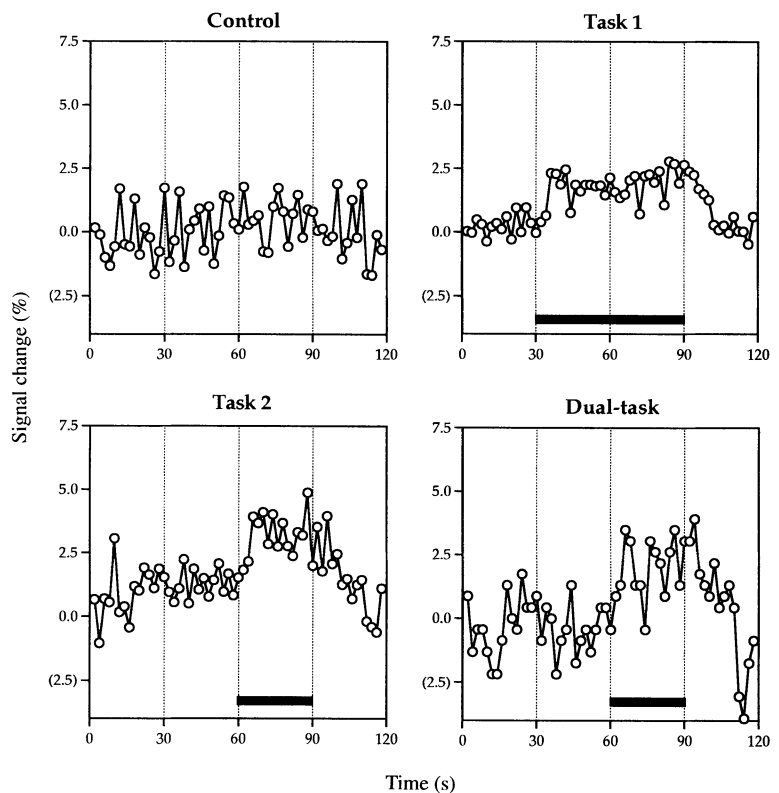


FIG. 3 Plots of the average change in signal intensity over the course of the entire task from selected regions of interest in one subject. 0–30 s, baseline; 30–60 s, single task; 60–90 s dual task; 90–120 s, baseline. Regions of interest were chosen from the parietal lobe (task 1 and task 2) and the dorsolateral prefrontal cortex (dual task), as well as from a control region which was not activated. These plots demonstrate that in task 1, task 2 and the dual task, signal intensity changes correlate with the experimental paradigm illustrated in Fig. 1. No significant task-specific signal-intensity changes occurred in the control region.

lateral occipital regions (BA 19) in all subjects. Significant activity above baseline on the semantic-judgement task (Fig. 2) was limited to the most posterior aspects of superior temporal gyrus (BA 22) in both hemispheres and in the left inferior parietal lobule (BA 39, 40). The full extent of the superior temporal gyrus was not within our chosen slice coverage. We did not observe frontal activation during these single-task conditions.

When the single-task conditions were compared to the dual-task conditions (Fig. 2), all subjects showed significantly increased activation bilaterally in dorsolateral prefrontal cortex (BA 9 and 46). Additional activation was found in the anterior cingulate region (five subjects) and left premotor cortex (two subjects). In these analyses, only one single task could be subtracted from the dual-task condition. Thus posterior activation that was associated with the second single task was also visualized along with frontal activation. Region-of-interest analyses confirmed that signal intensity changes correlated with the tasks (Fig. 3). Individual subject analysis revealed some variation across subjects in the areas of activation within the prefrontal cortex. In four subjects the prefrontal activation was greater in the right hemisphere.

To address the possibility that increased mental effort alone during the dual-task as compared to the single tasks could account for the frontal activation observed, an additional 6 normal, right-handed subjects (3 men, 3 women, age 18–37 years) performed the spatial-rotation task under more difficult conditions by increasing the stimulus frequency. In the first condition, mean accuracy of performance was similar to that during the dual-task paradigm (85%), and in the second condition, there was a significant decrement in performance (74%, $P < 0.005$). Although increasing task difficulty resulted in increased activation in posterior brain regions, no additional prefrontal activation was observed (Fig. 4).

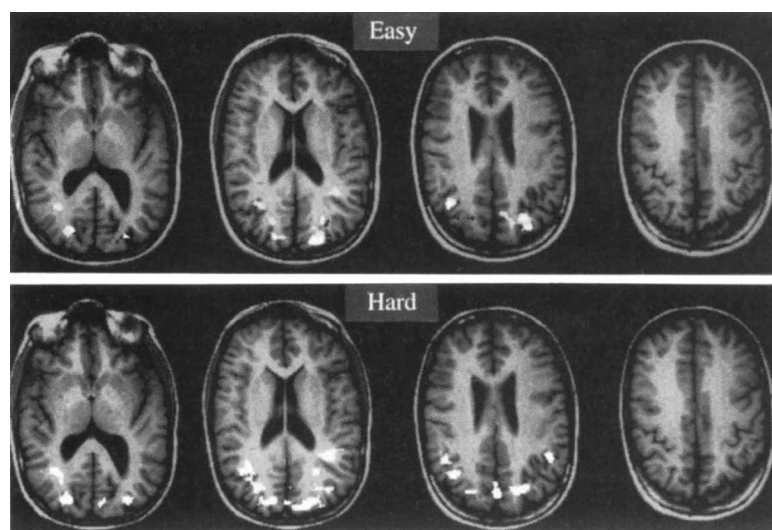
Our results demonstrate recruitment of the dorsolateral prefrontal cortex during the performance of two concurrent tasks, even though neither task activated prefrontal cortex when performed alone. It has been shown that dorsolateral prefrontal regions were among the areas recruited during verbal (that is,

phonological loop) and spatial (that is, visuospatial sketchpad) working-memory challenges in normal humans^{2–6}. Investigations with monkeys have also demonstrated that dorsolateral prefrontal cortex is essential for slave-system working memory^{7,8}. The single tasks used in the present study did not require holding information on-line over a delay period. Although it is conceivable that these (or any) tasks do require working memory to a small extent, it is unlikely that the robust prefrontal activation observed during the dual task is due to a summation of prefrontal activation present, but not detected, in the single tasks. Instead, our findings support the hypothesis that dorsolateral prefrontal cortex is involved in the allocation and coordination of attentional resources, a unique process observed by the CES component of working memory recruited during dual-task performance.

Our findings suggest that there is a partly overlapping neural substrate that underlies both CES and slave-system components of working memory, despite behavioural studies in normal humans that have demonstrated that the CES is a distinct component of working memory, separable from the slave systems¹. Behavioural dissociation of these cognitive processes is also supported by studies of brain-damaged patients who demonstrate significant CES deficits with normally functioning slave systems¹². There are several possible explanations for these findings. First, previous activation studies of slave-system working memory may not have used pure passive memory tasks and may require executive processes^{2,4}. Thus prefrontal activation in these studies may reflect CES functioning. Second, the spatial resolution of fMRI may not be sufficient to identify subregions of the frontal lobe that may subserve different working-memory components. Third, the same neuronal population within prefrontal cortex in different dynamic states may subserve several distinct cognitive operations.

A general problem affecting the interpretation of functional neuroimaging activation studies is that the experimental task is typically more demanding than the baseline or control task. In this study, the dual-task condition was likely to be more demanding than either single-task condition, making it necessary to elim-

FIG. 4 Regions significantly activated in the spatial-rotation task studied with two different levels of a difficulty in a single subject. In these studies, comparison of the same spatial task used in the dual-task studies was made against a sensorimotor control task which required subjects to respond left and right alternatively to three empty squares. The task consisted of four 40-s blocks of the dot-location task alternating with four 40-s blocks of the sensorimotor control task, accumulating 160 gradient-echo echo-planar images in each activation run. Activation maps were obtained using a pixel by pixel correlation analysis to identify pixels whose signal intensity over time followed a predefined task-related reference function²², using a threshold from $r > 0.2$, $P < 0.01$ (grey) to $r > 0.3$, $P < 0.0001$ (white); negative signal changes are not displayed. Both conditions activated identical regions in bilateral parietooccipital regions. There was greater activation (1.3% versus 0.8% signal change, $P < 0.001$) and spatial extent (145 versus 89 pixels, $P < 0.0001$) during the more difficult condition (left) compared to the less difficult task (right). Activation of prefrontal cortex was not observed.



inate the possibility that prefrontal cortex activation was due to a nonspecific increase in mental effort required to perform the dual task, rather than a specific type of working-memory processing, namely, a central executive system. In separate experiments, we addressed this issue by having subjects perform the spatial-rotation task alone at different levels of difficulty. Even at the more difficult condition, when performance was worse than that seen in the dual-task condition, we did not observe any prefrontal activation. We conclude that the prefrontal activation observed is related specifically to dual-task performance.

The anterior cingulate was also activated in most subjects only during the dual-task condition. Anterior cingulate activation has been observed in several cognitive neuroimaging studies^{13–15}, and this region has been proposed to be part of an anterior attentional system that is critical for response selection among competing, complex contingencies¹⁶. For example, using positron emission tomography¹³, anterior cingulate as well as dorsolateral prefrontal cortex was recruited in a divided-attention task during which subjects had to detect a change in the shape, colour or speed of a visual stimulus. These regions were not recruited when subjects had to attend selectively to only one of these attributes. Simultaneous attention to multiple-stimulus attributes is analogous to performing a dual task and is likely to require the CES of working memory. Thus anterior cingulate cortex activation is also consistent with our hypothesis for the neural basis of the CES. Moreover, recruitment of anterior cingulate and dorsolateral prefrontal cortex, which are anatomically interconnected¹⁷, suggests that the CES may comprise several components. This idea has been proposed in behavioural studies¹⁸, and is supported by single-neuron recording experiments in non-human primates¹⁹.

A potentially important finding in this study is the variability in the distribution of activated regions within the prefrontal cortex. This variability may reflect differing strategies used by neurologically intact subjects to perform a dual task. Investigation of other dual-task paradigms will provide additional information about the adaptive nature of distributed cognitive networks involved in working memory. Another source of variability in activation among subjects may arise from individual differences in the extent to which our dual-task paradigm placed demands on the CES. Studies that carefully monitor individual differences in available resource capacity for dual-task performance are necessary to address this issue. □

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Specificity of monosynaptic connections from thalamus to visual cortex

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IN cortical area 17 of the cat, simple receptive fields are arranged in elongated subregions that respond best to bright (on) or dark (off) oriented contours, whereas the receptive fields of their thalamic inputs have a concentric on and off organization¹. This dramatic transformation suggests that there are specific rules governing the connections made between thalamic and cortical neurons^{1–3} (see ref. 4). Here we report a study of these rules in which we recorded from thalamic (lateral geniculate nucleus; LGN) and cortical neurons simultaneously and related their receptive fields to their connectivity, as measured by cross-correlation analysis^{5,6}. The probability of finding a monosynaptic connection was high when a geniculate receptive field was superimposed anywhere over an elongated simple-cell subregion of the same signature (on or off). However, 'inappropriate' connections from geniculate cells

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