



Tuning in to the temporal dynamics of brain activation using functional magnetic resonance imaging (fMRI)

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Baddeley¹ introduced the term 'working memory' into the experimental psychology literature to replace the existing concept of a passive short-term memory store and to emphasize, within a single theoretical framework, both the temporary storage and the 'on-line' manipulation of information that occurs during a wide variety of cognitive activities. Since then, considerable evidence has accumulated to suggest that the lateral frontal cortex plays a critical role in certain aspects of working memory for both spatial and non-spatial material. This evidence comes from the study of patients with excisions of the frontal cortex²⁻⁵, from lesion and electrophysiological recording work in non-human primates^{6,7}, and more recently from functional neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI; see Ref. 8 for review).

One particular focus of many functional imaging studies has been to investigate whether there are functionally distinct subdivisions of the lateral frontal cortex that subserve different aspects of working memory and, if so, how the functions of these regions might best be described. By and large, no consensus has been reached yet; spatial and non-spatial working memory studies using a cornucopia of different tasks have produced a widely distributed pattern of overlapping activation foci within dorsolateral and ventrolateral frontal cortical regions⁸ (see Fig. 1). Here, one contributory factor is undoubtedly that the tasks used in different studies vary widely in terms of their specific mnemonic (e.g. processing) requirements and the nature (e.g. modality) of the material to be remembered. Moreover, few of these imaging studies have had sufficient temporal resolution to isolate the specific neural events that are related to any particular aspect of task performance, such as the sustained localized activity that is widely assumed to underlie the rehearsal processes that keep a stimulus 'in mind' after it is removed from view.

Two recent studies published in *Nature* have moved closer to addressing this issue using novel and innovative statistical techniques to demonstrate that high-speed fMRI can be used to accurately capture the time course of working memory processes within the human brain^{9,10}. In general, fMRI has been used to make functional maps of changes in cerebral venous oxygen concentration that correlate with neuronal activity. Typically, the subject performs the task of interest (e.g. a working memory task), followed by a 'control' task requiring many, but not all, of the same motoric, perceptual and cognitive components as the experimental task. The imaging data

are then reconstructed, smoothed and normalized for global blood flow, which may vary between different scans, and subtraction images are generated which represent regional differences in activity between the task of interest and the 'control' task. The two new studies^{9,10} have extended this basic approach by focusing on the temporal dynamics of regional activation in order to separate transient changes in activity, that are time-linked to stimulus presentation (and presumably, therefore, related to perceptual aspects of performance), from sustained activity during the delay period after the stimulus is removed from view.

The visual working memory task, employed by Courtney *et al.*¹⁰, required subjects to remember a sample face for eight seconds and then to respond by indicating whether a test face presented at the end of the delay was the same as, or different to, the sample face. Sustained changes in activity that were time-linked to the delay period between stimulus presentation and subject response (and presumably, therefore, related to mnemonic aspects of task performance) were observed in ventrolateral (Brodmann's area 45/47) and dorsolateral (areas 46 and 9/44) regions of the frontal lobe, as well as in more posterior extrastriate visual regions (areas 37 and 18/19). In contrast, transient changes in activity that were correlated with stimulus presentation were most pronounced in the ventral occipitotemporal regions of the extrastriate visual cortex.

Cohen *et al.*⁹ used a sequential letter task with a ten second delay between stimuli and varied the memory load parametrically across scans by asking subjects to judge whether currently presented letters were identical to those presented one, two or three back in the sequence. Again, the elegant statistical approach that was used allowed these authors to delineate activations that were related primarily to sensory and motor processes (those that peaked during stimulus presentation,

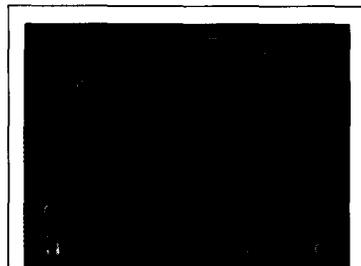


Fig. 1 A diagram illustrating the distribution of activation foci reported in recent functional neuroimaging studies of working memory. Red dots = spatial working memory studies; blue dots = non-spatial working memory studies (for a full description, see Ref. 8). The dots indicate the precise X (medial-to-lateral) and Z (inferior-to-superior) coordinates of statistically significant activation foci within the lateral frontal-lobe region, superimposed on a single-subject magnetic resonance imaging scan ($Y = 27$ mm) that has been transformed into standardized stereotaxic space. The coronal slice was chosen to represent best the dorsal-ventral distribution of activation foci and does not necessarily reflect the correct Y-coordinate (posterior-anterior position) for all of the peaks shown. The subject's left is on the left side of the figure.

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but did not vary with memory load), and activations that were related to mnemonic aspects of task performance (those that varied with the increasing memory load). In addition, however, the parametric task-design allowed 'executive' memory processes, such as updating and manipulating the contents of working memory (transient changes in activity that varied as a function of memory load), to be further distinguished from activations that were related to more basic working memory processes such as maintenance and rehearsal (those that varied with memory load and were sustained across delays). Sustained memory-related changes in activation were observed in dorsal (areas 9/46, 6 and 8) and ventral (area 44) lateral frontal-lobe regions as well as in posterior regions of the parietal cortex (areas 7 and 40), leading the authors to conclude that these areas are critically involved in the active maintenance of information within working memory. Transient memory-related changes, assumed to reflect 'executive control' processes, were observed in similar ventrolateral frontal (area 44) and posterior parietal (area 40) regions and in more posterior dorsal regions of the frontal lobe (area 6).

These two studies^{9,10} have important methodological and theoretical implications; in purely practical terms, they demonstrate that the spatial resolution of fMRI can be combined with information derived from the dynamic changes in activity that are related to specific components of task performance to provide new insights into the likely relationship between structure and function in the human brain. Moreover, they are directly relevant to a more fundamental issue, which has recently provoked considerable discussion in the frontal-lobe literature, and concerns the likely functional organization of working memory processes within the lateral frontal cortex.

Essentially, two divergent positions have emerged which, while focusing on a broadly similar anatomical distinction between the dorsolateral and the ventrolateral frontal cortical regions, differ fundamentally in terms of the precise functions ascribed to those regions. Goldman-Rakic^{6,11,12} has argued that working memory processes within the lateral frontal cortex are organized according to the type (e.g. modality) of information being processed, with dorsolateral frontal regions principally being concerned with memory for spatial material, while ventrolateral frontal regions subservise memory for non-spatial material. This 'domain-specific' theory has considerable theoretical and anatomical appeal as more posteriorly, extrastriate cortical regions appear to be organized into anatomically distinct pathways, functionally specialized for identifying spatial locations (the occipitoparietal pathway or 'dorsal stream') or object features (the

occipitotemporal pathway or 'ventral stream')¹³. Moreover, a number of recent imaging studies in human subjects have suggested that posterior neocortical regions that are specialized for the perceptual analysis of objects or spatial location also may participate in memory for that same type of information¹⁴⁻¹⁶.

An alternative theoretical framework for understanding the functional organization of lateral frontal regions in working memory processes has recently been proposed^{7,17,18}. According to this 'process-specific' view, there are two levels of executive processing within the lateral frontal cortex. The middle portion of the ventrolateral frontal cortex (i.e. areas 45 and 47) underlies active comparisons made about stimuli held in short-term memory and the active organization of sequences of responses based on conscious (i.e. willed), retrieval of information from posterior association systems. These 'explicit' processes are distinguished from the more passive (i.e. unconscious) encoding and retrieval that occurs when incoming or recalled information automatically 'triggers' stored representations on the basis of pre-existing associations - functions which are assumed to depend preferentially on the integrity of posterior temporal and parietal association areas. In contrast, the mid-dorsolateral frontal cortex (dorsal areas 46 and 9), constitutes a second level of executive processing and is recruited only when active manipulation and monitoring of information within working memory is required for the purposes of planned action.

While both of the models described above focus on a functional distinction between dorsolateral and ventrolateral regions of the frontal lobe, they make clearly divergent predictions about the likely role in working memory of these anatomically and cytoarchitecturally distinct cortical areas. On the one hand, the 'domain-specific' or 'modality-specific' model of lateral frontal organization predicts that 'informational domain, not process, will be mapped across the prefrontal cortex'^{11,12}. Accordingly, one might expect functional neuroimaging studies to demonstrate that spatial, visual and perhaps verbal working memory studies activate distinctly different lateral frontal-lobe regions with a reasonable level of consistency. A recent survey of the available literature suggests that this is not the case⁸ (see also Fig. 1). For example, overlapping activation foci within area 9/46 of the mid-dorsolateral frontal cortex have been reported frequently in unrelated spatial, visual and verbal working memory studies (Fig. 1). Similarly, in both the fMRI studies that appeared in *Nature*, regions of the mid-dorsolateral frontal cortex were activated, despite the fact that neither used spatial stimuli^{9,10}. These findings also concur fully with the results of a recent electro-

physiological recording study in the monkey, designed to investigate where and how information about object-identity is integrated with information about object-location in working memory¹⁹. Object-tuned ('what') neurons and location-tuned ('where') neurons were found to be distributed equally between the dorsolateral and ventrolateral regions of the frontal lobe.

The alternative process-specific model of lateral frontal-lobe organization rests on the assumption that a functional distinction can be drawn between the mid-dorsolateral and mid-ventrolateral frontal areas, based on the type or nature of the processes that are carried out by those regions^{17,18,20}. As this model allows polymodal representation of information within these two frontal regions, its predictions are in accordance with the fact that certain spatial, visual and verbal working memory tasks consistently activate the mid-dorsolateral frontal cortex. However, a central tenet of this theoretical position is that different cortical regions, and more specifically, different lateral prefrontal regions, can be shown to play distinct functional roles in working memory.

This hypothesis is precisely that being tested by Cohen and colleagues⁹ in *Nature*. Specifically, their statistical approach is designed to test a number of predictions, one of which is that, during a verbal working memory task, cortical regions that are involved in the active maintenance and rehearsal of information within working memory can be dissociated from those regions involved in other executive control processes such as updating and/or manipulating the contents of working memory. This prediction was broadly confirmed and functional differences were found between the dorsolateral frontal cortex and more ventral frontal regions, as well as between this anterior frontal region and more posterior regions within the parietal lobe. That is not to say, however, that these results are entirely consistent with the predictions of the process-specific model of lateral frontal-lobe function^{7,17,18}. In fact, on the basis of their own findings, Cohen *et al.*⁹ conclude that the mid-dorsolateral region of the frontal cortex is not exclusively concerned with issues of executive control at all, but rather, is critically and centrally involved in the active maintenance and rehearsal of information within working memory. Undoubtedly, the answer to this riddle will depend on how we choose to define terms such as executive control, 'rehearsal' and 'maintenance'.

The studies of Cohen *et al.*⁹ and Courtney *et al.*¹⁰ make a number of key assumptions about the nature and the time course of such mental operations and their likely effects on haemodynamic responses within the frontal lobe and other cortical regions. As Cohen *et al.*⁹ point out, sustained,



memory-dependent activity within the dorsolateral prefrontal cortex actually may reflect some sort of periodic (and presumably frequent) 'control signal' directed at more posterior cortical systems, rather than the active maintenance of information within working memory per se. Integrating these emerging cognitive concepts with new and exciting approaches to the analysis of functional neuroimaging data, such as those described by Cohen *et al.*⁹ and Courtney *et al.*¹⁰, will provide a significant challenge for the future.

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Response from Courtney, Ungerleider and Haxby

In his review of the functional brain imaging literature, Owen poses a contrast between two views of the functional organization of prefrontal cortical areas that participate in working memory, namely that between domain and processing specificity. He finds support for functional dissociations based on processing specificity but not for dissociations based on domain specificity. By contrast, we find support for both domain and processing specificity in human prefrontal cortex. In particular, we have demonstrated a distinction between areas that participate more in spatial as opposed to visual object working memory¹⁻³. In our view, Owen's failure to acknowledge this evidence is based on two flaws in the premises on which his review is based. First, he relies on comparisons between functional brain imaging studies, even though only comparisons within a study between carefully matched working memory tasks can address the question of domain specificity. Comparisons between studies allow only conclusions about whether an area shows any participation in a given working memory task. Dissociations between areas in functional brain imaging research, however, require experimental designs that allow conclusions about whether the level of participation of an area differs for different types of working memory. Second, his review focuses too narrowly on only those prefrontal regions that have the same Brodmann designations as areas in the monkey that have been implicated in working memory. This procrustean bias led him to ignore critical results from other parts of frontal cortex.

Owen's argument against domain specificity hinges on the fact that spatial, visual, and verbal working memory tasks all activate the mid-dorsolateral frontal cortex (area 46/9). His analysis of the existing literature on working memory lumps together

studies in which the comparison tasks vary widely. This type of meta-analysis cannot distinguish between the strengths of activations in prefrontal regions associated with spatial, visual object, and verbal working memory tasks. The test that can show a functional dissociation between working memory modalities is a contrast within a study between carefully matched working memory tasks. In our studies, for example, we compare location working memory (spatial) to face working memory (visual object) employing tasks that use identical stimuli and differ only in the working memory demands¹⁻³. With this design we have repeatedly found a dissociation between a dorsal area in the superior frontal sulcus (Brodmann area 8) associated with spatial working memory and ventral areas (areas 45/47) associated with visual object working memory. Thus, there is evidence for domain specificity contrary to Owen's view.

By focusing on area 46/9, Owen has assumed that the segregation would be between area 46/9 for spatial working memory versus area 45/47 for visual (object) working memory, as it is in the monkey⁴. However, our results show that spatial working memory activates prefrontal area 8 in the superior frontal sulcus in addition to area 46/9. Activation in this area has been generally ignored^{5,6} because it has been assumed that the activation was within premotor cortex or the frontal eye field. This is not the case, however, as we have recently shown using fMRI that the region that is selectively activated by spatial working memory is in a prefrontal area just anterior to the frontal eye field³. Therefore, the evidence to support domain specificity may come from area 8 playing a predominant role in spatial working memory rather than area 46/9.

The existence of domain specificity is not incompatible with the processing

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