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REVIEW

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The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging

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Abstract Evidence is now converging which suggests that, at the area level, working-memory processes within the dorsolateral and ventrolateral frontal cortices are organised according to the type of processing required, rather than according to the nature (i.e. domain) of the information being processed, as has been widely assumed. In a recent study using functional magnetic-resonance imaging (fMRI), performance of visual spatial and visual non-spatial working-memory tasks was shown to involve identical regions of the lateral prefrontal cortex when all factors unrelated to the type of stimulus material were appropriately controlled. These results concur fully with recent reviews of the imaging literature, which demonstrate that spatial, visuospatial and verbal working-memory studies have produced distributed patterns of overlapping activation foci within these lateral frontal regions. Moreover, two recent positron-emission tomography studies have demonstrated that either, or both, the ventrolateral and dorsolateral frontal regions can be activated in spatial working-memory tasks, depending on the precise executive processes that are called upon by the task being performed. Similarly, when the executive requirements of a simple verbal working-memory task (e.g. forwards versus backwards digit span) are manipulated, differential activation within these two frontal cortical areas is observed. The results provide further evidence that the mid-dorsolateral and mid-ventrolateral frontal cortical areas make distinct "executive" contributions to memory and correspond with a fractionation of working-memory processes in psychological terms.

Key words Dorsolateral · Ventrolateral · PET · fMRI · Working memory

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Introduction

While the importance of the prefrontal cortex for "higher-order" cognitive functions is largely undisputed, no consensus has been reached regarding the fractionation of functions within this region. In fact, although some degree of regional specialisation within the frontal lobe seems inevitable, by and large, most attempts to map specific cognitive functions onto neuroanatomical and/or cytoarchitectonic sub-divisions have been disappointing. Perhaps the most widely and passionately debated issue to have emerged in this field in recent years concerns the functional relationship between the dorsal and ventral regions of the lateral frontal cortex and, more specifically, how the "executive" processes assumed to be dependent upon these regions might contribute to aspects of working memory. The concept of working memory has been described and discussed in various ways; as a cognitive system for both the temporary storage and manipulation of remembered information (e.g. Baddeley 1986), as the type of memory that is active and only relevant for a short period of time (e.g. Fuster 1995; Goldman-Rakic 1995) and, most specifically, as the process by which a remembered stimulus is held "on-line" to guide behaviour in the absence of external cues or prompts (Goldman-Rakic 1987, 1996). In part, this descriptive variability reflects the relative interests of those working with different primate species; psychologists working mainly with humans often emphasise the "organisational" or "higher order" aspects of working-memory tasks, whereas those working with non-human primates tend to focus on those aspects of task performance related to the on-line retention or short-term storage of information. The problem of comparison between species is further compounded by Honig's (1978) definition of working memory as applied invariably in rat studies using Olton's radial-arm maze (Olton 1982), which also emphasises the "organisational" or "executive" component of task performance. This description is consistent with the view that working memory should be considered, more generally, in the context of the temporal organisation of action (e.g. Fuster 1997). Nevertheless, in the absence of a precise definition, few disagree that working memory is a fundamental set of processes and an integral component of many cognitive operations, from complex decision making to selective attention (Baddeley 1986).

The prefrontal cortex, which has been the focus of much recent debate regarding the neural basis of working memory processes, is cytoarchitectonically diverse, both in the human brain and in the macaque brain, and comprises a number of specific areas that have distinct patterns of connectivity with other brain regions. Essentially, two divergent positions have emerged which, whilst focusing on a broadly similar distinction between the anatomically and cytoarchitectonically distinct dorsolateral and ventrolateral frontal cortical regions, differ fundamentally in terms of the precise functions ascribed to those regions. On the basis of lesion and electrophysiological-recording studies in the monkey (e.g. Funahashi et al. 1989; Wilson et al. 1993; Levy and Goldman-Rakic 1999), Goldman-Rakic (1987, 1994, 1995) has argued that working-memory processes within the lateral frontal cortex are organised according to the type (e.g. domain) of information being processed, with dorsolateral frontal regions being principally concerned with memory for spatial material, whilst ventrolateral frontal regions subserve memory for non-spatial material. According to this "domain-specific" or "material-specific" model, "informational domain, not process, will be mapped across prefrontal cortex" (Goldman-Rakic 1994, 1995).

Intuitively, this domain-specific theory has some theoretical appeal since, more posteriorly, extrastriate cortical regions are organised, at least in part, into anatomically distinct pathways, functionally specialised for identifying spatial locations (the occipitoparietal pathway or "dorsal stream") or object features (the occipitotemporal pathway or "ventral stream") (Ungerleider and Mishkin 1982). Whilst these posterior association areas project reciprocally to widespread frontal-lobe regions, a certain degree of topographical order appears to be maintained (Barbas 1988; Cavada and Goldman-Rakic 1989; Bates et al. 1994; Rodman 1994; Webster et al. 1994; Carmichael and Price 1995).

An alternative general theoretical framework for understanding the role played by the prefrontal cortex in mnemonic processing and its relationship to more posterior cortical association systems has been proposed by Petrides (1994), based largely on lesion studies in the monkey. According to that model, basic memory functions, including storage and immediate processing of incoming and recalled information, are carried out not within the frontal lobes, but rather within sensory specific and multimodal posterior association areas in the parietal and temporal cortices. The frontal lobes may, however, receive and act upon this information via bi-directional connections between the posterior cortical association areas and the ventrolateral frontal cortex, which, in turn, is closely connected to the mid-dorsolateral frontal cortex, or via direct connections between dorsal regions of the frontal cortex and the medial temporal lobe. Thus, according to this view, the ventrolateral frontal cortex constitutes the first level of interaction between posterior cortical regions and the entire lateral frontal cortex. In this capacity, this region is assumed to be critical for various "second order" memory processes, such as comparisons between, or judgements about the occurrence or non-occurrence of remembered stimuli and the initiation of explicit (i.e. intentional) retrieval of information from long-term memory. In contrast, the mid-dorsolateral frontal cortex is assumed to provide a third level of processing within memory and is recruited when active manipulation or "monitoring" of remembered information is required. According to this view, therefore, working-memory processes within dorsolateral and ventrolateral frontal regions are organised according to the *nature* of the processing required rather than according to the domain of the information to be remembered (Petrides 1994, 1995).

In this article, these two models of lateral-frontal lobe organisation will be evaluated in the light of recent functional neuroimaging studies of spatial, visual and verbal working memory. While focusing, for the most part, on the delineation and neural instantiation of *working memory* processes, it is assumed that the various operations involved are drawn from a single set of "executive" components, which are likely to contribute equally to many other types of tasks that do not necessarily involve, or depend upon, working memory.

Functional neuroimaging studies of spatial and non-spatial (visual) working memory

Until recently, direct investigation of the functional organisation of working-memory processes within the human brain was limited to comparisons between groups of patients with damage to different cortical and/or subcortical regions (e.g. Petrides and Milner 1982; Owen et al. 1990, 1995, 1996b). In patient studies, it is not possible to establish which areas of the frontal cortex are involved in a given cognitive process with any degree of anatomical precision, since the excisions are rarely confined to specific cytoarchitectonic areas. In recent years, however, functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have provided a unique opportunity for assessing the relationship between patterns of cortical and subcortical activation and different aspects of cognitive processing in healthy control volunteers.

Although many recent neuroimaging studies have investigated various components of mnemonic processing, relatively few have attempted to neuroanatomically delineate specific aspects of working-memory processing within the frontal lobe. One approach to this problem is to draw careful comparisons among groups of related studies in order to determine whether consistent patterns of activation occur in association with various types of memory task. Since most functional neuroimaging stud-

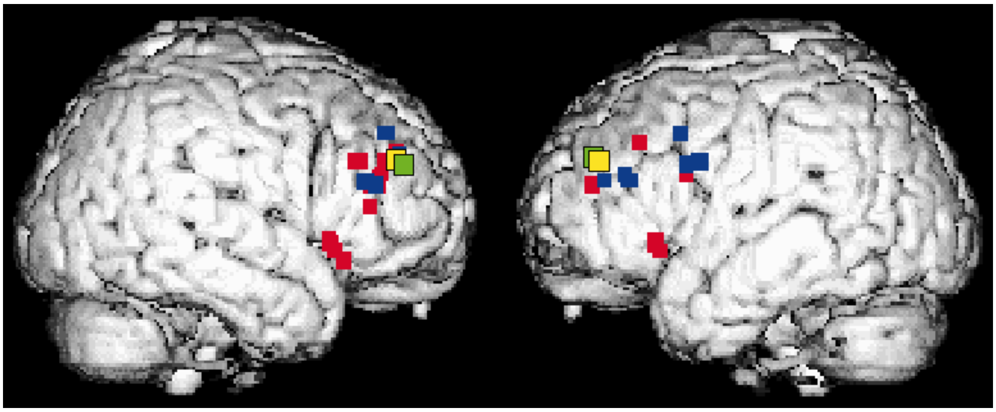


Fig. 1 A schematic diagram illustrating the distribution of activation foci reported in the studies of spatial and non-spatial (visual) working memory (for details, see text). All data have been transformed into standardised sterotaxic space and rendered onto the surface of a three-dimensional magnetic-resonance image. All foci falling within the mid-dorsolateral (areas 9/46, 46, 9) and mid-ventrolateral (44/45, 47) frontal cortices are shown. Activation foci from spatial working-memory tasks are shown in *red*. Activation foci from non-spatial working-memory tasks are shown in *blue*. The *yellow* and *green squares* indicate the precise stereotaxic co-ordinates of the peaks observed during the analogous spatial and visual working-memory tasks, respectively, employed by Owen et al. (1998) (see text)

ies have used the common stereotaxic co-ordinate system based on the three-dimensional atlas of Talairach and Tournoux (1988), direct comparisons across studies are possible. In one recent review of the literature (Owen 1997; Fig. 1), the stereotaxic co-ordinates of activation foci reported within the dorsolateral and ventrolateral frontal cortices during fourteen spatial working-memory tasks (from Jonides et al. 1993; McCarthy et al. 1994, 1996; Smith et al. 1995, 1996; Baker et al. 1996; Goldberg et al. 1996; Owen et al. 1996a, 1998) were compared with those observed during six non-spatial (visual) working-memory tasks (Petrides et al. 1993a; Smith et al. 1995; Baker et al. 1996; Courtney et al. 1996; McCarthy et al. 1996; Owen et al. 1998). The two models of lateral frontal organisation described above make clearly divergent predictions about the likely role in working memory of the dorsolateral and ventrolateral frontal cortical regions. According to the domain-specific model (Goldman-Rakic 1994, 1995), one might expect the results of functional neuroimaging studies to demonstrate that spatial and non-spatial working-memory studies activate distinctly different lateral frontal-lobe regions with a reasonable level of consistency. Examination of the data presented in Fig. 1 suggests that this is not the case. For example, overlapping activation foci within area 9/46 of the mid-dorsolateral frontal cortex have been frequently reported in studies of both spatial and non-spatial (visual) working memory. In fact, across spatial working-memory studies, the mean stereotaxic z-coordinates (inferior-to-superior) for the activation foci falling within areas 9 and 46 are +29 mm (left hemisphere) and +24 mm (right hemisphere). For non-spatial tasks, the corresponding values are +28 mm and +28 mm (for details, see Owen 1997). This simplistic analysis, which takes no account of task-related differences between studies, does demonstrate just how similar the activation foci generated by studies of spatial and non-spatial working memory are; if anything, the trend in the right hemisphere is in the opposite direction of that which would be predicted by the domain-specific hypothesis of lateral frontal organisation.

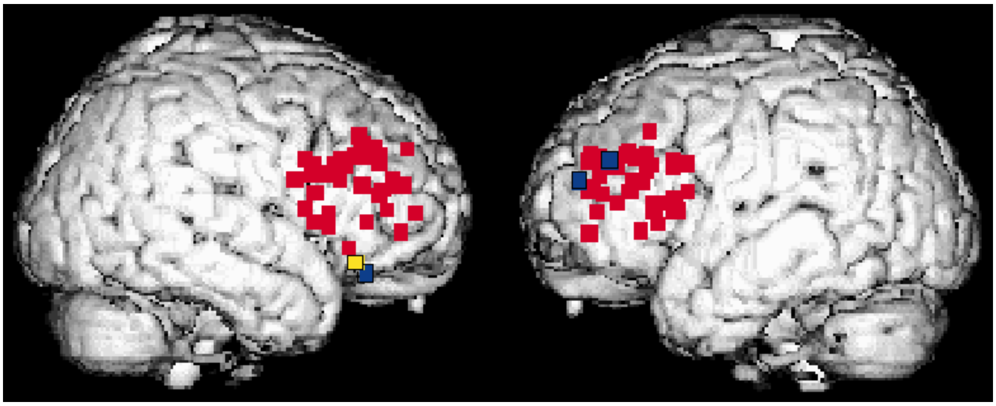
One logistic problem in comparing the results of unrelated studies is that the tasks used often differ both in terms of their mnemonic (e.g. processing) requirements and in terms of the nature of the material to be remembered (e.g. domain; spatial or non-spatial). In a few cases, however, formally identical spatial and non-spatial working-memory tasks have been used within the same study, and the results of these investigations probably provide the least ambiguous material addressing this issue. For example, we recently used fMRI to compare two experimental tasks that had similar processing requirements (the ability to monitor and manipulate an ongoing series of stimuli within working memory), but differed in the type of stimuli to be remembered (locations versus patterns) (Owen et al. 1998). The first task (spatial working memory) required that subjects continually monitor a sequence of highlighted locations on the screen, responding after each stimulus by selecting the location that was highlighted two steps earlier in the sequence. In a control condition, which required no memory, subjects followed a similar sequence, but responded by touching each location as it was highlighted. In the second task (visual pattern working memory), the same subjects were required to monitor a series of visual patterns presented in one location on the screen, responding after each stimulus by selecting the pattern that was presented one-step earlier in the sequence. In the control condition, which required no memory, each item in a similar series of visual patterns was identical, and subjects responded on each trial by touching the same pattern. Both experimental tasks have the same mnemonic requirements, the only difference being that one required memory for location and the other required memory for abstract patterns with location being irrelevant. Moreover, the two tasks were very closely matched in terms of task difficulty, since within-subject performance measures were statistically indistinguishable. When activity in the spatial working-memory task was compared with that in the spatial control condition, significant increases in signal intensity were observed bilaterally in the mid-dorsolateral frontal cortex in five of the six subjects. In the sixth subject, this change only reached significance in the right hemisphere. The group mean stereotaxic co-ordinates of these activation foci were x=–38, y=42, z=30 (left hemisphere) and x=35, y=44, z=33 (right hemisphere). The pattern of frontal signal-intensity changes observed when the non-spatial working-memory task was compared with the non-spatial control task was almost identical. Thus, significantly increased signal intensity was observed bilaterally in the mid-dorsolateral cortex in five of the six subjects studied and only in the right mid-dorsolateral frontal region in the sixth subject (group mean coordinates; x=–39, y=44, z=32 for the left and x=34, y=45, z=32 for the right). These findings clearly suggest that the mid-dorsolateral frontal region will be activated when subjects have to monitor and manipulate information within working memory, regardless of the domain-specific nature of that information (in this case, spatial or non-spatial). For comparison with the results of previous studies, the group mean stereotaxic co-ordinates reported in that study (Owen et al. 1998) are also plotted in Fig. 1. For both tasks, the peak regional cerebral blood flow (rCBF) changes within the mid-dorsolateral frontal cortex fall within the cluster of activation foci that have been reported in previous studies of spatial and visual working memory. A similar pattern of results has been reported recently by Postle et al. (2000); in that study, equivalent spatial and non-spatial visual working-memory tasks failed to yield dissociable patterns of activation within the prefrontal cortex, although material-specific activation foci were observed in posterior association cortex.

It might be argued that the "visual" working-memory tasks included in the studies described above (Owen et al. 1998; Postle et al. 2000) involve processes that could be considered to be "spatial" in nature and that it is the neural correlates of these processes that emerge as activation foci in the mid-dorsolateral frontal region. However, three observations argue against this hypothesis. First, as in most studies of this type, the non-mnemonic control tasks employed involve the same amount of "spatial information" as the working-memory task of interest; it is reasonable to assume, therefore, that the effects of this variable on CBF would be "subtracted out" when comparisons are made between the two tasks. Second, many working-memory tasks with more explicit spatial components do not activate areas 9/46 of the mid-dorsolateral frontal cortex (Jonides et al. 1993; Smith et al. 1995; Owen et al. 1996a). Third, several recent studies have demonstrated that certain verbal working-memory paradigms also activate similar regions of the mid-dorsolateral frontal cortex (e.g. Cohen et al. 1994; Braver et al. 1997; Smith et al. 1996), even in conditions that involved no visuospatial stimulation at all (e.g. Petrides et al. 1993b).

Functional neuroimaging studies of verbal working memory

Many recent functional neuroimaging studies of working memory have employed verbal stimuli, such as numbers or letters (presented either visually or auditorily), and provide additional material for assessing models of lateral frontal organisation in humans. In one recent review, the stereotaxic co-ordinates of activation foci reported within the dorsolateral and ventrolateral frontal cortices during 27 verbal working-memory studies (Grasby et al. 1993, 1994; Paulesu et al. 1993; Petrides et al. 1993b; Becker et al. 1994; Cohen et al. 1994, 1997; Andreasen et al. 1995; Awh et al. 1996; Coull et al. 1996; Fiez et al.

Fig. 2 A schematic diagram illustrating the distribution of activation foci reported in studies of verbal working memory (for details, see text). All data have been transformed into standardised sterotaxic space and rendered onto the surface of a three-dimensional magnetic-resonance image. All foci falling within the mid-dorsolateral (areas 9/46, 46, 9) and mid-ventrolateral (44/45, 47) frontal cortices are shown. Activation foci from verbal working-memory tasks are shown in *red*. The *yellow* and *blue squares* indicate the precise stereotaxic co-ordinates of the peaks observed during the forwards and backwards digit-span task described in the text, respectively (Owen et al. 2000)



1996; Salmon et al. 1996; Schumacher et al. 1996; Smith et al. 1996; Braver et al. 1997; Jonides et al. 1997, 1998; D'Esposito et al. 1998, 1998; Goldberg et al. 1998; de Zubicaray et al. 1998; Callicot et al. 1999; Collette et al. 1999; Rypma et al. 1999; Barch et al. 1997; Van der Linden et al. 1999) were compared (Owen et al. 2000). Like studies of spatial and visual working memory, a widely distributed pattern of activation foci across both dorsal and ventral frontal areas was observed (Fig. 2). One contributory factor is undoubtedly that the tasks used in different studies vary widely in terms of their specific mnemonic (e.g. processing) requirements. However, it is clear from Fig. 2 that these studies offer no evidence to suggest that, at the area level at least, the lateral frontal cortex is topographically organised according to the nature of the material being processed. In fact, given the considerable overlap between activation foci reported in Fig. 2 and those observed in studies of spatial and non-spatial visual working memory (Fig. 1), it is clear that, in humans, the dorsolateral and ventrolateral frontal regions are broadly polymodal and may each be activated by a variety of tasks involving stimuli of different domains.

Levels of executive processing within the lateral frontal cortex

The "process-specific" model of lateral frontal-lobe organisation 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 (Petrides 1994, 1995). Since this model allows for polymodal representation of information *within* these two frontal regions, its predictions concur fully with the fact that certain spatial, visual and verbal working-memory tasks consistently activate a similar region of the mid-dorsolateral frontal cortex (Figs. 1 and 2). However, one central requirement of this model is that, within a given domain (i.e. spatial or non-spatial), the mid-dorsolateral and mid-ventrolateral prefrontal cortical regions can be shown to play distinct functional roles in working memory. Examination of the studies represented in Fig. 1 offers some, albeit tentative, evidence that this may indeed be the case. Thus, in general, the spatial working-memory tasks that have produced activation foci in mid-ventrolateral area 47 tend to emphasise the active retrieval of one, or a few, pieces of information and the sequencing of responses based directly on that stored information. For example, in the studies by Jonides and colleagues (Jonides et al. 1993; Smith et al. 1995, 1996), the subjects were simply required to remember the location of three simultaneously presented stimuli and then to decide whether or not a probe circle occupied one of those same three locations following a 3-s delay.

In contrast, the spatial working-memory tasks producing increases in rCBF more dorsally, in areas 9 and 46, are often more complex and require additional processing within memory. For example, several studies have used tasks that require the subject to "monitor" or "manipulate" an on-going series of spatial locations within working memory and to make comparisons between each new stimulus and stimuli presented earlier in the sequence (e.g. McCarthy et al. 1994, 1996; Owen et al. 1996a; Smith et al. 1996; for a further description, see Owen 1997). McCarthy et al. (1994, 1996) used functional MRI to measure changes in rCBF while subjects judged whether each of a series of 14 or 15 stimuli was located in a position that had already been occupied earlier in the sequence. The key feature of such tasks appears to be that the response required following each stimulus is invariably not specified directly by that stimulus, but rather has to be computed by comparing that stimulus with information assimilated earlier in the trial (e.g. from previous stimuli).

Similar properties characterise many of the non-spatial working-memory tasks that have been shown to activate the mid-dorsolateral frontal cortex (Fig. 1). In the visual domain, for example, Petrides et al. (1993b) presented subjects with a series of cards, each containing the same eight abstract designs in random positions. The subjects had to select a different design from each card until all eight designs had been selected. Clearly, this type of task requires that the subject constantly monitors an on-going series of visual stimuli within working memory and makes comparisons between each new stimulus and stimuli presented earlier in the sequence. Compared with a control condition, which made minimal demands on working memory, significant increases in rCBF were observed, bilaterally, in the mid-dorsolateral frontal cortex (areas 9/46). Similar findings have been reported in the verbal working-memory literature when conceptually similar tasks are employed. For example, in one parametric fMRI study using letter stimuli, a significant relationship was observed between dorsolateral prefrontal activity and "memory load", which was varied using the widely employed "n-back" paradigm (Braver et al. 1997). This task again requires that subjects maintain and continually update an on-going record of recent stimuli, generating each response by comparing the most recent stimulus with stimuli assimilated earlier in the sequence.

In an attempt to investigate the role of dorsolateral and ventrolateral frontal regions directly, we have recently conducted a series of studies using PET and fMRI, employing spatial, visual and verbal stimuli in tasks that make differing demands on various aspects of executive processing (Owen et al. 1996a, 1999, 2000; Stern et al. 2000). For example, one hypothesis tested was that frontal activation would be confined to the mid-ventrolateral region of the frontal cortex when the experimental task required the subject to hold a sequence of five previously presented spatial locations in memory and, then, to respond directly by touching those same locations following a delay (Owen et al. 1996a, 1999). Thus, the emphasis of the task was on the short-term retention of spatial information; no manipulation of, or computation based

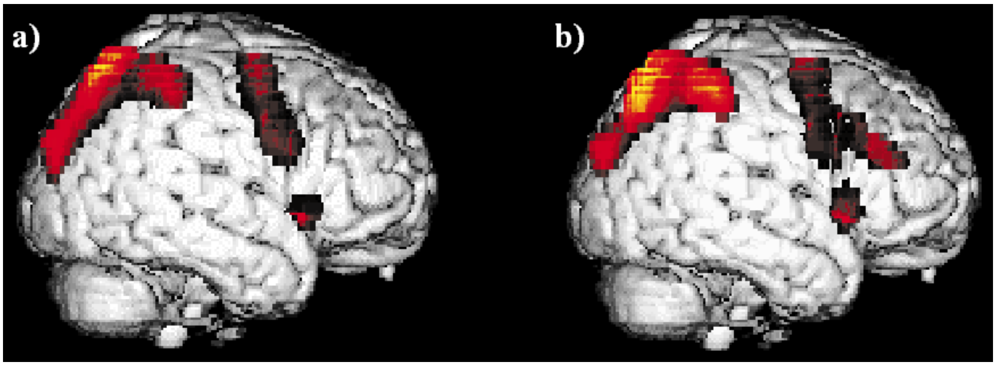


Fig. 3a, b Schematic illustration of the averaged positron-emission-tomography subtraction images rendered onto the surface of a standard three-dimensional magnetic-resonance image. **a** Spatial span minus visuomotor control. Within the prefrontal cortex, a significant regional cerebral-blood-flow (rCBF) change is evident within mid-ventrolateral area 47. **b** Spatial manipulation minus visuomotor control. Within the prefrontal cortex, significant rCBF changes are evident within mid-ventrolateral area 47 and, in addition, within mid-dorsolateral areas 9 and 9/46. The two working-memory conditions differ only with respect to rCBF changes in the mid-dorsolateral frontal cortex (areas 9 and 9/46)

on, this information was necessary. During this variation on the spatial block-tapping test (or "spatial span") of Corsi (see Milner 1971), a significant rCBF increase was observed in ventrolateral area 47 of the right hemisphere at stereotaxic coordinates almost identical to those reported in the studies by Jonides et al. (1993) and Smith et al. (1995, 1996), described above. Similarly, in a second task that required the subjects to execute a fixed sequence of responses to eight previously learned locations, ventrolateral frontal area 47 was significantly activated, bilaterally (Owen et al. 1996a), relative to the same control condition. During both tasks, however, rCBF changes within the dorsolateral frontal region did not approach significance. The second general hypothesis tested was whether there would be significant activation within the mid-dorsolateral frontal cortex (i.e. areas 9 and 46) when the demands of the task were changed to increase the on-going manipulation of information required within working memory. For example, in two tasks, the subject was required to remember which of a set of previously selected locations had been "marked" with a blue circle and to avoid re-selecting those particular locations. Thus, success depended on the ability to maintain, and continually update, an on-line record of which particular locations had been "marked" and, in this sense, the task is conceptually similar to those used by McCarthy et al. (1994) and Petrides et al. (1993b). When the two tasks were compared to a visuomotor control condition, highly significant activation foci were observed in the mid-dorsolateral frontal cortex (area 46/9) of the right hemisphere as well as bilaterally in ventrolateral area 47 (Owen et al. 1996a).

In a follow-up PET study, the five-item spatial span task was used again, but compared with a variation on the widely used spatial "two-back" procedure (Owen et al. 1999). In that task, the subjects were required to monitor a sequence of colour-changing circles on the screen, responding immediately after each stimulus by selecting the circle that changed colour two steps earlier in the sequence. Thus, on each "trial" of the on-going sequence, one of the five red circles was randomly selected by the computer and momentarily changed colour to blue and then back again to red, indicating that it was the next in the series to be remembered. The subject responded immediately not by touching the circle just indicated, but by touching the one two steps earlier in the sequence (i.e. n–2 or "two-back"). Following a fixed delay of 500 ms, the next circle in the sequence changed colour and so on for the entire period of the scan. In the third scanning condition, a matched visuomotor control task, five red circles were again presented in random locations on the screen. On each trial, one of the red circles changed colour to blue and the subject responded immediately by touching that circle and so on. Pilot testing and behavioural results during the scan revealed that, in order to equate the two working-memory tasks for level of difficulty, the parameters should be set to a sequence of five stimuli for the spatial span task and "n–2" for the spatial manipulation task. This provision also ensured that the time between the presentation of a stimulus and the subjects' response *to that stimulus* (e.g. the actual memory time) was identical for the two tasks (for details, see Owen et al. 1999). Moreover, this experimental design ensured that the amount of information that had to be remembered and retrieved during the scan was equivalent for the two working-memory tasks.

As predicted, during the spatial span task, which simply required active (i.e. conscious) retrieval and reproduction of stored information, a significant rCBF increase was observed in the mid-ventrolateral prefrontal cortex at co-ordinates very similar to those reported previous by Owen et al. (1996a) (Fig. 3). In contrast, both the mid-ventrolateral and the mid-dorsolateral prefrontal regions were significantly activated during the two-back task, which required "on-line" manipulation of information within working memory. Moreover, when the spatial span task was subtracted from the spatial manipulation task, the only surviving rCBF difference was located in the mid-dorsolateral prefrontal cortex

Taken together, the results of these two PET studies clearly suggest that, in human subjects, both dorsolateral and ventrolateral frontal cortical areas can be activated by spatial working-memory tasks. Moreover, whether one or both of these regions is recruited appears to depend on the precise cognitive processes that are called upon by the particular task being performed.

In a recent study using fMRI, Courtney et al. (1998) showed that sustained activity during a task that required memory for three locations was observed in the caudal most part of the superior frontal sulcus, immediately anterior to the area defined as the frontal eye field on the basis of activity observed during an occulomotor task. According to a recent cytoarchitectonic analysis of this region (Petrides and Pandya 1994), this peak is located within area 8 [Note that, in both the monkey and in the human brain, the physiologically defined frontal eye field does not correspond to area 8 proper, but rather to the border between area 8 and rostral area 6 (Stanton et al. 1989; Paus 1996)]. A peak in the same location has been reported in previous studies of spatial working memory (e.g. Jonides et al. 1993; Owen et al. 1996a) as well as in studies of spatial attention (e.g. Corbetta et al. 1993; Nobre et al. 1997). A similar peak was also observed in the study described above (Owen et al. 1999) when the visuomotor control task was subtracted from either the spatial span task or the spatial manipulation task. However, as noted in that study, when the spatial span task was subtracted from the spatial manipulation task, there was *no* difference in this region, the only surviving rCBF difference being in the more anteriorly located mid-dorsolateral prefrontal cortex. Given these results, it is now clear that the activation observed in the mid-dorsolateral prefrontal cortex during these tasks is related to the monitoring and manipulation of information within working memory, whereas the peak observed in the posterior dorsolateral cortex (area 8) in this study and in previous studies (e.g. Jonides et al. 1993; Owen et al. 1996a; Courtney et al. 1998) is more likely related to the maintenance of visuospatial attention to the cued locations during the delay period of working memory tasks. Such an interpretation would be entirely consistent with the fact that area 8 is anatomically linked to prestriate visual areas (Barbas and Mesulam 1981). Thus, the mid-ventrolateral, mid-dorsolateral and the posterior dorsolateral prefrontal regions may all be involved in spatial working-memory tasks, but for entirely different reasons.

In a more recent PET study, a direct analogue of the spatial span task was employed to investigate whether these findings could be extended to the verbal domain (Owen et al. 2000). During one experimental task, subjects were required to hold a sequence of five auditorily presented numbers in memory (e.g. 7, 3, 8, 2, 9) and then to respond by (verbally) producing those numbers, in order, following a short delay (e.g. 7, 3, 8, 2, 9). Since the emphasis of this verbal working-memory task was on the active (i.e. conscious) retrieval of remembered information and not on the manipulation of that information, it was predicted that the mid-ventrolateral, but not the mid-dorsolateral prefrontal cortex would be activated. During the second experimental task, the subject was required to listen to similar sequences of numbers, reproducing each sequence *in reverse order* following a short delay (e.g. 9, 2, 8, 3, 7). Since, like the forward digit span task, this task involved the continuous retrieval of information from working memory, it was predicted that the mid-ventrolateral prefrontal cortex would be similarly activated during the two conditions. In addition, however, the backward digit span task places significant demands on the manipulation of the information within working memory; thus, the task requires that the remembered information is re-ordered in order to programme the appropriate sequence of responses. On this basis, the backward digit task was expected to activate, additionally, the mid-dorsolateral prefrontal region. In a third “control” condition, each trial involved an identical digit string, (e.g. 1, 1, 1, 1, 1) and subjects were required to respond by repeating the sequence. In all three conditions, stimuli were presented at a rate of one digit per second with a 6-s intertrial interval (during which time the subject responded). To control for the non-specific effects of task difficulty, each subject underwent a pilot testing session prior to scanning in order to determine their individual forwards and backwards digit spans. During scanning, the number of digits presented in the two experimental conditions was set according to the maximum number of digits that could be recalled accurately in three successive trials.

As predicted, when the forward digits span task was compared to the control, significant activation was observed in right mid-ventrolateral area 47 at co-ordinates slightly anterior to those reported previously in studies of spatial span (Owen et al. 1996a, 1999; see also Jonides et al. 1993). For comparison with previous studies of verbal working memory, the location of this activation focus is represented schematically in Fig. 2. No significant blood-flow changes were observed in the mid-dorsolateral frontal region. In contrast, when the backward digits condition was compared with the control task, significant increases in rCBF were observed in a similar region of the right mid-ventrolateral frontal cortex (area 47) and, in addition, in the left mid-dorsolateral frontal cortex (area 9/46). For comparison with previous studies of verbal working memory, the location of this activation focus is represented schematically in Fig. 2. When the two verbal working-memory tasks were compared directly (backwards minus forwards), only one significant rCBF change emerged, in areas 9 and 9/46 of the mid-dorsolateral frontal cortex (Fig. 2). This focus was located within the left hemisphere, at stereotaxic coordinates almost identical to those observed in the right hemisphere, during tasks which required manipulation of information within *spatial* working memory (Fig. 3; also see Owen et al. 1999). The reverse subtraction yielded no significant rCBF changes within the entire grey-matter volume.

Discussion

It appears, therefore, that the weight of evidence from neuroimaging studies in humans favours the hypothesis that, at the area level at least, the lateral frontal cortex is topographically organised according to the nature of the process being carried out, rather than according to the nature of the material being processed, as previously thought (Wilson et al. 1993; Goldman-Rakic 1995; Courtney et al. 1998; also see Courtney et al. 1996, 1997). However, it is important to emphasise that the findings discussed here do not rule out the possibility that some functional differentiation based on stimulus material might still exist *within* these particular frontal cortical regions. For example, it is plausible that the functional neuroimaging methods used in the studies described in this review have sufficient spatial resolution to detect differences *between*, but not *within* these anatomical regions. Certainly among the mid-dorsolateral activation foci reported in Figs. 1 and 2, there is considerable overlap between studies of spatial, non-spatial and verbal working memory in all three planes (x, y, z). In the ventrolateral cortex, however, there does appear to be some reasonably consistent evidence for differences between those studies that have used spatial stimuli and those that have used non-spatial stimuli in the anterior-posterior (y) plane. Thus, the spatial working-memory tasks used by Jonides et al. (1993), Owen et al. (1996a, 1999) and Smith et al. (1995) all yielded rather posterior ventrolateral activation foci at y co-ordinates of between 14 mm and 24 mm. In two non-spatial studies that employed face stimuli, ventrolateral activation foci were reported rather more anteriorly at y co-ordinates of between 33 mm and 40 mm (Haxby et al. 1995; Courtney et al. 1996). In the verbal working-memory study described in detail above (Owen et al. 2000), ventrolateral activation foci were also observed rather more anteriorly (y=30 and y=34) than those reported in spatial working-memory studies that employed analogous tasks (e.g. Owen et al. 1996a, 1999). Nevertheless, even if such subtle differences in activation were to be confirmed in later studies, they would still not be evidence supporting a functional separation between the anatomically and cytoarchitectonically distinct dorsolateral and ventrolateral frontal-lobe regions that are the focus of this review. Moreover, this general pattern of overlapping activation foci concurs fully with the results of a recent electrophysiological recording study in the monkey designed to investigate where and how information about object-identity is integrated with information about object-location in working memory (Rao et al. 1997). In that study, approximately half of the neurones with delay-related activity were tuned both to visual pattern (“what”) and location (“where”). Furthermore, neurones that were tuned only to location or only to visual pattern were equally distributed between the dorsolateral and the ventrolateral prefrontal cortex, neurones tuned to location not being predominant in the dorsolateral prefrontal cortex (Rao et al. 1997; for a further discussion, see Rushworth and Owen 1998).

Finally, recent findings suggest that further insights about the role of human prefrontal cortex in working memory are likely to emerge from comparisons with studies of other types of task assumed to be similarly dependent on the frontal lobe, such as those requiring episodic memory. For example, Fletcher et al. (1998b) reported activation in the mid-ventrolateral frontal cortex during a paired-associates task that required subjects to retrieve previously learned category exemplars in response to a series of category names. In contrast, during a second condition that required subjects to freely recall items from a previously learned list, activation in the mid-dorsolateral frontal cortex was observed (Fletcher et al. 1998b). This dissociation within the frontal-lobes is almost identical to that described above for two types of spatial *working*-memory task (Owen et al. 1999), raising the general issue of developing a theory which is sufficiently comprehensive to incorporate the main findings from ostensibly different types of mnemonic task, but which remains emancipated from a strict localisationalist perspective. In this respect, a fruitful approach may be to assume that the various processes involved in working memory, episodic memory encoding and retrieval, and other “executive” functions not discussed here are drawn from a single set of underlying components, although they may be differentially represented in different tasks. Thus, a general role for the ventrolateral frontal cortex in memory may be to trigger active low-level encoding strategies, such as rehearsal, and to initiate explicit (i.e. intentional) retrieval of information from long-term memory. In the case of working-memory tasks, this would correspond to the relatively straightforward mapping of stimuli to responses, such as that which is assumed to occur in spatial and digit span tasks (e.g. Owen et al. 1996a, 1999) or even simple delayed matching-to-sample paradigms (e.g. Elliott and Dolan 1999). In the case of long-term episodic memory (e.g. verbal paired associate learning), these “active” encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g. a category exemplar) to a specific stimulus (e.g. a category name) (e.g. Fletcher et al. 1998a, 1998b). Indeed, a number of recent episodic-memory tasks that have produced predominantly ventral frontal activation have involved fairly “low-level” mnemonic processes, such as face encoding (Haxby et al. 1996), word-pair encoding (Kapur et al. 1996), short-term word recognition (Andreasen et al. 1995), face recognition (Haxby et al. 1996) and learned picture recognition (Kapur et al. 1995).

In contrast, the mid-dorsolateral frontal cortex may mediate more complex types of processing within memory and will be recruited when active manipulation or “monitoring” of remembered information is required. For example, in the self-ordered spatial working-memory tasks that are sensitive to frontal-lobe damage (Owen et al. 1990, 1996b) and activate both dorsal and ventral frontal-lobe areas (Owen et al. 1996a), an encoding strategy for determining the optimal sequence of choices is required that must be constantly updated or “monitored” during its execution (for a further discussion, see Owen et al. 1996b). Similarly, one key component of the free recall task described by Fletcher et al. (1998b), which activated the dorsolateral frontal cortex, is that each response cannot be made in isolation, but rather can only be made by “monitoring” responses made and information assimilated earlier in each trial. For example, the subject knows, in this case, that there are a specific number of items to be recalled and has to check with each new item produced that it has not been produced before. In general, widespread activation of both ventral and dorsal frontal-lobe areas has been reported during complex episodic memory tasks, such as encoding of temporal order (Cabeza et al. 1997), encoding new associations between nouns and categories (Dolan and Fletcher 1997), word-list encoding with “maximal organisation” (Fletcher et al. 1998a), long-term word recognition (Andreasen 1995), cued recall (Buckner et al. 1995, 1996; Petrides et al. 1995; Cabeza et al. 1997; Fletcher et al. 1998b) and free recall (Petrides et al. 1995).

It would be na, of course, to assume that it will be possible to recast the results of all previous studies of working memory and episodic memory in this light and a systematic re-analysis has not be attempted here. In addition, while this review has focused specifically on the role that various frontal-lobe regions may play in *mnemonic* processing, it is quite clear that a more comprehensive understanding of lateral frontal-lobe organisation will only be achieved by stepping beyond the realm of memory function. For example, similar frontal-lobe regions are widely assumed to contribute to many other aspects of “executive control” that do not directly involve or depend upon working memory; high-level attentional set-shifting behaviour and active inhibition of prepotent responses, being just two examples. Whether such processes can be adequately incorporated within the two-stage conceptual framework suggested by the data reviewed here, will remain a significant challenge for the future.

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References

Andreasen NC, O’Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, Watkins GL, Boles Ponto LL, Hichwa RD (1995) Short-term and long-term verbal memory: a positron emission tomography study. Proc Natl Acad Sci USA 92:5111–5115

Awh E, Jonides J, Smith EE, Schumacher EH, Koeppe RA, Katz S (1996) Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. Psychol Sci 7:25–31

Baddeley AD (1986) Working memory. Oxford University Press, New York

Baker SC, Frith CD, Frackowiak RSJ, Dolan RJ (1996) Active representation of shape and location in man. Cereb Cortex 6:612–619

Barbas H (1988) Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. J Comp Neurol 276:313–342

Barbas H, Mesulam M-M (1981) Organization of afferent input to subdivision of area 8 in the rhesus monkey. J Comp Neurol 200:407–431

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD (1997) Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 35:1373–1380

Bates JF, Wilson FAW, O Scalaidhe SP, Goldman-Rakic PS (1994) Area TE connections with inferior prefrontal regions responsive to complex objects and faces. Soc Neurosci Abstr 20: 434.10

Becker JT, Mintun MA, Diehl DJ, Dobkin J, Martidis A, Madoff DC, DeKosky ST (1994) Functional neuroanatomy of verbal free recall: a replication study. Hum Brain Map 1:284–292

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC (1997) A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5:49–62

Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME (1995) Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci 15:12–29

Buckner RL, Raichle ME, Miezin FM, Petersen SE (1996) Functional anatomic studies of memory retrieval for auditory words and visual pictures. J Neurosci 16:6219–6235

Cabeza R, Mangels J, Nyberg L, Habib R, Houle S, Mcintosh AR, Tulving E (1997) Brain regions differentially involved in remembering what and when: a PET study. Neuron 19:863–870

Callicot JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, Goldberg TE, Weinberger DR (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 9:20–26

Carmichael ST, Price JL (1995) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol 363:642–664

Cavada C, Goldman-Rakic PS (1989) Posterior parietal cortex on rhesus monkey. II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. J Comp Neurol 287:422–445

Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC (1994) Activation of prefrontal cortex in a non-spatial working memory task with functional MRI. Hum Brain Map 1:293–304

Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith, EE (1997) Temporal dynamics of brain activation during a working memory task. Nature 386:604–608

Collette F, Salmon E, Van der Linden M, Chicherio C, Belleville S, Degueldre C, Delfiore G, Franck G (1999) Regional brain activity during tasks devoted to the central executive of working memory. Brain Res Cogn Brain Res 7:411–417

Corbetta M, Miezin FM, Shulman GL, Petersen SE (1993) A PET study of visuospatial attention. J Neurosci 13:1202–1226

Coull JT, Frith CD, Frackowiak RSJ, Grasby PM (1996) A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34:1085–1095

Courtney SM, Ungerlieder LG, Keil K, Haxby JV (1996) Object and spatial visual working memory activate separate neural systems in human cortex. Cereb Cortex 6:39–49

Courtney SM, Ungerleider LG, Kell KK, Haxby JV (1997) Transient and sustained activity in a distributed system for human working memory. Nature 386:608–611

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. Science 279:1347–1351

D’Esposito M, Ballard D, Aguirre GK, Zarahn E (1998) Human prefrontal cortex is not specific for working memory: a functional MRI study. Neuroimage 8:274–282

D’Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J, Tang J (1998) Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 7:1–13

Dolan RJ, Fletcher PC (1997) Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 388: 582–585

Elliot R, Dolan RJ (1999) Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. J Neurosci 19:5066–5073

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE (1996) A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci 16:808–822

Fletcher P, Shallice T, Dolan RJ (1998a) The functional roles of prefrontal cortex in episodic memory. I. Encoding. Brain 121: 1239–1248

Fletcher P, Shallice T, Frith CD, Frackowiak RSJ, Dolan RJ (1998b) The functional roles of prefrontal cortex in episodic memory. II Retrieval. Brain 121:1249–1256

Funahashi S, Bruce CJ, Goldman-Rakic PS (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 61:1–19

Fuster JM (1995) Memory in the cerebral cortex: an empirical approach to neural networks in the human and nonhuman primate brain. MIT press, Cambridge

Fuster JM (1997) The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe, 3rd edn. Lippincott-Raven, Philadelphia

Goldberg TE, Berman KF, Randolph C, Gold JM, Weinberger DR (1996) Isolating the mnemonic component in spatial delayed response: a controlled PET ^{15}O-labeled water regional cerebral blood flow study in normal humans. Neuroimage 3:69–78

Goldberg TE, Berman KF, Fleming K, Ostrem J, Van Horn JD, Esposito G, Mattey VS, Gold JM, Weinberger DR (1998) Uncoupling cognitive workload and prefrontal cortical physiology: A PET rCBF study. Neuroimage 7:296–303

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and the regulation of behavior by representational memory. In: Plum F, Mountcastle V (eds) Handbook of physiology. Section 1, the nervous system, Vol 5. American Physiological Society, Bethesda, pp 373–417

Goldman-Rakic PS (1994) The issue of memory in the study of prefrontal functions. In: Thierry AM, Glowinski J, Goldman-Rakic PS, Christen Y (eds) Motor and cognitive functions of the prefrontal cortex. Springer, Berlin Heidelberg New York, pp 112–122

Goldman-Rakic PS (1995) Architecture of the prefrontal cortex and the central executive. Ann NY Acad Sci 769:71–83

Goldman-Rakic PS (1996) The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philos Trans R Soc Lond 351:1445–1453

Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ (1993) Functional mapping of brain areas implicated in auditory-verbal memory function. Brain 116:1–20

Grasby PM, Frith CD, Friston KJ, Simpson J, Fletcher PC, Frackowiak RSJ, Dolan RJ (1994) A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. Brain 117:1271–1282

Haxby JV, Ungerleider LG, Horwitz B, Rapoport SI, Grady CL (1995) Hemispheric differences in neural systems for face working memory: a PET-rCBF study. Hum Brain Map 3:68–82

Haxby JV, Ungerleider LG, Horwitz B, Maisog JM, Rapoport SI, Grady CL (1996) Face encoding and recognition in the human brain. Proc Natl Acad Sci USA 93:922–927

Honig WK (1978) Studies of working memory in the pigeon. In: Hulse SH, Fowler H, Honig WK (eds) Cognitive processes in animal behaviour. Lawrence Erlbaum, Hillsdale, pp 211–248

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA (1993) Spatial working memory in humans as revealed by PET. Nature 363:623–625

Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S, Koeppe RA (1997) Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 9:462–475

Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, Marshuetz C, Willis CR (1998) The role of parietal cortex in verbal working memory. J Neurosci 18: 5026–5034

Kapur N, Friston KH, Young A, Frith CD, Frackowiak RSJ (1995) Functional role of the prefrontal cortex in memory retrieval: a PET study. Cortex 31:99–108

Kapur S, Tulving E, Cabeza R, Mcintosh AR, Houle S, Craik FIM (1996) The neural correlates of intentional learning of verbal materials: a PET study. Brain Res Cogn Brain Res 4:243–249

Levy R, Goldman-Rakic PS (1999) Association of storage and processing functions in the dorsolateral prefrontal cortex of the non-human primate. J Neurosci 19:5149–5158

McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder F, Goldman-Rakic P, Shulman RG (1994) Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. Proc Natl Acad Sci USA 91:8690–8694

McCarthy G, Puce A, Constable RT, Krystal JH, Gore JC, Goldman-Rakic PS (1996) Activation of human prefrontal cortex activation during spatial and non-spatial working memory tasks measured by functional MRI. Cereb Cortex 6:600–611

Milner B (1971) Interhemispheric differences in the localisation of psychological processes in man. Br Med Bull 27:272–277

Nobre AC, Sebestyen GN, Gitelman DR, Mesulam MM, Frackowiak RSJ, Frith CD (1997) Functional localization of the system for visuospatial attention using positron emission tomography. Brain 120:515–533

Olton DS (1982) Spatially organised behaviours of animals: behavioural and neurological studies. In: Potegal M (ed) Spatial abilities. Academic Press, New York, pp 325–360

Owen AM (1997) The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. Eur J Neurosci 9:1329–1339

Owen AM, Downes JD, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 28:1021–1034

Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW (1995) Visuo-spatial short term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 33:1–24

Owen AM, Evans AC, Petrides M (1996a) 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

Owen AM, Morris RG, Sahakian BJ, Polkey CE, Robbins TW (1996b) Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Brain 119:1597–1615

Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M (1998) Functional organisation of spatial and non-spatial working memory processes within the human lateral frontal cortex. Proc Natl Acad Sci USA 95:7721–7726

Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SPMJ, Carpenter TA, Minhas PS, Turkheimer FE, Williams EJ, Robbins TW, Sahakian BJ, Petrides M, Pickard JD (1999) Redefining the functional organisation of working memory processes within human lateral prefrontal cortex. Eur J Neurosci 11:567–574

Owen AM, Lee ACH, Williams EJ (2000) Dissociating aspects of verbal working memory within the human frontal lobe: further evidence for a 'process-specific' model of lateral frontal organization. Psychobiology (in press)

Paulesu E, Frith CD, Frackowiak RSJ (1993) The neural correlates of the verbal component of working memory. Nature 362: 342–345

Paus T (1996) Location and function of the human frontal eye-filed: a selective review. Neuropsychologia 34:475–483

Petrides M (1994) Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In: Boller F, Grafman J (eds) Handbook of neuropsychology, Vol 9. Elsevier, Amsterdam, pp 59–82

Petrides M (1995) Functional organization of the human frontal cortex for mnemonic processing. Ann NY Acad Sci 769: 85–96

Petrides M, Milner B (1982) Deficits on subject-ordered tasks after frontal and temporal lobe lesions in man. Neuropsychologia 20:249–262

Petrides M, Pandya DN (1994) Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller F, Grafman J (eds) Handbook of neuropsychology, Vol 9. Elsevier, Amsterdam, pp 17–58

Petrides M, Alivisatos B, Evans AC, Meyer E (1993a) Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 90:873–877

Petrides M, Alivisatos B, Evans AC, Meyer E (1993b) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 90:878–882

Petrides M, Alivisatos B, Evans AC (1995) Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. Proc Natl Acad Sci USA 92:5803–5807

Postle BR, Stern CE, Rosen BR, Corkin S (2000) An fMRI investigation of cortical contributions to spatial and non-spatial visual working memory. Neuroimage (in press)

Rao SC, Rainer G, Miller EK (1997) Integration of what and where in the primate prefrontal cortex. Science 276:821–824

Rodman HR (1994) Development of inferior temporal cortex in monkey. Cereb Cortex 4:484–498

Rushworth MFS, Owen AM (1998) The functional organization of the lateral frontal cortex: conjecture or conjuncture in the electrophysiology literature. Trends Cogn Sci 2:46–53

Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JDE (1999) Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 9:216–226

Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, Luxen A, Franck G (1996) Regional brain activity during working memory tasks. Brain 119:1617–1625

Schumacher EH, Lauber E, Awh E, Jonides J, Smith E, Koeppe RA (1996) PET evidence for an amodal verbal working memory system. Neuroimage 3:79–88

Smith E, Jonides JJ, Koeppe RA, Awh E, Schumacher EH, Minoshima S (1995) Spatial versus object working memory: PET investigations. J Cogn Neurosci 7:337–356

Smith E, Jonides JJ, Koeppe RA (1996) Dissociating verbal and spatial working memory using PET. Cereb Cortex 6:11–20

Stanton GB, Deng SY, Goldberg ME, McMullen NT (1989) Cytoarchitectonic characteristics of the frontal eye fields in macaque monkeys. J Comp Neurol 282:415–427

Stern CE, Owen AM, Petrides M, Look RB, Tracey I, Rosen BR (2000) Activity in ventrolateral and mid-dorsolateral prefrontal cortex during non-spatial visual working memory processing: evidence from functional magnetic resonance imaging (in press)

Talairach J, Tournoux P (1988) Co-planar stereotactic atlas of the human brain: 3-Dimensional proportional system: an approach to cerebral imaging. Georg Thieme, Stuttgart New York

Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW (eds) Analysis of visual behavior. MIT Press, Cambridge, pp 549–586

Van der Linden M, Collette F, Salmon E, Delfiore G, Degueldre C, Luxen A, Franck G (1999) The neural correlates of updating of information in verbal working memory. Memory 7:549–560

Webster MJ, Bachevalier J, Ungerlieder LG (1994) Connections of inferior temporal areas TEO and TE with parietal and frontal cortx in macaque monkeys. Cereb Cortex 4:470–483

Wilson FAW, Scalaidhe SPO, Goldman-Rakic PS (1993) Dissociations of object and spatial processing domains in primate prefrontal cortex. Science 260:1955–1958

Zubicaray GI de, Williams SCR, Wilson SJ, Rose SE, Brammer MJ, Bullmore ET, Simmons A, Chalk JB, Semple J, Brown AP, Smith GA, Ashton R, Doddrell DM (1998) Prefrontal cortex involvement in selective letter generation: a functional magnetic resonance imaging study. Cortex 34:389–401