
MINI-REVIEW

The Functional Organization of Working Memory Processes Within Human Lateral Frontal Cortex: The Contribution of Functional Neuroimaging

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Abstract

Recent functional neuroimaging studies have provided a wealth of new information about the likely organization of working memory processes within the human lateral frontal cortex. This article seeks to evaluate the results of these studies in the context of two contrasting theoretical models of lateral frontal-lobe function, developed through lesion and electrophysiological recording work in non-human primates (Goldman-Rakic, 1994, 1995; Petrides, 1994, 1995). Both models focus on a broadly similar distinction between anatomically and cytoarchitecturally distinct dorsolateral and ventrolateral frontal cortical areas, but differ in the precise functions ascribed to those regions. Following a review of the relevant anatomical data, the origins of these two theoretical positions are considered in some detail and the main predictions arising from each are identified. Recent functional neuroimaging studies of working memory processes are then critically reviewed in order to assess the extent to which they support either, or both, sets of predictions. The results of this meta-analysis suggest that lateral regions of the frontal lobe are not functionally organized according to stimulus modality, as has been widely assumed, but that specific regions within the dorsolateral or ventrolateral frontal cortex make identical functional contributions to both spatial and non-spatial working memory.

Introduction

The term 'working memory' was introduced into the experimental psychology literature by Baddeley (1986) to replace the existing concept of a passive short-term memory store and to emphasize, within a single model, 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 cortex (Petrides and Milner, 1982; Owen *et al.*, 1990, 1995, 1996d; for review see Petrides, 1989), from lesion and electrophysiological recording work in non-human primates (for reviews see Goldman-Rakic, 1987 and Petrides, 1994), and more recently from functional neuroimaging studies in humans (e.g. Jonides *et al.*, 1993; Petrides *et al.*, 1993a, b; McCarthy *et al.*, 1994; Smith *et al.*, 1995, 1996; Courtney *et al.*, 1996; Gold *et al.*, 1996; Goldberg *et al.*, 1996; Owen *et al.*, 1996a, b; Sweeney *et al.*, 1996). One fundamental issue, which has recently provoked considerable discussion in the frontal lobe literature, is 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. Essentially, two divergent positions

have emerged which, whilst 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 (1987, 1994, 1995), has argued that working memory processes within the lateral frontal cortex are organized according to the type (e.g. modality) of information being processed, 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 'modality-specific' model, 'informational domain, not process, will be mapped across prefrontal cortex' (Goldman-Rakic, 1994, 1995).

An alternative theoretical framework regarding the functional organization of the lateral frontal cortex has been proposed by Petrides (1994, 1995). According to this view, working memory processes within dorsolateral and ventrolateral frontal regions are organized according to the *nature* of the processing required rather than according to the modality of the information to be remembered. Specifically, the ventrolateral frontal lobe regions are principally concerned with the active organization of sequences of responses based on conscious, explicit retrieval of information from posterior association systems. By contrast, dorsolateral frontal regions subserve

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a secondary level of executive processing and are recruited only when active manipulation and monitoring of information within working memory are required. According to this two-stage 'process-specific' model, both spatial and non-spatial stimuli held in working memory may be processed within the ventrolateral and/or the dorsolateral frontal cortex, depending upon the particular demands of the task being performed.

The central goal of this article is to re-evaluate these two models of lateral-frontal lobe function in the light of recent functional neuroimaging studies of spatial and non-spatial working memory. To this end, the functional anatomy of working memory as it exists outside the frontal lobe will be largely ignored, although this emphasis should not be taken to suggest that the frontal cortex is either wholly or uniquely involved in mediating working memory processes. Accordingly, a brief anatomical description of the dorsolateral and ventrolateral frontal cortices and their principal connections will be given, followed by a detailed account of the two models of lateral frontal lobe function mentioned above. The results of recent functional neuroimaging studies of working memory will then be critically reviewed in order to assess the extent to which they have clarified how the human lateral frontal cortex is functionally organized for mnemonic processing.

Anatomical considerations

The frontal cortex is not a homogeneous region of the brain but comprises several architectonic areas that differ in their connections with other cortical and subcortical areas (Pandya and Barnes, 1987). Relative to the enormous amount of information that is available about the structural and functional organization of the monkey brain, very little is known of the connections between specific cortical areas in humans. In spite of this, a recent reparation and comparative cytoarchitectonic analysis of the human and macaque frontal cortex has revealed a remarkable degree of topographic and architectural similarity between the two species in this region (Petrides and Pandya, 1994). This article will focus on two particular regions of the frontal lobe, generally referred to as the dorsolateral frontal cortex and the ventrolateral frontal cortex. It is important to emphasize that these terms, as used in this article and in the anatomical literature, apply to defined regions of the lateral frontal cortex which are anatomically and cytoarchitectonically quite distinct in both monkeys and in humans (Fig. 1).

In the monkey, the ventrolateral frontal cortical region (Fig. 1a) lies below the sulcus principalis, occupying the inferior frontal convexity and comprising architectonic areas 47/12, 45 and the most ventral sector of area 46 (Petrides and Pandya, 1994). In the human brain the ventrolateral frontal cortex largely occupies the inferior frontal gyrus and comprises architectonic areas 47/12 and 45 (Fig. 1b). The dorsolateral frontal region in the monkey may be considered to include the cortex lying within and around the banks of the sulcus principalis (areas 9 and 46), as well as the adjacent cortical area which extends medially as far as the cingulate sulcus (area 9). In the human brain, dorsolateral areas 9 and 46 occupy the middle part of the superior and middle frontal gyri, a considerable proportion of this cortex lying within the depths of the middle frontal sulcus.

In the monkey it has been shown that regions of the lateral frontal cortex are reciprocally connected with multiple posterior regions. The ventrolateral frontal cortex receives visual information directly from the inferotemporal cortex (Kuyppers *et al.*, 1965; Jones and Powell, 1970; Chavis and Pandya, 1976; Barbas, 1988; Ungerleider *et al.*, 1989), whilst visuospatial information from the more posterior parietal cortex enters just below and within the sulcus principalis (Petrides

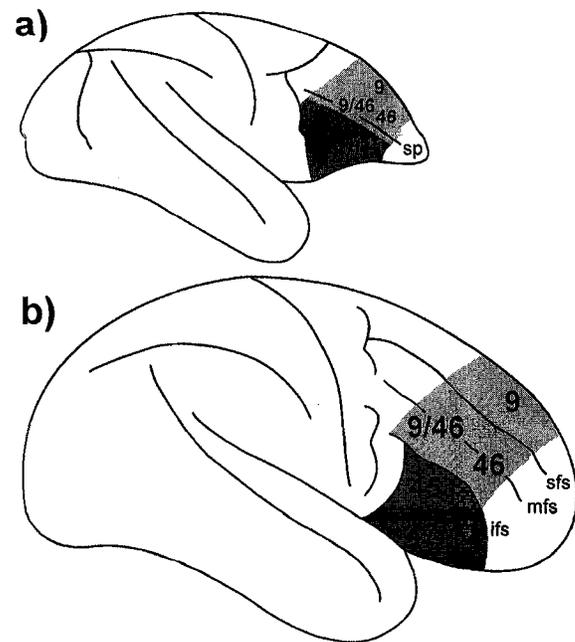


FIG. 1. Schematic drawing of the lateral surface of the macaque brain (a) and the human brain (b) to indicate the location of the dorsolateral frontal cortex (areas 9, 46 and 9/46) and the ventrolateral frontal cortex (areas 45, 47, 12). Adapted from Petrides and Pandya (1994). ifs, inferior frontal sulcus; mfs, middle frontal sulcus; sfs, superior frontal sulcus; sp, sulcus principalis.

and Pandya, 1984; Schwartz and Goldman-Rakic, 1984; Cavada and Goldman-Rakic, 1989). The region of the lateral frontal cortex located dorsal to the sulcus principalis (dorsal areas 9 and 46) is closely connected with the ventrolateral frontal cortex (Barbas and Pandya, 1989; Watanabe-Sawaguchi *et al.*, 1991), and at the same time with the limbic region of the medial temporal lobe (Adey and Meyer, 1952; Nauta, 1964; Goldman-Rakic *et al.*, 1984). On the basis of the available anatomical data, therefore, the possibility clearly exists for modality-specific fields within both the dorsolateral and the ventrolateral frontal cortices.

Models of lateral frontal lobe function: origins

Whilst the focus of this review will be the contribution of functional neuroimaging studies in humans, it is important to acknowledge that both current theoretical positions regarding the functional organization of the lateral frontal cortex arose out of work with non-human primates. It has been known for many years that dorsolateral frontal lesions restricted to the cortex lining the sulcus principalis in the monkey produce severe impairments in certain spatial memory tasks such as spatial delayed response and delayed alternation (Mishkin, 1957; Gross and Weiskrantz, 1962; Butters and Pandya, 1969; Goldman and Rosvold, 1970; Funahashi *et al.*, 1993), but do not impair performance on non-spatial analogues of these tasks (Passingham, 1975; Mishkin and Manning, 1978). In contrast, lesions of the ventrolateral frontal cortex, extending below the sulcus principalis, impair performance on non-spatial delayed matching-to-sample and non-spatial object alternation (Passingham, 1975; Mishkin and Manning, 1978). However, the domain-specific working memory hypothesis, by which dorsal and ventral regions of the lateral frontal cortex are assumed to be specialized for processing spatial and non-spatial visual information respectively, gained considerable

momentum recently with a series of elegant single-cell electrophysiological recording studies by Goldman-Rakic and colleagues (Funahashi *et al.*, 1989, 1990, 1993; Wilson *et al.*, 1993). Funahashi *et al.* (1989, 1990) recorded from single neurons in the dorsal and ventral banks of the middle and posterior regions of the sulcus principalis during an oculomotor variant of the classical delayed response task that required monkeys to make deferred eye movements towards or away from a cued location. Neurons in this region appeared to spatially code the location of an object throughout the visual field in a manner analogous to the visual receptive fields of visual cortical neurons. In a subsequent study, Wilson *et al.* (1993) recorded from neurons in the inferior prefrontal convexity, comprising ventrolateral area 47/12, during an oculomotor delayed response task in which responses were either guided by remembered locations or by patterns. Neurons that exhibited a selective neuronal response to stimulus patterns were found in and around ventrolateral area 47/12, whilst few spatially responsive neurons were found in this region. On the basis of this evidence, Goldman-Rakic (1995) has suggested that dorsolateral and ventrolateral prefrontal regions support different informational domains rather than different processes.

This domain-specific theory has considerable theoretical and anatomical appeal since, 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') (Ungerleider and Mishkin, 1982). 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 may also participate in memory for that same type of information (Haxby *et al.*, 1994; Kohler *et al.*, 1995; Moscovitch *et al.*, 1995; Martin *et al.*, 1996; Owen *et al.*, 1996c, e). 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 theoretical framework for understanding the functional organization of lateral frontal regions in working memory processes has recently been proposed (Petrides, 1994, 1995, 1996). 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. According to this model, therefore, it is the nature of the processing rather than the informational domain that defines the fundamental difference between the dorsolateral and ventrolateral regions of the frontal cortex.

Like the domain-specific hypothesis of lateral frontal lobe function, this alternative model is based in part on the effects of selective lesions to dorsal or ventral regions of the lateral frontal cortex in the monkey. For example, as Petrides (1995, 1996) has pointed out,

lesions of the ventrolateral frontal cortex (areas 45 and 47/12) in the monkey have been shown to impair spatial, as well as non-spatial, versions of the delayed alternation task (Mishkin *et al.*, 1969). Second, whilst lesions confined to the principalis region impair spatial delayed response and spatial delayed alternation (Mishkin, 1957; Gross and Weiskrantz, 1962; Butters and Pandya, 1969; Goldman and Rosvold, 1970; Funahashi *et al.*, 1993), more dorsal lesions that spare the sulcus principalis, but nevertheless include extensive damage to dorsolateral area 9, impair performance on certain non-spatial working memory tasks that require monitoring of self-ordered, or externally ordered, choices among a known set of stimuli, e.g. when performance depends upon remembering which of a known set (of more than two) items have already been selected and which remain to be selected (Petrides, 1991, 1995). On this basis it has been suggested that it is the mnemonic demands of the tasks rather than the modality of the material to be processed which will determine whether impairment will be observed following a lesion of the dorsolateral or ventrolateral regions of the frontal cortex.

Lateral frontal lobe function: functional neuroimaging studies

Until recently, direct investigation of the functional organization of working memory processes within the human brain has been 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, 1996d). 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. The most widely used blood flow activation techniques use regional cerebral blood flow (rCBF) as an indirect index of neuronal (synaptic) activity. Using PET, rCBF is measured by determining the spatial distribution of a positron-emitting tracer, ^{15}O , throughout the brain, during a 60–120 s time window. More recently, 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 memory task), in one scan or set of scans and a 'control' task requiring many, but not all, of the same motoric, perceptual and cognitive components during another scan or set of scans. The imaging data are then reconstructed, smoothed and normalized for global CBF, which may vary between different scans. The data are then usually transformed into a standardized stereotaxic coordinate system based on the three-dimensional atlas of Talairach and Tournoux (1988). The reconstructed, normalized and transformed CBF images are then averaged across all subjects included in a particular study and subtraction images are generated. These images represent the difference between the rCBF during the task of interest and that during the 'control' task. Statistical parametric maps (Friston *et al.*, 1991), or *t*-maps (Worsley *et al.*, 1993), are then generated and the stereotaxic coordinates (x, y, z), of local maxima are calculated within the standardized stereotaxic system.

Although many recent imaging studies have investigated various components of working memory, few have explicitly assessed how the lateral frontal cortex is functionally organized for mnemonic processing. Thus, careful comparisons among a number of unrelated

studies are required in order to determine the extent to which functional neuroimaging has been helpful in clarifying the role played by different frontal lobe regions in working memory. Since most functional neuroimaging studies have used the common stereotaxic coordinate system based on the three-dimensional atlas of Talairach and Tournoux (1988), direct comparisons of activation foci across studies is possible. One issue of importance here is that the tasks used in unrelated studies 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. modality: spatial or non-spatial). Accordingly, when comparing different studies two general questions of interest can be asked. First, do unrelated working memory studies that use stimuli of the same modality (e.g. spatial location) consistently activate the same or similar frontal lobe regions regardless of the specific processing requirements of the particular tasks employed? If this is the case, then the data are consistent with the suggestion that 'informational domain, not process, is mapped across prefrontal cortex' (Goldman-Rakic, 1996). Second, do working memory studies that use stimuli of one particular modality (e.g. spatial) consistently activate the same or similar frontal lobe regions as studies that use stimuli of a different modality (e.g. non-spatial) when the processing demands of the two tasks are kept broadly similar? If this is the case, then the data are consistent with the model proposed by Petrides (1994, 1995, 1996), according to which the modality of the stimuli are less important in determining which frontal areas will be activated than the type of processing required within working memory.

The following sections will seek to address these questions by reviewing relevant functional neuroimaging studies to date, with the following provisions. (i) Tasks will be considered to be 'spatial' if successful performance depends, centrally and critically, on memory for one or more locations from a reasonably large number of potential targets, and does not depend on memory for non-spatial characteristics of these stimuli. Thus, studies involving stimuli presented 'to the left' or 'to the right' of the subject will not be considered in detail, and likewise tasks involving working memory in the context of other complex cognitive operations such as 'response alternation' (e.g. Gold *et al.*, 1996) will be excluded. (ii) In addition, in order that direct comparisons may be made with the lesion and electrophysiological recording studies in non-human primates that have provided the theoretical framework upon which current models of lateral frontal lobe function are based, the section on 'non-spatial' working memory will focus on tasks that involve visual stimuli such as patterns, shapes and faces (i.e. non-verbal stimuli). Although all of these visual working memory paradigms have components that can be considered to be 'spatial' in nature, the locations of the stimuli to be remembered are irrelevant to the tasks being performed. Working memory studies involving verbal stimuli such as words, letters and numbers will be considered briefly in the final discussion.

Do different spatial working memory tasks activate similar lateral frontal regions?

Several recent studies have employed tasks that are clearly designed to emulate the electrophysiological recording paradigm that has been used to test spatial working memory in non-human primates (Funahashi *et al.*, 1989, 1990). These tasks generally involve many independent trials and require the subject to maintain only one piece or a few pieces of information in memory for the duration of each trial, thereby emphasizing the short-term retention of spatial information within working memory. For example, in one study by Jonides and colleagues (Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996) the subjects were required to remember the location of three

dots presented simultaneously on a computer screen for a delay period of 3 s and then to decide whether or not a probe circle occupied one of these same three locations. Blood flow during this memory task was compared with that during a 'perception' condition in which the probe circle and three dots appeared simultaneously on the screen and the same decision had to be made. Within the right frontal cortex, a significant change in blood flow was observed, ventrolaterally, in area 47 (Fig. 2a and Table 1). No significant activation was reported in area 46 of the mid-dorsolateral frontal cortex. In a follow-up study (Smith *et al.*, 1995), subjects were scanned during a task that required them to remember the locations of two simultaneously presented shapes and then, following a 3 s delay, to decide whether or not a single probe shape occupied one of those same locations. Compared with a control condition (which was similar in all respects except that the delay was reduced to 250 ms), a significant increase in rCBF was observed in right ventrolateral area 47, whilst activation in dorsolateral area 46 failed to reach significance according to standard statistical criteria. Baker *et al.* (1986) used a single-trial-per-scan procedure that was slightly more complex in requiring subjects to remember the location of a circle presented on a screen and then to touch that location ~45 s later, after the PET acquisition had been completed. Compared with a control condition, which required subjects to maintain fixation throughout the scan, significant rCBF increases were observed, bilaterally, in areas 9/46 and more ventrally in areas 44/45 of the right hemisphere.

Other investigators have employed more complex spatial working memory tasks that are conceptually more similar to the types of paradigm that have been used to assess spatial memory in the rat, such as the radial arm maze (Olton, 1982). These tasks generally involve only a few trials during the scanning period, but during each trial the subject is required to remember many pieces of spatial information sequentially and to compare each newly acquired spatial location with others acquired earlier during that particular trial. For example, McCarthy *et al.* (1994) used fMRI 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. During two control conditions that required no memory, the subjects simply had to make perceptual judgements about each of the stimuli (e.g. respond when the stimulus was red). The single slice chosen for the study allowed examination of frontal areas 9, 46, 23 and often 47. Relative to the control tasks, the spatial memory task yielded a significantly increased magnetic resonance signal in area 46 of the dorsolateral frontal cortex which was most consistent in the right hemisphere. Standardized stereotaxic (Talairach) coordinates were not computed for this activation focus, although in a follow-up fMRI investigation using an almost identical procedure (McCarthy *et al.*, 1996) a significantly increased magnetic resonance signal was observed in the same region; the reported stereotaxic coordinates (Fig. 2i and Table 1) place the peak change in the magnetic resonance signal well within area 9/46 of the right mid-dorsolateral frontal cortex.

Using a slightly more constrained variant of this task, Smith *et al.* (1996) required subjects to decide whether each of a continuous series of stimuli was presented in the same location as the stimulus presented three back in the sequence. Such 'n-back' tasks are very demanding and require the subject to continually adjust the information held in working memory to incorporate the most recently presented stimulus, whilst simultaneously rejecting or ignoring more temporally distant stimuli. Blood flow during this task was compared with that during a 'low-memory' control condition that required the subject to judge whether each stimulus was presented in one of three key locations identified at the start of the experiment. Within the prefrontal

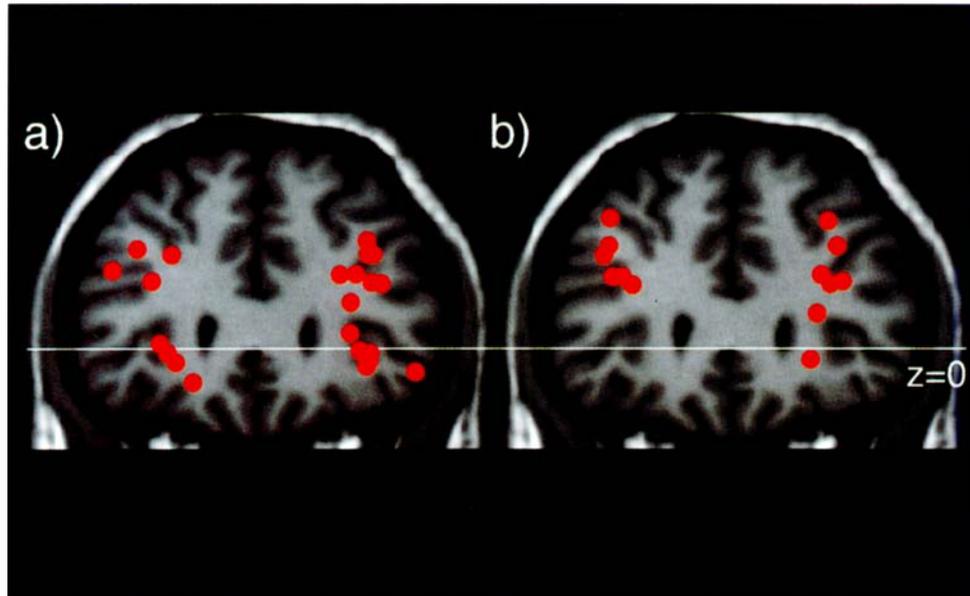


FIG. 2. A schematic diagram illustrating the distribution of activation foci reported in the studies listed in Tables 1 and 2. (a) Spatial working memory tasks. (b) Non-spatial (visual) working memory tasks. The red dots indicate the precise x (medial-to-lateral) and z (inferior-to-superior) coordinates of statistically significant activation foci within the lateral frontal lobe region, superimposed on a single-subject MRI scan ($y = 27$ mm), that has been transformed into standardized stereotaxic space. The coronal slice was chosen to best represent 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.

TABLE 1. Stereotaxic coordinates of significant increases in the dorsolateral or ventrolateral frontal cortices during tests of spatial working memory, by study

Spatial working memory tasks	Left hemisphere			Right hemisphere			
	x	y	z	x	y	z	
Jonides <i>et al.</i> (1993)				35	19	-2	(area 47)
Smith <i>et al.</i> (1995, 1996) (experiment I)				33	19	-2	(area 47)
Smith <i>et al.</i> (1995) (experiment II)				32	18	-1	(area 47)
Owen <i>et al.</i> (1996a) (Spatial Span)				36	20	-5	(area 47)
Owen <i>et al.</i> (1996a) (Learned Spatial Sequence)	-26	18	-5	50	24	-9	(area 47)
McCarthy <i>et al.</i> (1994)					NA		(area 9/46)
McCarthy <i>et al.</i> (1996)				37	40	29	(area 9/46)
Smith <i>et al.</i> (1996)	-33	44	20	35	28	29	(area 46)
Owen <i>et al.</i> (1996a) (Spatial Monitoring I)				35	30	29	(area 9/46)
Owen <i>et al.</i> (submitted)	-38	42	30	35	44	33	(area 9/46)
Goldberg <i>et al.</i> (1996)				30	34	12	(area 46)
				36	34	20	(area 46)
	-20	40	-12				(area 11)
	-46	8	24				(area 44)
Owen <i>et al.</i> (1996a) (Spatial Monitoring II)				39	37	20	(area 9/46)
	-29	20	-1	35	18	-3	(area 47)
Owen <i>et al.</i> (1996a) (Spatial Monitoring III)				31	37	23	(area 9/46)
	-28	20	-3				(area 47)
Baker <i>et al.</i> (1996)	-32	26	36				(area 9)
				28	38	24	(area 9/46)
				26	16	8	(area 44/45)

Activation foci in Tables 1 and 2 represent peaks of statistically significant changes in normalized CBF. The stereotaxic coordinates are expressed in millimetres and are based on the system used in the brain atlas of Talairach and Tournoux (1988): x is the medial-to-lateral distance relative to the midline (positive = right hemisphere); y is anterior-to-posterior distance relative to the anterior commissure (positive = anterior); z is superior-to-inferior distance relative to the anterior commissure-posterior commissure line (positive = superior). All studies discussed in the text are included where precise stereotaxic and/or cytoarchitectonic areas are given.

NA, not available.

cortex significant changes in rCBF were observed, bilaterally, in areas 9/46 (Fig. 2i and Table 1).

Goldberg *et al.* (1996) employed another variant of this task that was designed to isolate the mnemonic (short-term retention) aspect of the spatial delayed response task, although it still retained many of the characteristics of the more complex tasks described above. On each trial, subjects were required to remember the locations of four targets within an array of twenty dots and then, after a delay of 7 s, to judge whether the positions occupied by four new dots were the same as or different from those that had been occupied by the remembered target dots. The control condition differed from the experimental task only in that the response array was presented immediately after the stimulus array. Relative to the control condition, significant rCBF changes were observed in both ventrolateral (areas 44, 11/47) and dorsolateral (area 46) regions of the frontal cortex (Fig. 2i and Table 1).

In summary, recent functional imaging studies have unequivocally demonstrated that spatial working memory tasks may involve either or both the mid-ventrolateral frontal cortex or the mid-dorsolateral frontal region in human subjects. Thus, the activation foci observed in different studies were generally located within ventrolateral area 47, at coordinates $z < 1$ mm (Table 1 and Fig. 2), according to stereotaxic convention, or within dorsolateral areas 9 and 46, the human homologue of the sulcus principalis region of monkeys, at coordinates $z > 20$ mm. Moreover, the pattern of findings across studies suggests that this apparent anatomical dissociation may reflect a functional distinction that is driven by differences in the requirements of the tasks employed. For example, all of the tasks that produced activation foci in ventrolateral area 47 required the subject to maintain only one or a few locations in memory for the duration of each trial, thereby emphasizing the short-term retention of spatial information within working memory (Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996). In contrast, the tasks that produced changes in rCBF more dorsally, in areas 9 and 46, generally required the subject to constantly monitor and manipulate an ongoing 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; Smith *et al.*, 1996; see also Owen *et al.*, 1996b). One exception to this general pattern is the study by Baker *et al.* (1996) in which dorsolateral activation foci were reported bilaterally in areas 9/46 during a task that required the subject to remember a single spatial location. One possible explanation is that these foci reflect the use of more complex mnemonic strategies by the subjects in order to maintain the representation during the unusually long time delay used (e.g. +45 s).

In an attempt to investigate the role of dorsolateral and ventrolateral frontal regions further, Owen *et al.* (1996a) have recently used PET with MRI and five different tasks within a single group of 16 subjects to demonstrate that either or both of these two lateral frontal areas can be activated during spatial working memory tasks, depending upon the precise executive processes that are called upon by the task that is being performed. For example, one hypothesis tested in this study 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. Thus, the emphasis of the task was on the short-term retention of spatial information: no manipulation of, or computation based on, this information was necessary. In a matched visuomotor control condition using identical stimuli the subject would simply respond each time one of the stimuli (e.g. locations) on the screen changed colour. A significant rCBF

increase was observed in ventrolateral area 47 of the right hemisphere (Table 1), at stereotaxic coordinates almost identical to those reported previously by Jonides *et al.* (1993) and Smith *et al.* (1995, 1996) when the memory condition was compared with the visuomotor control condition. 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 (Owen *et al.*, 1996a). The second general hypothesis tested in the study by Owen *et al.* (1996a) 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 ongoing 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 reselecting 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 resembles that used by McCarthy *et al.* (1994, 1996). When the two tasks were compared with the same 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).

Taken together, these functional imaging studies clearly demonstrate that in human subjects both dorsolateral and ventrolateral frontal cortical areas can be activated in 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.

Do different non-spatial working memory tasks activate similar lateral frontal regions?

A few studies of visual working memory have employed tasks that are conceptually similar to the electrophysiological recording paradigm that has been used to test non-spatial working memory in primates (Wilson *et al.*, 1993). For example, Courtney *et al.* (1996) have recently used a task that required subjects to remember three faces presented sequentially, and after a short delay to indicate whether or not a test face was the same as one of those presented previously. In a sensorimotor control condition that required no memory, subjects were presented with three scrambled pictures of faces on the screen and then responded to a fourth scrambled face by making alternating left- and right-hand responses. Within the frontal cortex a significant change in rCBF was observed ventrolaterally in area 47 of the right hemisphere (Table 2). In the same hemisphere a significant change was also observed slightly more dorsally at the border of areas 45 and 46, whilst in the left hemisphere area 44 (Broca's area) was significantly activated. In a related study by Haxby *et al.* (1995) subjects were presented with a single unfamiliar face and were then required to select that face from two alternatives following a delay which varied between scans. Compared with a control condition that required the subjects to make alternating left- and right-hand responses to three nonsense patterns, significant increases were observed in both dorsolateral (area 46) and ventrolateral/orbital (areas 47/11) frontal areas at various delay intervals. However, few of these activation foci survived when rCBF during the memory tasks was compared with that during a simultaneous face matching task, suggesting that they may reflect the neural correlates of perceptual rather than mnemonic aspects of the working memory

TABLE 2. Stereotaxic coordinates of significant increases in the dorsolateral or ventrolateral frontal cortices during tests of non-spatial (visual) working memory, by study

Non-spatial working memory tasks	Left hemisphere			Right hemisphere			
	x	y	z	x	y	z	
Courtney <i>et al.</i> (1996)				22	40	-4	(area 47)
				32	36	20	(area 45/46)
Smith <i>et al.</i> (1995) (experiment I)	-40	8	28				(area 44)
	-39	3	29				(area 44)
Petrides <i>et al.</i> (1993b)	-38	10	40				(area 9)
	-35	30	22	35	32	21	(area 46)
McCarthy <i>et al.</i> (1996)	-37	40	22	31	40	40	(area 9/46)
Owen <i>et al.</i> (submitted)	-39	44	32	34	45	32	(area 9/46)
Baker <i>et al.</i> (1996)	-30	32	24				(area 9/46)

task employed. However, with a 16 s delay this subtraction did yield a significant rCBF change in a left inferior frontal region, whilst with a 21 s delay a more dorsal peak was observed in the same hemisphere (stereotaxic coordinates not reported). A conceptually similar design was employed by Smith *et al.* (1995); the task used required that subjects remember two unfamiliar geometric shapes for a delay period of 3 s and then decide whether or not a probe object presented in the centre of the screen was identical to one of the target objects. Compared with a control condition (which was similar in all respects except that the delay was reduced to 250 ms), a significant increase in rCBF was observed at the border of areas 44 (Broca's area) and 6 (premotor cortex), at stereotaxic coordinates very similar to those reported in the study by Courtney *et al.* (1996). No significant activation was reported in the mid-dorsolateral frontal cortex (i.e. area 9/46). Baker *et al.* (1996) used a single-trial-per-scan delayed matching procedure in which subjects were required to remember a rectangle (with sides of variable length) presented prior to the scan and then to select it from two alternatives after scanning was complete (~45 s later). Relative to a resting control condition which required subjects to maintain fixation during the scan, a significant rCBF increase was observed in dorsolateral area 9/46.

Other studies have used more complex visual working memory tasks that generally involve fewer trials during the scanning period, but require the subject to remember many pieces of visual information sequentially, comparing each newly acquired stimulus with others acquired earlier during that particular trial. 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 paradigm differs from those described above (Smith *et al.*, 1995; Courtney *et al.*, 1996), in that the subject is required to constantly monitor an ongoing series of visual stimuli within working memory and to make comparisons between each new stimulus and stimuli presented earlier in the sequence. In the control condition, subjects had to respond on each trial to one particular design which was identified immediately prior to the scan. Compared with this control, which made minimal demands on working memory, significant increases in rCBF were observed bilaterally in the mid-dorsolateral frontal cortex (areas 9/46) during the working memory task. Using a similar type of task, McCarthy *et al.* (1997) used fMRI to measure changes in rCBF while subjects judged whether each of a series of 20 shapes was identical to one that had already been presented earlier in the sequence. The control condition was a perceptual target detection task requiring subjects to respond whenever a stimulus with a bright dot superimposed upon it

was presented. Like the study by Petrides *et al.* (1993b), significant activation foci were reported bilaterally in dorsolateral areas 9 and 46.

In summary, rather fewer neuroimaging studies have focused on the functional anatomy of visual working memory processes than on spatial working processes, although the results have yielded a similar dispersion of activation foci within the lateral frontal cortex. There is, however, some consistency in the regions that are significantly activated by tasks that make similar cognitive demands. For example, two of the tasks that simply required the retention of visual information over short delays failed to activate the more dorsal regions of areas 9 and 46 that have been implicated in many previous working memory studies (Smith *et al.*, 1995; Courtney *et al.*, 1996). In contrast, two conceptually similar tasks that required the subjects to monitor an ongoing series of visual stimuli whilst making comparisons between each new stimulus and those presented earlier in the sequence activated the mid-dorsolateral frontal region (areas 9 and 46) bilaterally (Table 2).

The fact that the relatively simple delayed matching task used by Baker *et al.* (1996) did activate the left dorsolateral frontal cortex may reflect the use of more complex maintenance strategies by the subjects during the unusually long time delay used (e.g. +45 s). Similarly, in a comparison between the delayed and simultaneous face matching tasks used by Haxby *et al.* (1995), more dorsal activation foci were observed in the left prefrontal cortex when longer delays were used.

Together, these functional imaging studies fail to support the hypothesis that non-spatial (visual), working memory paradigms will consistently activate any particular frontal lobe region and suggest instead that, like spatial working memory, non-spatial working memory processes are distributed across the lateral frontal cortex.

Do spatial and non-spatial working memory tasks activate similar lateral frontal regions?

As argued above, one logistic problem in comparing the results of unrelated working memory studies is that the tasks used often differ both in terms of their processing requirements and in terms of the nature, or the modality, of the material to be remembered. 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 for addressing the question posed above. For example, in one (spatial) working memory condition of the fMRI study by McCarthy *et al.* (1996; described above), the subjects were required to judge whether each of a series of squares was located in a position that had already

been occupied earlier in that same sequence. During a conceptually similar non-spatial working memory task, the subjects were required to judge whether each of a series of irregular shapes presented in the centre of the screen had appeared earlier in that same sequence of shapes. In the right hemisphere, the mean peak change in magnetic resonance signal was located in the mid-dorsolateral frontal region (area 9/46) for both the spatial and the non-spatial version of the task. Within this region, the stereotaxic coordinates for the peak observed during the non-spatial working memory task were rather more dorsal (>1 cm) than those for the peak observed during the spatial working memory. During the non-spatial working memory task, a small change was also observed in the left frontal lobe at coordinates that, although slightly (<1 cm) ventral to the right-sided activation peaks observed during the spatial working memory task, are still well within dorsolateral areas 9 and 46. Broadly similar results were reported by Baker *et al.* (1996), who compared a spatial delayed response task with a non-spatial shape matching task (described above). Both tasks activated dorsolateral areas 9/46, and the peak change was greater in the right hemisphere for the spatial task and in the left hemisphere for the non-spatial task. In addition, the spatial task activated a more ventral region in areas 44/45 of the right hemisphere that was not observed during the non-spatial task.

A number of other studies that have compared spatial with non-spatial working memory directly have produced rather ambiguous results with respect to the hypotheses under review in this article. For example, in the study by Courtney *et al.* (1996) mentioned above, subjects were presented with three faces in sequence and were then required to judge whether or not the characteristics (during the non-spatial working memory condition) or the location (during the spatial working memory condition) of a test face were identical to one of those seen previously by making left-hand ('no') or right-hand ('yes') responses. In the sensorimotor control condition subjects were presented with three scrambled pictures of faces in different locations on the screen and then responded to a fourth scrambled face by making alternating left- and right-hand responses. Relative to the sensorimotor control condition, the non-spatial working memory task activated two right frontal regions: at the border of areas 45 and 46, and ventrolateral area 47/11. In contrast, the spatial working memory task produced no prefrontal activity at all. When the two tasks were compared directly, the only frontal lobe activity observed during the spatial working memory condition was in the premotor cortex, whilst during the non-spatial working memory condition a strong activation focus in the right mid-dorsolateral frontal region (area 9/46) was observed. It is not entirely clear why this spatial working memory task failed to activate either the mid-dorsolateral or the ventrolateral frontal regions that have been consistently activated in other studies. One possibility is that, although the sensorimotor task did not explicitly require memory for spatial material, it did involve stimuli presented in different locations on the screen, and may therefore have incidentally engaged spatial working memory processes, the neural correlates of which may therefore have been 'subtracted out' when comparisons were made between the tasks.

Smith *et al.* (1995) explicitly compared working memory for location with working memory for visual patterns (see above for description of experimental and control tasks), and found that, whilst right ventrolateral area 47 was activated during the spatial working memory task, the visual working memory condition only activated a more dorsal and posterior region in area 44. In a follow-up experiment (Smith *et al.*, 1995) in which identical irregular shapes were used during all the scanning conditions, the right ventrolateral frontal cortex (area 47) was again activated during the spatial working

memory task whilst the non-spatial task yielded no significant prefrontal activity.

In summary, when only those studies that have attempted to compare spatial with non-spatial working memory directly are considered, the pattern of findings is rather equivocal. In two studies the two modalities activated similar (dorsolateral) frontal regions (McCarthy *et al.*, 1996; Baker *et al.*, 1996), in another only object working memory activated dorsolateral and ventrolateral frontal regions (Courtney *et al.*, 1996), whilst in a third only the spatial working memory task activated the (ventrolateral) frontal cortex (experiment II in Smith *et al.*, 1995). We have recently attempted to clarify this issue (Owen, A. M., Stern, C. E., Petrides, M., Look, R. B., Tracey, I. and Rosen, B. R., submitted for publication) using fMRI and 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). 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 the same location on the screen, responding after each stimulus by selecting a pattern that was presented 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. The two experimental tasks had 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. 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 mean stereotaxic coordinates (Table 1) 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 (Table 2). 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 (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 modality-specific nature of that information (i.e. spatial or non-spatial).

Discussion

Recent functional neuroimaging studies have provided a wealth of new information regarding the involvement of different lateral frontal lobe regions in various tests of spatial and non-spatial working memory. The primary purpose of this article has been to evaluate whether the results of these studies support either of two contrasting theoretical models of lateral frontal lobe function. Whilst both of these models 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 hypothesis of frontal lobe function predicts that modality, not process, will be mapped across the prefrontal cortex (Goldman-Rakic, 1994, 1995); accordingly, one might reasonably 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 Tables 1 and 2 suggests that this is not the case. For example, overlapping activation foci within area 9/46 of the mid-dorsolateral frontal cortex has been reported frequently in studies of both spatial and non-spatial (visual) working memory (Fig. 2). Across studies, the mean stereotaxic z -coordinates (inferior-to-superior) for the activation foci falling within areas 9 and 46 can be computed, revealing that, for spatial tasks, mean $z = +29$ mm (left hemisphere) and $z = +24$ mm (right hemisphere), and for non-spatial tasks the corresponding values are $z = +28$ mm and $z = +28$ mm. 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 from that which would be predicted by the domain-specific hypothesis of lateral frontal organization.

It might be argued that many of the 'visual' working memory tasks included in these studies 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, in most of these studies 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.*, 1996; Smith *et al.*, 1996), even in conditions that involve no visuospatial stimulation at all (e.g. Petrides *et al.*, 1993b).

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 (Petrides, 1994, 1995). Since this model allows 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. This is assuming, of course, that all of these tasks involve a similar non-modality-specific process that can be shown to depend critically on this region. Any classification of studies in this way is necessarily *post hoc*, although examination of the data presented in Tables 1 and 2 does suggest some similarity between those spatial and non-spatial working memory tasks that activated dorsolateral frontal regions in terms of the amount of on-line manipulation of stored information that is required. That is to say, the response that is 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). Conversely,

those tasks that do not activate this region (but activate more ventral regions of the frontal lobe) tend to emphasize instead the short-term retention of information and the sequencing of responses based directly on that stored information (e.g. Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996; Owen *et al.*, 1996a).

It should be emphasized that, if this process-specific functional distinction between the mid-dorsolateral and the mid-ventrolateral frontal cortices exists, then the two putative levels of mnemonic processing described are certainly intimately related and likely to be involved simultaneously, but to varying degrees, in many working memory tasks. Examination of Tables 1 and 2 and data from related studies of verbal working memory (e.g. Cohen *et al.*, 1994; Petrides *et al.*, 1995) again confirms this prediction; certain spatial, verbal and visual working memory tasks have been shown to activate dorsolateral and ventrolateral cortical areas simultaneously. Moreover, Owen *et al.* (1996a) have recently demonstrated that, for spatial working memory at least, it is possible to engage either or both of these processing systems by manipulating the exact requirements of the task.

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 organized topographically according to the nature of the process being carried out rather than according to the nature of the material being processed. One question which must be asked, however, is how this conclusion can be reconciled with the results of the seminal electrophysiological recording studies in monkeys (Funahashi *et al.*, 1989, 1990; Wilson *et al.*, 1993), which provided the main impetus for the domain-specific theory of lateral frontal organization. Two hypotheses may explain this apparent discrepancy. The first intriguing possibility is that the data from the electrophysiological recording studies in monkeys are entirely consistent with the human functional neuroimaging data, but reflect the subtle changes in processing requirements that can occur with minor—but fundamental—alterations in task design. For example, perhaps the eight-location spatial delayed-response task used by Funahashi *et al.* (1989, 1990) placed greater demands on the processing resources of the dorsolateral frontal cortex than the two-choice pattern delayed-response task used by Wilson *et al.* (1993), for reasons unrelated to the stimulus modality *per se*. Similarly, like many of the imaging studies described above, the spatial and non-spatial tasks used in the electrophysiological recording study by Wilson *et al.* (1993) were not strictly analogous in all respects and differed not only in terms of the input (i.e. locations or patterns) but also in terms of the complexity (i.e. conditionality) of the relationship between stimuli and their associated responses. For example, in the spatial delayed response task used the monkeys were required to direct their gaze to an actual remembered location following a delay, whilst in the pattern delayed response task the monkeys would direct their gaze to the left if one particular pattern had been remembered and to the right if a second pattern had been remembered. Similar, subtle differences in task design may explain some of the apparently conflicting results between functional imaging studies. For example, the three-item spatial working memory tasks used by Jonides *et al.* (1993) activated ventrolateral area 47, whilst a seemingly similar three-item spatial working memory task used by Owen *et al.* (1996a; Spatial Monitoring I) activated only dorsolateral area 9/46. In the former case, however, subjects had to respond simply by deciding whether or not the location of a probe stimulus had been seen previously, whilst in the latter study subjects had to decide which of a given array of previously unknown locations had been presented and which had not, an analytically more complex process which may have preferentially engaged dorsolateral mechanisms.

The second, likely, possibility is that, within the dorsolateral and ventrolateral processing systems posited by Petrides (1994, 1995), there is further specialization based on the sensory modality of the information being processed. Whilst functional differentiation may be measurable at the cellular level using electrophysiological techniques in the monkey (Funahashi *et al.*, 1989, 1990), the functional neuroimaging methods used in humans to date may have sufficient spatial resolution to detect differences between, but not within, these anatomical regions. Certainly among the mid-dorsolateral activation foci reported in Figure 2, there is considerable overlap between studies of spatial (Table 1) and non-spatial (Table 2) 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) and Smith *et al.* (1995) all yielded rather posterior ventrolateral activation foci at y coordinates between 18 and 24 mm. In two non-spatial studies that employed face stimuli, ventrolateral activation foci were reported rather more anteriorly at y coordinates between 33 and 40 mm (Haxby *et al.*, 1995; Courtney *et al.*, 1996), suggesting that there may be some functional specialization based on stimulus modality within the ventrolateral frontal region. This hypothesis has considerable theoretical as well as anatomical appeal, for it suggests that both 'process' and 'domain' may be represented across the lateral frontal cortex, albeit at different neuro-anatomical levels. Thus, at one level the dorsolateral and ventrolateral frontal cortical regions may be broadly polymodal and each dedicated to a particular type or class of cognitive process. Within these gross anatomical regions, however, unimodal fields may exist, each dedicated to a particular informational domain. Testing such a model using functional neuroimaging in humans will provide a significant challenge for the future.

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Abbreviations

fMRI	functional magnetic resonance imaging
PET	positron emission tomography
rCBF	regional cerebral blood flow

References

- Adey, W. R. and Meyer, M. (1952) An experimental study of hippocampal afferent pathways from prefrontal and cingulate areas in the monkey. *J. Anat.*, **86**, 58–75.
- Baddeley, A. D. (1986) *Working Memory*. Oxford University Press, New York.
- Baker, S. C., Frith, C. D., Frackowiak, R. S. J. and Dolan, R. J. (1996) Active representation of shape and location in man. *Cerebral 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. and Pandya, D. N. (1989) Architecture and intrinsic connections of prefrontal cortex in rhesus monkey. *J. Comp. Neurol.*, **286**, 353–375.
- Bates, J. F., Wilson, F. A. W., O'Scalaidhe, S. P. and Goldman-Rakic, P. S. (1994) Area TE connections with inferior prefrontal regions responsive to complex objects and faces. *Soc. Neurosci. Abstr.*, **20**, 434.10.
- Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E. and Noll, D. C. (1996) A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage*, **3**, S532.
- Butters, N. and Pandya, D. N. (1969) Retention of delayed-alternation: effect of selective lesions of sulcus principalis. *Science*, **165**, 1271–1273.
- Carmichael, S. T. and Price, J. L. (1995) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol.*, **363**, 642–664.
- Cavada, C. and Goldman-Rakic, P. S. (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.
- Chanis, D. A. and Pandya, D. N. (1976) Further observations on cortico-frontal connections in the rhesus monkey. *Brain Res.*, **117**, 369–386.
- Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D. and Noll, D. C. (1994) Activation of prefrontal cortex in a non-spatial working memory task with functional MRI. *Hum. Brain Mapping*, **1**, 293–304.
- Courtney, S. M., Ungerleider, L. G., Keil, K. and Haxby, J. V. (1996) Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex*, **6**, 39–49.
- Friston, K. J., Frith, C. D., Liddle, P. F. and Frackowiak, R. S. J. (1991) Comparing functional (PET) images: the assessment of significant change. *J. Cereb. Blood Flow Metab.*, **11**, 690–699.
- Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.*, **61**, 1–19.
- Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. (1990) Visuospatial coding of primate prefrontal neurons revealed by oculomotor paradigms. *J. Neurophysiol.*, **63**, 814–831.
- Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. (1993) Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic 'scotomas'. *J. Neurosci.*, **13**, 1479–1497.
- Gold, J. M., Berman, K. F., Randolph, C., Goldberg, T. E. and Weinberger, D. R. (1996) PET validation of a novel prefrontal task: Delayed Response Alternation. *Neuropsychology*, **10**, 3–10.
- Goldberg, T. E., Berman, K. F., Randolph, C., Gold, J. M. and Weinberger, D. R. (1996) Isolating the mnemonic component in spatial delayed response: a controlled PET ¹⁵O-labelled water regional cerebral blood flow study in normal humans. *Neuroimage*, **3**, 69–78.
- Goldman, P. S. and Rosvold, H. E. (1970) Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. *Exp. Neurol.*, **27**, 291–304.
- Goldman-Rakic, P. S. (1987) Circuitry of primate prefrontal cortex and the regulation of behavior by representational memory. In Plum, F. and Mountcastle, V. (eds), *Handbook of Physiology, Section 1, The Nervous System, Vol 5*. American Physiological Society, Bethesda, MD, pp. 373–417.
- Goldman-Rakic, P. S. (1994) The issue of memory in the study of prefrontal functions. In Theiry, A. M., Glowinski, J., Goldman-Rakic, P. S. and Christen, Y. (eds), *Motor and Cognitive Functions of the Prefrontal Cortex*. Springer-Verlag, Berlin, pp. 112–122.
- Goldman-Rakic, P. S. (1995) Architecture of the prefrontal cortex and the central executive. *Ann. N.Y. Acad. Sci.*, **769**, 71–83.
- Goldman-Rakic, P. S. (1996) The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Phil. Trans. R. Soc. Lond. Ser. B*, **351**, 1445–1453.
- Goldman-Rakic, P. S., Selemon, L. D. and Schwartz, M. L. (1984) Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience*, **12**, 719–743.
- Gross, C. G. and Weiskrantz, L. (1962) Evidence for dissociation of impairment on auditory discrimination and delayed response following lateral frontal lesions in monkeys. *Exp. Neurol.*, **5**, 453–476.
- Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P. and Grady, C. L. (1994) The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *J. Neurosci.*, **14**, 6336–6353.
- Haxby, J. V., Ungerleider, L. G., Horwitz, B., Rapoport, S. I. and Grady, C. L. (1995) Hemispheric differences in neural systems for face working memory: a PET-rCBF study. *Hum. Brain Mapping*, **3**, 68–82.
- Jones, E. G. and Powell, T. P. S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93**, 793–820.
- Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S. and Mintun, M. A. (1993) Spatial working memory in humans as revealed by PET. *Nature*, **363**, 623–625.

- Kohler, S., Kapur, S., Moscovitch, M. and Winocur, G. (1995) Dissociation of pathways for object and spatial vision: a PET study in humans. *NeuroReport*, **6**, 1865–1868.
- Kuypers, H. G. J. M., Szwarcbart, M. K., Mishkin, M. and Rosvold, H. E. (1965) Occipito-temporal corticocortical connections in the rhesus monkey. *Exp. Neurol.*, **11**, 245–262.
- Martin, A., Wiggs, C. L., Ungerleider, L. G. and Haxby, J. V. (1996) Neural correlates of category-specific knowledge. *Nature*, **379**, 649–652.
- McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., Goldman-Rakic, P. and Shulman, R. G. (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, R. T., Krystal, J. H., Gore, J. C. and Goldman-Rakic, P. S. (1996) Activation of human prefrontal cortex during spatial and non-spatial working memory tasks measured by functional MRI. *Cerebral Cortex*, **6**, 600–611.
- Mishkin, M. (1957) Effects of small frontal lesions of delayed alternation in monkeys. *J. Neurophysiol.*, **20**, 615–622.
- Mishkin, M. and Manning, F. J. (1978) Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Res.*, **143**, 313–323.
- Mishkin, M., Vest, B., Waxler, M. and Rosvold, H. E. (1969) A re-examination of the effects of frontal lesions on object-alternation. *Neuropsychologia*, **7**, 357–363.
- Moscovitch, M., Kapur, S., Kohler, D. and Houle, S. (1995) Distinct neural correlates of visual long-term memory for spatial location and object identity: a positron emission tomography study in humans. *Proc. Natl Acad. Sci. USA*, **92**, 3721–3725.
- Nauta, W. J. H. (1964) Some efferent connections of the prefrontal cortex in the monkey. In Warren, J. M. and Akert, K. (eds), *The Frontal Granular Cortex and Behavior*. McGraw-Hill, New York, pp. 397–409.
- Olton, D. S. (1982) Spatially organised behaviours of animals: behavioural and neurological studies. In Potegal, M. (ed.), *Spatial Abilities*. Academic Press, New York, pp. 325–360.
- Owen, A. M., Downes, J. D., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. (1990) Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, **28**, 1021–1034.
- Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E. and Robbins, T. W. (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, A. M., Evans, A. C. and Petrides, M. (1996a) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cerebral Cortex*, **6**, 31–38.
- Owen, A. M., Doyon, J., Petrides, M. and Evans, A. C. (1996b) Planning and spatial working memory examined with positron emission tomography (PET). *Eur. J. Neurosci.*, **8**, 353–364.
- Owen, A. M., Milner, B., Petrides, M. and Evans, A. C. (1996c) Memory for object-features versus memory for object-location: a positron emission tomography study of encoding and retrieval processes. *Proc. Natl Acad. Sci. USA*, **93**, 9212–9217.
- Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. (1996d) 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, A. M., Milner, B., Petrides, M. and Evans, A. (1996e) A specific role for the right parahippocampal region in the retrieval of object-location: a positron emission tomography study. *J. Cognit. Neurosci.*, **8**, 588–602.
- Pandya, D. N. and Barnes, C. L. (1987) Architecture and connections of the frontal lobe. In Poremba, E. (ed.), *The Frontal Lobes Revisited*. IRBN Press, New York, pp. 41–72.
- Passingham, R. E. (1975) Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). *Brain Res.*, **92**, 89–102.
- Petrides, M. (1989) Frontal lobes and memory. In Boller, F. and Grafman, J. (eds), *Handbook of Neuropsychology*, Vol. 3. Elsevier, Amsterdam, pp. 59–82.
- Petrides, M. (1991) Monitoring of selections of visual stimuli and the primate frontal cortex. *Proc. R. Soc. Lond. Ser. B*, **246**, 293–298.
- Petrides, M. (1994) Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In Boller, F. and 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. N.Y. Acad. Sci.*, **769**, 85–96.
- Petrides, M. (1996) Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Phil. Trans. R. Soc. Lond. Ser. B*, **351**, 1455–1462.
- Petrides, M. and Milner, B. (1982) Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia*, **20**, 249–262.
- Petrides, M. and Pandya, D. N. (1994) Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller, F. and Grafman, J. (eds), *Handbook of Neuropsychology*, Vol. 9. Elsevier, Amsterdam, pp. 17–58.
- Petrides, M., Alivisatos, B., Evans, A. C. and 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, A. C. and 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. and Evans, A. C. (1995) Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proc. Natl Acad. Sci. USA*, **92**, 5803–5807.
- Rodman, H. R. (1994) Development of inferior temporal cortex in monkey. *Cerebral Cortex*, **4**, 484–498.
- Schwartz, M. L. and Goldman-Rakic, P. S. (1984) Callosal and intrahemispheric connectivity of the prefrontal association cortex in rhesus monkey: relation between intraparietal and principal sulcal cortex. *J. Comp. Neurol.*, **226**, 403–420.
- Smith, E. E., Jonides, J. J., Koeppel, R. A., Awh, E., Schumacher, E. H. and Minoshima, S. (1995) Spatial versus object working memory: PET investigations. *J. Cognit. Neurosci.*, **7**, 337–356.
- Smith, E. E., Jonides, J. J. and Koeppel, R. A. (1996) Dissociating verbal and spatial working memory using PET. *Cerebral Cortex*, **6**, 11–20.
- Sweeney, J. A., Minutun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R. and Carl, J. R. (1996) Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J. Neurophysiol.*, **75**, 454–468.
- Talairach, J. and Tournoux, P. (1988) *Co-planar Stereotactic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. Georg Thieme, Stuttgart.
- Ungerleider, L. G. and Mishkin, M. (1982) Two cortical visual systems. In Ingle, D. J., Goodale, M. A. and Mansfield, R. J. W. (eds), *Analysis of Visual Behavior*. MIT Press, Cambridge, MA, pp. 549–586.
- Ungerleider, L. G., Gaffan, D. and Pelak, V. S. (1989) Projections from inferior temporal cortex to prefrontal cortex via the unicate fascicle in rhesus monkeys. *Exp. Brain Res.*, **76**, 473–484.
- Watanabe-Sawaguchi, K., Kubota, K. and Arikuni, T. (1991) Cytoarchitecture and intrafrontal connections of the frontal cortex of the brain of the hamadryas baboon (*Papio hamadryas*). *J. Comp. Neurol.*, **311**, 108–133.
- Webster, M. J., Bachevalier, J. and Ungerleider, L. G. (1994) Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. *Cerebral Cortex*, **4**, 470–483.
- Wilson, F. A. W., Scaldie, S. P. O. and Goldman-Rakic, P. S. (1993) Dissociations of object and spatial processing domains in primate prefrontal cortex. *Science*, **260**, 1955–1958.
- Worsley, K. J., Evans, A. C., Marrett, S. and Neelin, P. (1993) Detecting and estimating the regions of activation in CBF activation studies in human brain. In Uemura, K., Lassen, N., Jones, T. and Kanno, I. (eds), *Qualification of Brain Function: Tracer Kinetics and Image Analysis in Brain PET*. Excerpta Medica, London, pp. 535–548.