The functional organization of the lateral frontal cortex: conjecture or conjuncture in the electrophysiology literature?

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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. Since Fuster and Alexander's first description of 'working memory cells' the field has continued to be driven by electrophysiological recording studies, the results of which have provided the impetus for an abundance of studies using alternative methodologies, most notably, functional neuroimaging. However, even within the electrophysiological literature, there is considerable disagreement about how the functions of different prefrontal regions might best be described, a consideration that has implications for the interpretation of related studies in human subjects. In this article, we review the electrophysiological evidence for functional segregation within the frontal cortex in the context of related data from primate lesion studies and functional neuroimaging in humans, and attempt to reconcile the key findings with emerging cognitive models of lateral frontal lobe organization.

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In recent years, working memory has been described and discussed in various ways: as a cognitive system for both the temporary storage and manipulation of remembered information[1,2], as the type of memory that is active and only relevant for a short period of time[3,4] and, most notably, as the specific process by which a remembered stimulus is held 'on-line' to guide behaviour in the absence of external cues or prompts[5,6]. In part, this descriptive variability reflects the relative interests of those working with different primate species: psychologists working mainly with humans often emphasize the 'organizational' 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 compounded by Honig's definition of working memory[7], as applied invariably in rat studies using Olton's radial arm maze[8], which also emphasizes the 'organizational' 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 organization of action[9]. 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[1].

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 monkey brain, and comprises a number of specific areas which have distinct patterns of connectivity with other brain regions (see Box 1). It is not surprising, therefore, that one question that has been widely investigated is whether working memory processes can be fractionated within the prefrontal cortex.

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Box 1. The anatomy of the prefrontal cortex

The frontal cortex is not a homogenous region of the brain but comprises several architectonic areas that differ in terms of their connections with other brain regions[a–f]. The dorsolateral prefrontal region (PFdl) may be considered to include the cortex lying within and around the banks of the principal sulcus and comprises cytoarchitectonic areas 9 and 46. The ventral prefrontal cortex (PFv) lies below on the inferior convexity and comprises cytoarchitectonic areas 12 (or 47/12) and 45. Homologous regions have also been identified in the human prefrontal cortex. PFdl comprises the midpart of the superior and middle frontal gyri above the inferior prefrontal sulcus, a considerable proportion of this cortex lying within the depths of the middle frontal sulcus[e,g]. The PFv comprises the tissue below the inferior frontal sulcus.

The prefrontal areas of the macaque monkey brain have distinct connections with posterior visual areas. There are particularly prominent connections between the PFdl and the parietal cortex and dorsal stream visual areas that are important for spatial vision[f,h,i]. In the case of the PFv, greater emphasis is usually placed on its connections with the temporal lobe and ventral stream visual areas that are important for pattern and object vision[b,c,j]. It is now clear, however, that the PFv is also interconnected with some dorsal stream parietal areas[i,k]. It is possible that within the PFv there is some regional segregation between the terminations of the temporal lobe and parietal lobe connections.

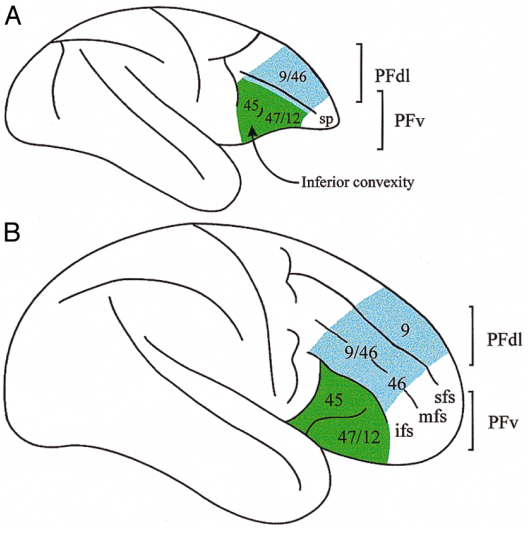

Fig. Prefrontal cortex in macaque and human brains. Schematic drawing of the lateral surface of the macaque monkey brain **(A)** and the human brain **(B)** to indicate the location of the dorsolateral frontal cortex (PFd1: areas 9, 46 and 9/46) and the ventrolateral frontal cortex (PFv: areas 45, 47 and 12). ifs, inferior frontal sulcus; mfs, middle frontal sulcus; sfs, superior frontal sulcus; sp, sulcus principalis. (Adapted from Ref. e.)

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Electrophysiological evidence for a domain-specific model of frontal cortical organization

In one recent and influential electrophysiological recording study, Wilson *et al.* suggested that the functional contribution of different frontal regions may lie in the particular sensory type or 'modality' of information being retained in working memory[10]. They argued that the dorsal and ventral prefrontal cortices (PFdl and PFv), respectively, were specialized for the maintenance of spatial or object visual information in working memory. This conclusion was based on a study in which monkeys were taught to make saccades in one of two directions (left or right), depending on which of two instructing cues was shown. In a spatial version of the task, the monkey's cue was simply the position of a dot on a screen (left or right); the monkey made saccades in the direction of the cue. In the second non-spatial version of the task, each of two patterns, which appeared in the centre of the screen, indicated the saccade direction. There was a 2.5 sec delay between the offset of cue presentation and the time at which the monkeys were trained to respond (when a fixation point disappeared). Neurons in the PFv appeared to be preferentially involved in the pattern-based version of the working memory task; 24 of 31 PFv neurons with delay-dependent activity responded more to patterns than to locations. Although conclusions about the specific roles of the PFdl and PFv were drawn, the reported recordings were, for the main part, limited to the PFv.

Because previous studies by the same group had shown that PFdl neurons are active during spatial delayed response (DR) tasks[11–13], Goldman-Rakic and colleagues argued that the segregation of form and spatial information into ventral (occipito-temporal) and dorsal (occipito-parietal) visual

pathways[14,15], which might be established as early as the retina[16], is maintained in distinct anterior extensions within the ventrolateral and dorsolateral regions of the frontal lobe[6]. This notion, which is sometimes referred to as the domain-specific theory of prefrontal function, proposes a single, basic working memory mechanism, which is distributed throughout the prefrontal cortex, with regional subdivisions dealing, rather selectively, with distinct types of sensory information. It is important to emphasize here that the dorsolateral and ventrolateral frontal cortical regions, which are central functional components of the model, are anatomically and cytoarchitectonically quite distinct in both monkeys and humans (see Box 1).

As an account of lateral frontal organization, the modality-specific model has been exceedingly influential in providing a theoretical framework for many research studies and has received some corroboration, most notably from several functional neuroimaging studies in humans, which have been interpreted as supporting the proposed dichotomy between spatial and object working memory[17–20].

Conjecture: some problems for the domain-specific model

A recent electrophysiological recording study from Rao *et al.* has, however, cast some doubt over the validity of the domain-specific model of lateral frontal organization[21]. In that study, neurons were mapped in a 12 mm by 12 mm area, centred on the principal sulcus. Neurons were found, both ventral and dorsal to the principal sulcus, that encoded either, or both, the location and the identity of stimuli presented in a novel delayed response procedure. The task comprised three stages. In the first stage, a monkey saw one of four objects (the sample stimulus) at the centre of a screen, where it was trained to foveate. After an initial delay period, the monkey was shown the sample object again, but now presented in one of four positions surrounding the central fixation spot. As well as the sample stimulus, a distracting object was shown at another location. The monkey was required to make no response at this stage. Following a second delay period, the monkey was presented with four dots at each of the possible four surrounding positions and was required to saccade to the position in which the match, rather than the distractor, had appeared. Only 7% of prefrontal task-related cells were selective for object identity (that is, they fired preferentially during the first delay period), although 41% were selective for spatial location (that is, they fired preferentially during the second delay period). In contrast, 52% of task-related cells were selective for both an object's identity in the first delay period and its location during the second delay period. Even more remarkable was the apparent flexibility of some neurons as the emphasis of the task changed during its various stages. Thus, once the target object's identity was no longer relevant (during the second 'where' delay period), many of the 'what-and-where' cells no longer appeared to code for object identity as they had done during the first delay period. This finding suggests prefrontal 'memory cells' are flexible – they can code different stimulus attributes at different times according to task demands. The finding, however, is at odds with the modality-specific model of working memory function which, by definition, would predict a 'one neuron–one function' system of organization within the frontal lobe. It is, however, consistent with a view of the prefrontal cortex as a functionally sophisticated region, capable of processing multiple aspects of complex stimuli.

Conjuncture: a re-evaluation of the data

Before considering the results of these two recent studies, it is important to place the findings in an appropriate historical context. The question of spatial versus non-spatial memory specialization in the prefrontal cortex was first investigated by Fuster and colleagues[22,23]. In their studies, monkeys were taught two tasks each involving a 10 sec delay between stimulus and response. In one task, the sample was a coloured light and the correct matching response was to press a button of that colour. In the other task, the sample was a light in a certain location and the correct matching response was to press a button in the same location. Although cells with delay-dependent activity were common in both the PFdl and PFv, there was no statistically significant evidence for topographic segregation based on stimulus modality.

The question which must be asked then, is how the evidence from the study by Wilson *et al.*[10] can be reconciled with the results of Fuster and colleagues[22,23] and Rao *et al.*[21] There are three methodological issues which may be relevant.

PFdl and specificity for spatial visual stimuli

First, whereas Rao *et al.*[21] described recordings from both the PFdl and the PFv, Wilson *et al.* presented quantitative data for the PFv only[10]. Thus, the claim that the PFdl plays a special role in spatial visual processing was not convincing because data for just one PFdl neuron was presented. Although related studies have suggested that many PFdl neurons show activity changes during the spatial DR (see Refs 11–13), these studies did not include any test of pattern DR. The data of Fuster and Rao, which bear directly on this issue, suggest no significant preference for encoding either form or spatial visual information in Pfdl (Refs 21,23).

Wilson *et al.* did note that PFdl neurons fired during both the spatial DR and the pattern DR, although no quantitative data were presented in that study[10]. On this basis, it was suggested that the activity observed in the PFdl may reflect the encoding of the response direction and, in this respect, the results do not differ from those reported by Rao and co-workers[21]. Therefore, in essence, both studies agree that the modality of a visual stimulus does not necessarily affect whether or not a PFdl neuron will fire.

PFv and specificity for pattern visual stimuli

A second difficulty in interpreting the results of Wilson and colleagues relates to the unusual nature of their pattern DR task. Whereas in pattern DR the association between the stimulus and the response is a learned and arbitrary one, the spatial DR task involves a simpler, more compatible stimulus response mapping; the saccadic response is directed to the position of the cue that instructed it. A substantial literature (see Refs 24–27 for reviews) suggests that such

Box 2. The evidence for domain specificity from human functional brain imaging

While human brain imaging studies cannot begin to approach the resolution of single-unit recording studies, they do have the advantage of recording activity simultaneously throughout a larger area of the brain. Any modality-specific regions, wherever they are within the frontal lobes, should be apparent on analysis. Two recent meta-analyses of the functional neuroimaging literature on working memory[a,b] concluded that both spatial- and form/pattern-based tasks 'activated' both dorsal and ventral divisions of the prefrontal cortex. There was, however, a suggestion that two clusters of sites could be seen within the PFv: tasks with pattern, colour or face stimuli tend to activate a region of PFv ~2 cm in front of the part of PFv activated by moving or spatial stimuli. However, this segregation was not apparent in two preliminary reports of functional magnetic resonance imaging studies that directly contrasted object and spatial working memory[c,d]. Such evidence leaves open the possibility of modality-based specialization within the prefrontal cortex, although it is clearly not at the PFdl/PFv area level specified by Goldman-Rakic and colleagues. It is, however, consistent with the connections of the PFv with both the temporal and parietal lobes (see Box 1).

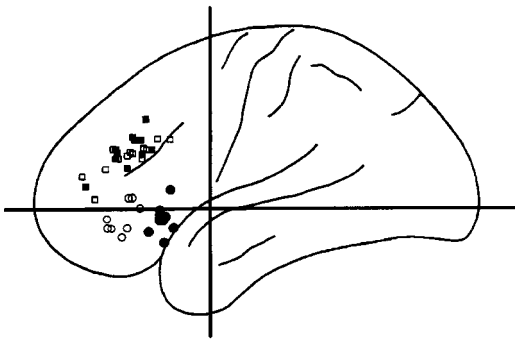

Fig. A schematic diagram illustrating the distribution of activation foci reported in recent imaging studies of working memory. Filled squares, location of activation foci produced by spatial memory tasks in the PFdl; unfilled squares, location of activation foci produced by form/face memory tasks in the PFdl; filled circles, location of activation foci produced by spatial memory tasks in the PFv; unfilled circles, location of activation foci produced by form/face memory tasks in the PFv. (Adapted from Ref. b.)

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learned, arbitrary associations depend critically on various regions of the frontal lobe. Furthermore, some recent preliminary evidence has suggested that the Pfv, as opposed to the PFdl, is especially important for such tasks[28]. Therefore, the preference of the PFv neurons recorded by Wilson *et al.* for the pattern DR task may not simply reflect the fact that visual patterns were presented; it may be a consequence of the non-standard stimulus response mapping that links the patterned stimuli with the spatial response. In contrast, Rao *et al.* required their monkeys to attend first to the centre of the screen and subsequently to a peripheral location, without the need for an arbitrary conditional association between a stimulus and a location[21]. Similarly, the design used by Fuster and co-workers also involved a simple and compatible pairing of sample stimuli and matching responses[23].

Electrode placement

The discrepancy between the recent results of the Wilson *et al.* and Rao *et al.* studies might also be explained by slight differences in electrode placement, which could mean that the groups recorded in different cytoarchitectonic areas. Although Rao and colleagues state that they mapped a 12 mm by 12 mm area centred on the sulcus principalis, neither they nor Wilson present detailed histological maps of the site of electrode penetrations made during their studies. If Rao and co-workers did not record more ventrally than 6 mm below the principal sulcus, as implied, they would not have included the full extent of inferior convexity area of PFv. There is disagreement about precisely where the border is to be drawn between areas usually assigned to the PFdl and the PFv (see Refs 29–32). The border, however, is likely to be at least 5 mm ventral to the principal sulcus in the more caudal parts of the prefrontal cortex[32]. The border is probably much closer to the principal sulcus in more anterior parts of prefrontal cortex. It remains a possibility that the form-specialized neurons reported in the Wilson *et al.* study are very ventral and that Rao and colleagues would have found more evidence for regional differentiation of function if they had sampled a greater number of more ventral neurons.

Functional subdivision within the prefrontal cortex: new conjectures

The question remaining is whether or not there are sufficient grounds for proposing any level of functional subdivision within the prefrontal cortex (see Boxes 2 and 3). A further study by Ó Scalaidhe *et al.* has suggested a highly specialized role for PFv in face processing[33]. In that study, the distribution of neurons that fired selectively to pictures of other monkeys' faces were mapped across the prefrontal region. Unlike the earlier paper from this group[10], there was little ambiguity about the proposed location of the face-selective neurons. All except two (95%), were located in the PFv, with the majority clearly situated in the inferior convexity, ventral to the principal sulcus and dorsal to the lateral orbital sulcus. In contrast, none of the 480 neurons recorded in the sulcus principalis or the 300 neurons recorded in the superior convexity were selective for faces.

Box 3. Domain-specific functional segregation within area 8 and the frontal eye fields

There are other frontal lobe areas that are preferentially connected with either the dorsal or ventral visual stream areas in the parietal lobe and the temporal lobes and may also be candidates for sensory domain-specific processing. Dorsal area 8A, or 8Ad (Ref. a) is part of the frontal eye field situated just behind the PFdl area, and it may be especially involved in processing spatial information. It receives an input from the dorsal visual stream areas mainly in the parietal but not the temporal lobe[b–d]. In the macaque monkey, both cell recording[e] and lesion studies[f,g] are consistent with this area having an important role in spatial delay oculomotor tasks. In recent human functional neuroimaging studies of spatial, but not non-spatial memory[h,i], activation has been recorded in an area far behind the middle frontal gyrus that may be homologous to 8Ad. Activation has also been seen in human area 8 in tasks that lack a spatial component[j,k]. The foci in these cases are located ventrally and anteriorly and may be situated in a human homologue of the ventral part of area 8A – area 8Av. This area has connections with both the ventral form processing areas of the temporal lobe and the dorsal spatial processing areas of the parietal lobe[b–d].

It remains to be seen, however, if any of these more posterior frontal activation foci can be distinguished from similar areas that are activated during spatial attention tasks with no working memory component. Tasks with just a spatial attention component activate the more dorsal area, while tasks with just a form/pattern attention component activate the more anterior ventral area[k–m].

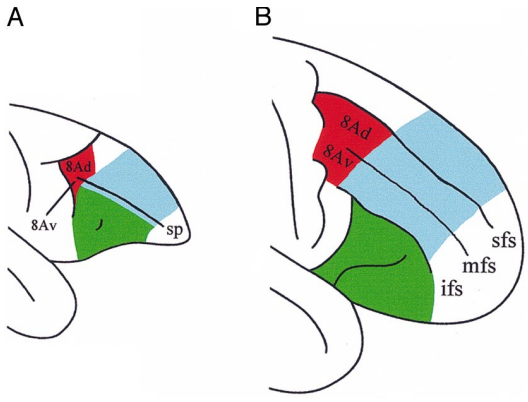

Fig. Lateral frontal cortex in macaque and human brains. Schematic drawing of the lateral surface of the macaque monkey brain **(A)** and the human brain **(B)** to indicate the location of dorsal areas 8Ad and 8Av. ifs, inferior frontal sulcus; mfs, middle frontal sulcus; sfs, superior frontal sulcus; sp, sulcus principalis. (Adapted from Ref. a.)

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The authors do not attempt to reconcile their results with the apparent absence of any functional specialization reported in the earlier study by Rao *et al.*[21], although this issue clearly needs to be addressed. To this end, it is important to emphasize that while the latest results reported by Ó Scalaidhe *et al.* argue for a preponderance of face-selective cells in the PFv, they do not necessarily demonstrate or suggest an absence of face-responsive cells in the PFdl. Rather, they demonstrate that PFdl cells that respond to faces are not *selective* for faces; to be considered such, the responses to faces would have had to have been twice that of the responses to anything else, according to the author's criterion. Moreover, by focusing on face stimuli, the paper does not discuss the possibility that there might be selectivity for patterns other than faces within either the PFv or PFdl.

It is also the case that the latest report of PFv face-selective cells[33] does not demonstrate an absence of spatial processing effects in the PFv, as no tests of spatial selectivity of the sort used by Rao *et al.* were reported. In spite of this, the finding that spatial manipulations do modulate the activity of PFv neurons[21] should not be over-interpreted as indicating that this area plays no role in the processing of pattern stimuli. By analogy, it is now clear[34] that the spatial direction of attention modulates the activity of cells in area V4 of the ventral visual stream (the 'occipito–temporal pathway'), even though it is clear that this area is essential for form vision[35].

The third and most important issue is that, although both studies[21,33] used form stimuli, the face stimuli used in the latter investigation may have had a particular salience

Box 4. Is the frontal lobe really essential for working memory?

Are delays important for prefrontal cells?

In addition to the electrophysiological studies described above there is a wealth of literature from primate lesion studies and electrophysiology in the temporal lobe that bears on the issue of domain specificity in working memory. For example, although several studies have suggested that restricted dorsolateral lesions have no effect on tasks unless they have both a spatial component[a,b] (but see Refs c,d) and a delay component[e–g] (but see Ref. h); no similar consensus has been reached regarding the role of the PFv in non-spatial memory tasks. In fact, lesions here impair a wide range of tasks, regardless of whether they involve object or spatial information[a,b,i] and impair object matching even when the sample and the match are simultaneously present and there is no delay component[j]. Thus, once a simultaneous version of a task has been relearned, the imposition of a delay between sample and match poses no more of a problem for a monkey with a PFv lesion than it does prior to surgery.

Such a finding may at first seem at odds with the delay period activity of the cells recorded by both Wilson *et al.*[k] and Rao *et al.*[l] However, the fact that single cells in monkeys are active or that whole regions in human subjects are activated during functional imaging of delays does not necessarily mean that the cells' function is simply to bridge delays. Cells in other brain areas such as the premotor cortex are known to have activity that persists during delay periods[m–o], but in this case it appears that this is just one aspect of the area's broader role in movement selection. By analogy, the role of the PFv may also not be confined to maintaining working memory representations.

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for monkeys. As noted by Ó Scalaidhe and co-workers themselves, it may be the salience of the stimuli, rather than the fact that the stimuli are forms, which marks them out for processing in the PFv. Finally, it is critically important for the ongoing debate regarding the functional organization of working memory processes in the lateral frontal cortex to emphasize that the paradigm used by Ó Scalaidhe *et al.*, unlike those used by Wilson *et al.* and Rao *et al.*, did not require memory. In fact, all neuronal responses were measured during passive viewing of form stimuli (such as faces) and, in this respect, do not differ significantly from similar neurons found in the inferior temporal cortex[36–38] (see Boxes 4 and 5).

Several recent lines of evidence have suggested that, if any functional subdivision does exist between the dorsolateral and ventrolateral frontal cortical regions, then it is not based on stimulus modality. Moreover, the available evidence suggests that the functions of both the ventrolateral and dorsolateral regions of the prefrontal cortex extend beyond the short-term maintenance of information. As discussed above, the PFv is essential for learning arbitrary stimulus response associations that are not handled by other specialized brain areas[25,26,28]. In addition, the prefrontal cortex has been shown to play an essential role in switching attention to behaviourally relevant aspects of the world[39–41]; while some neurons appear to have a preference for stimuli, such as faces, that are always particularly salient for primates[10,33], others encode whatever is the currently relevant stimulus dimension[21,42,43]. For example, Sakagami and Niki trained their monkeys to make or withhold a response depending on which stimulus they were shown[43]. On some blocks of trials the relevant dimension of the stimulus was its colour, on other trials it was its position or shape. The PFv neurons appeared to encode the stimulus dimension of current interest to the monkey. This is reminiscent of the flexible switching between the encoding of pattern or spatial position during task stages reported by Rao *et al.*[21] Flexible encoding of task-relevant variables is consistent with accounts of prefrontal function that emphasize its importance in the switching and the top-down modulation of attention[39–41,44,45]. Compromising such an attentional function would cause a failure to realize when a stimulus was of any relevance; this could plausibly underlie the finding that monkeys with PFv lesions ignore the irrelevant no-go cues on an asymmetrically rewarded go/no-go task[46]. These two putative functional roles, conditional response selection and attentional switching, are not mutually inconsistent and may both depend upon the integrity of the PFv. For example, Li *et al.*

Box 5. Delay activity outside the frontal lobe

Visual form-specific neurons with activity that is sustained during a delay have also been found in area TE and in perirhinal cortex in the anterior temporal lobe[a–c]. Delay-dependent activity has even been recorded in the primary sensory cortex of the somatosensory system when monkeys were trained to perform a haptic delayed response task[d]. The existence of such neurons demonstrates that 'working memory' may be sustained by the activity of cells outside of the frontal lobe. The visual temporal lobe neurons have also been recorded in object matching tasks in which distracting, non-match objects were presented in the delay between the first presentation of the object and its later presentation as the target match. Until recently, it appeared that the delay activity of PFv neurons was unique, in that a form-selective response was sustained even when distracting objects were presented during the delays[e]; by contrast, the temporal cortical delay activity does not survive the presentation of intervening stimuli[f]. Just recently, however, Suzuki and colleagues, have shown that delay activity in another more medial temporal lobe area, the entorhinal cortex, is similar to that seen in the PFv, in that it continues even during the presentation of intervening stimuli[g]. In conclusion, PFv is not solely concerned with sustaining memory through delays (Box 4), nor is it the sole area that is able to sustain memory through delays. It is the interactions between the prefrontal areas and the more posterior cortices that underlie an organism's ability to accommodate delays in its behaviour. This issue has received comparatively little attention[h–j] and the nature of the prefrontal cortex's contribution to the interaction is not clear.

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taught monkeys a conditional response task and recorded from PFv cells while the monkeys learned to associate each of the learned responses with a new cue[47]. Initial results showed that some PFv cells were particularly modulated during the process of learning the selection rule associated with each of the novel stimuli.

Regarding the PFdl region, alternatives to the domain-specific model also tend to ascribe functions to this area that go beyond simply holding information 'on-line'. For example, Owen and colleagues[48] have provided evidence to support a two-stage model of working memory processing within the human lateral frontal cortex[26]. According to that model, the mid-dorsolateral frontal cortex is only recruited in working memory tasks when active manipulation or 'monitoring' of that information is required. This role may be similar to the function of the 'central executive' in relation to working memory[1]. Moreover, as this model allows polymodal representation of information within frontal regions, it concurs with the fact that, in functional imaging studies, overlapping activation foci within areas 9/46 of the mid-dorsolateral frontal cortex have been reported frequently in studies of spatial, non-spatial (visual) and verbal working memory (for reviews, see Refs 49,50). Although different types of stimuli were used in each of these studies, in all of the tasks employed the response required for each stimulus was not specified directly by that stimulus, but rather had to be computed by comparing that stimulus with information assimilated earlier in the trial (for instance, from previous stimuli). For example, McCarthy and co-workers, used functional magnetic resonance imaging to demonstrate changes in PFdl regional cerebral blood flow (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[51]. In contrast, spatial and non-spatial working memory studies which activate PFv, but not PFdl, tend to emphasize the short-term retention of information and the sequencing of responses based directly on that information[48,52,53].

To conclude, the available evidence does not support a modality-based system of organization within the lateral prefrontal cortex. Moreover, if the frontal lobes participate in working memory they certainly do not do so in isolation; rather they operate as one component of a distributed neural system. The question that now needs to be resolved is what are the specific contributions of the prefrontal regions to this distributed system. We suggest that the PFdl contributes to the manipulation of information within memory. In contrast, the role of the PFv may be in selecting information currently of relevance; this is a prerequisite for any putative working memory function and also for the formation of longer-term associations.

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