

## The mid-ventrolateral frontal cortex and attentional control

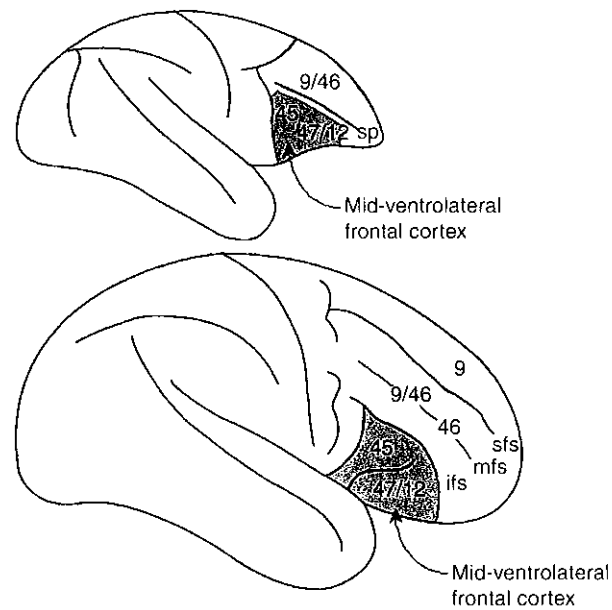
Adrian M. Owen and Adam Hampshire

### Introduction

For many years it has been known that medial temporal-lobe damage in humans produces profound memory impairments, while patients with frontal-lobe lesions often perform normally on many standard tests of memory (Lee *et al.*, 2000a; Petrides, 1994). The pattern that has emerged from functional neuroimaging studies in healthy volunteers is quite different, with increases in activity reported in medial temporal and frontal-lobe areas during many different memory tasks (Buckner *et al.*, 1995, 1999; Fletcher & Henson, 2001; Lee *et al.*, 2000a). One region that has been consistently activated is the mid-ventrolateral frontal cortex which, in humans, lies below the inferior frontal sulcus and includes Brodmann areas 45 and 47 (Brodmann, 1909) (see Figure 11.1). Activity in this region has been reported frequently during spatial, verbal and pattern *working* memory tasks (Owen *et al.*, 1996a, 2000; Stern *et al.*, 2000), but also during *episodic* memory tests of encoding and retrieval (Fletcher *et al.*, 1998; Lee *et al.*, 2000b; Owen *et al.*, 1996b).

Broadly speaking, these data support psychological models of memory in the sense that they confirm that certain common 'executive' or 'control' processes are vital to many different aspects of normal mnemonic processing. However, they go further than that in two important ways; first, by identifying that, within the frontal lobe, it is the mid-ventrolateral region that is central to this process or set of processes (e.g. Petrides, 1994; Owen 1997). Second, by demonstrating that activity in this region may just as easily map onto existing psychological models of other cognitive systems that are related to, but quite distinct from, theories of memory, e.g. *attention*. Thus, the fact that activation in the mid-ventrolateral frontal cortex has also been widely reported in tasks that do not place any significant demands on memory at all (e.g. Dove *et al.*, 2000, Cools *et al.*, 2002, Rushworth *et al.*, 1997) suggests that the function, or functions, of this region are not restricted to the memory domain, but rather, form part of a more general role in cognitive control processes. A corollary of this position, of course, is that these psychological systems may be less distinct (both functionally and neurally) than current cognitive models would have us believe.

In this chapter, we will review recent neuroimaging evidence that suggests that the mid-ventrolateral region of the frontal cortex plays a specific role in *intended action*; that is, any behaviour (e.g. an action or a thought), that is consciously *willed* by the agent responsible



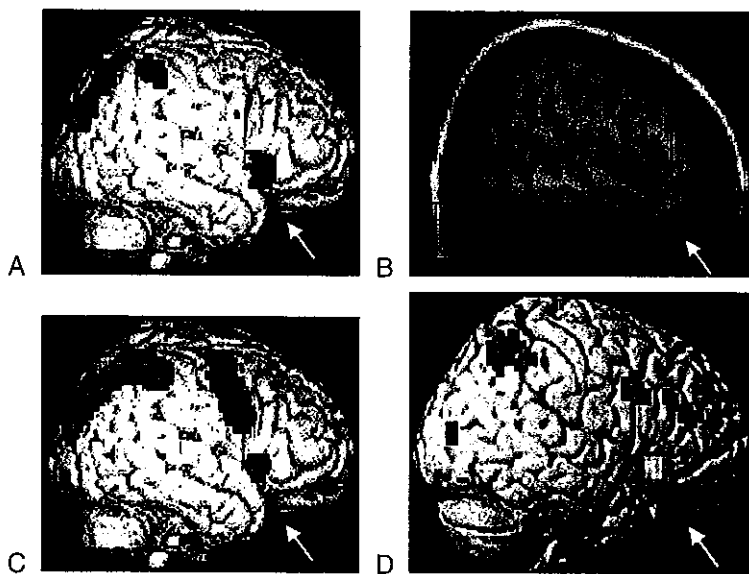
**Figure 11.1** Schematic drawing of the lateral surface of the macaque brain (top) and the human brain (bottom), to indicate the location of the ventrolateral frontal cortex (areas 45, 47, 12). Adapted from Petrides and Pandya (1994). sp = sulcus principalis. ifs = inferior frontal sulcus. mfs = middle frontal sulcus. sfs = superior frontal sulcus.

for carrying out that behaviour. In this sense, it makes contributions to both memory and attention in a manner that cannot be predicted by current psychological models of either cognitive system. We will also argue that the basis for this role lies in the capacity that this region has for tuning rapidly to those aspects of any given task that are currently relevant, whilst becoming unresponsive to that same information when the task demands change. Although consistent with psychological models of memory and attention, these conclusions could not have been reached based solely on the predictions of those models. On this basis we argue that data from functional neuroimaging studies in healthy volunteers, neuropsychological investigations in patients and evidence from lesion and electrophysiological studies in the macaque have informed, and will continue to inform, psychological theories of memory.

### The mid-ventrolateral frontal cortex and memory

Although many functional neuroimaging studies have activated the mid-ventrolateral frontal cortex in a variety of behavioural contexts, few have explicitly set out to investigate the role of this region directly. However, a significant number of early imaging studies did report activity in this region during tasks that emphasised the explicit retrieval of one, or a few, pieces of information and the sequencing of responses based directly on that stored information. For example, in one early positron emission tomography (PET) study (Jonides *et al.*, 1993; also see Smith *et al.*, 1995), healthy volunteers were required to

remember the location of three simultaneously presented stimuli and then to decide whether or not a probe circle occupied one of those same three locations following a three second delay. Activation was observed in the mid-ventrolateral frontal cortex, but not in more dorsal regions of the frontal lobe. In a subsequent PET study of spatial span, the participants were required to remember a sequence of five previously presented locations, and then to respond directly by touching those same locations following a delay (Owen *et al.*, 1996a). The emphasis of the task was on the explicit encoding of spatial information and the uncued recall of this information following a short delay. A significant regional cerebral blood flow (rCBF) increase was observed in ventrolateral area 47 of the right hemisphere (Figure 11.2A), similar in location to that reported previously by Jonides and colleagues (1993). In a second task that required the volunteers to execute a fixed sequence of responses to eight previously learned locations, ventrolateral frontal area 47 was again significantly activated, bilaterally (Owen *et al.*, 1996a). During both of these tasks, rCBF changes within other frontal regions, including the dorsolateral frontal cortex did not approach significance. In a subsequent PET study, the 5-item spatial span task was used again, but compared with a variation on the more commonly used spatial '2-back' procedure (Owen *et al.*, 1999). Again, during the spatial span task, which (unlike the 2-back task) only required the retrieval and reproduction of stored information, a significant



**Figure 11.2** Four independent neuroimaging studies of memory activating an almost identical location within the mid-ventrolateral frontal cortex. (A) spatial span (adapted from Owen *et al.*, 1996a) (B) digit span (adapted from Owen *et al.*, 2000) (C) spatial span (adapted from Owen *et al.*, 1999). (D) Intentional retrieval of previously remembered abstract patterns (adapted from Dove *et al.*, 2006). Right hemisphere only is shown. Activity in the mid-ventrolateral frontal cortex is indicated with an arrow in each study.

rCBF increase was observed in the mid-ventrolateral prefrontal cortex at co-ordinates very similar to those reported previously (Jonides *et al.*, 1993; Owen *et al.*, 1996a) (Figure 11.2C).

To assess whether these effects were domain specific, a direct analogue of the spatial span task was developed (Owen *et al.*, 2000), based on the classic digit span paradigm. During one experimental task, subjects were required to hold a sequence of five auditorily presented numbers in memory (e.g. 7, 3, 8, 2, 9), and then to respond by (verbally) producing those numbers, in order, following a short delay. As predicted, when this digit span task was compared to a control task, significant activation was observed in right mid-ventrolateral area 47 at co-ordinates similar to those reported previously in studies of spatial span (Owen *et al.*, 1996a, 1999; see also, Jonides *et al.*, 1993; Smith *et al.*, 1995) (Figure 11.2B). In contrast, a backwards digit span task, identical in every respect (except the sequence had to be recalled in reverse order), activated both the mid-ventrolateral and the mid-dorsolateral frontal cortices.

In summary, these early imaging findings suggest that the mid-ventrolateral frontal cortex, but not more dorsal regions of the frontal lobe, is required for simple memory tasks that involve only the active encoding and/or retrieval of information. Moreover, this role appears to be independent of the modality of the stimuli to be remembered/recalled.

Given these results, it is somewhat surprising that patients with frontal-lobe lesions are typically unimpaired on such tasks (D'Esposito & Postle, 1999). One likely explanation for this apparent discrepancy is that the methods used to test patients on these types of task have not been sensitive enough to elicit existent (yet subtle) deficits. In support of this possibility, although most previous studies of spatial span have reported no significant deficit in frontal-lobe patients (Canavan *et al.*, 1989; Greenlee *et al.*, 1997; Miotto *et al.*, 1996; Owen *et al.*, 1990), in almost all cases these studies have reported a numerical decrease in the performance of the patients relative to the healthy controls. We have recently developed a more sensitive paradigm for measuring spatial span (Bor *et al.*, 2005), which employs a technique that allows for a continuum of span scores, unlike the method of testing that is more commonly used which produces discrete (integer) results. Using this task, the mean span score for a group of patients with large frontal-lobe lesions was shown to be significantly reduced compared to patients with smaller frontal-lobe lesions and a matched group of healthy controls (Bor *et al.*, 2005). Unfortunately, no direct relationship between the performance deficit and damage to the mid-ventrolateral part of the frontal cortex could be established; in fact, if anything, it was patients with more extensive damage to the mid-dorsolateral frontal cortex who were most impaired. However, in patient studies it is very difficult to establish which areas of the frontal cortex are involved in a given cognitive process with any degree of anatomical precision as the excisions are rarely confined to one, or even a few, cytoarchitectonic areas. In fact, we are not aware of any neuropsychological study in patients that has convincingly demonstrated a direct association between damage to the mid-ventrolateral region of the frontal cortex and a specific pattern of cognitive impairment. More generally, however, in the last 50 years, numerous neuropsychological studies have reported, or implied, a general dissociation between the performance of patients with frontal-lobe damage on tests of

recognition and recall (for review, see Wheeler *et al.*, 1995). Such patients are more often impaired on memory tasks that require the active encoding and/or recall (especially free recall) of information, yet remain largely unimpaired on recognition memory tasks that can be solved on the basis of stimulus familiarity alone. Again, it has not been possible to relate this pattern of impairment to damage within any particular frontal-lobe region, although across the various studies, some of these patients will undoubtedly have sustained damage to the mid-ventrolateral frontal cortex.

Although the early imaging studies described above suggest that the mid-ventrolateral frontal cortex plays an important role in various types of span task, the long acquisition period of PET (typically 60–90 seconds per scan) precludes any more precise conclusions being drawn about the specific processes involved. Advances in event-related functional magnetic resonance imaging (fMRI) have made the measurement of transient cognitive events feasible by allowing short events with brief inter-stimulus-intervals to be estimated independently within a noisy background of other task-related events. In one recent fMRI study, (Dove *et al.*, 2006), colourful stimuli, based on examples of abstract art, were presented and volunteers were instructed on random trials either to just examine each piece ('incidental' encoding) or to try and remember it for later test ('intentional' encoding). Retrieval was examined by asking volunteers, on random trials, whether or not they remembered seeing specific pieces ('intentional' retrieval). In a fourth condition, designed to provide a control for these retrieval trials, volunteers were instructed to re-view stimuli that had been shown previously to elicit recognition ('incidental' re-viewing). Importantly, at the critical interval of each trial, i.e. when the stimulus was presented, all sensory and motor factors were held constant across all conditions. The only difference between conditions was how the volunteer chose to implement an *intention* based on a prior instruction. Intentional encoding led to significantly improved recall over incidental encoding, although, importantly, performance for incidentally encoded stimuli was significantly above chance. When incidental encoding was compared to the non-events, no significant activity was observed in the mid-ventrolateral frontal cortex, although significant increases in signal intensity were observed in the parahippocampal gyrus/hippocampus bilaterally. In contrast, when intentional encoding was compared to incidental encoding, significant signal intensity changes were observed in the mid-ventrolateral frontal cortex, but not in the parahippocampal gyrus/hippocampus. Thus, activity in the mid-ventrolateral frontal cortex was specifically associated with the act of *intentionally encoding* stimuli while non-intentional encoding (as indexed by later recognition performance), yielded no activity in this region. When incidental re-viewing and non-events were compared, again, no significant activity was observed in the mid-ventrolateral frontal cortex, although significant signal intensity changes were observed in the parahippocampal gyrus/hippocampus bilaterally. In contrast, when intentional retrieval was compared to incidental re-viewing, the mid-ventrolateral frontal cortex was activated bilaterally, but no significant differences in activity were observed in the medial temporal lobe (Figure 11.2D). Thus, activity in the mid-ventrolateral frontal cortex was specifically associated with the act of *intentionally recalling* whether stimuli had been seen previously, while re-viewing stimuli with no particular intention in mind, yielded no activity in this region.

In a follow-up study, these results were extended to examine the response of the mid-ventrolateral frontal cortex to a more diverse range of stimulus types, including abstract art, faces, and scenes (Dove *et al.*, 2008). Again, this region was only significantly active in the conditions where the volunteer was explicitly instructed to try and remember, or recall, a stimulus regardless of its type (face, scenes, or abstract art). In contrast, stimulus-specific activity was observed in the fusiform face area (to faces) and the parahippocampal place area (to scenes), irrespective of whether an instruction to encode or recall had been given or not. In fact, the task instruction was the only factor that modulated activity in mid-ventrolateral cortex, whereas other factors such as stimulus type, task type, or stimulus repetition did not have any effect at all (Dove *et al.*, in press).

The results of these two studies demonstrate that simply changing the task instructions at encoding and retrieval to encourage intentional processing results in an increase in signal intensity in the mid-ventrolateral frontal cortex, but not in other regions of the brain that are known to be involved in memory for those stimuli. These findings suggest that the implementation of an intended act, or plan to remember or recall, may be the common factor that underlies activation of the mid-ventrolateral frontal cortex during many previous neuroimaging studies of memory (e.g. Jonides *et al.*, 1993; Owen *et al.*, 1996a, 1999, 2000; Smith *et al.*, 1995; Henson *et al.*, 1999; Wagner *et al.*, 1998; Courtney *et al.*, 1997). In the case of short-term or working memory tasks, this might correspond to the relatively straightforward mapping of stimuli to responses such as that which occurs in spatial and digit span tasks (e.g. Owen *et al.*, 1996a, 1999), or even simple delayed matching to sample paradigms (e.g. Elliott & Dolan, 1999). In the case of long-term episodic memory (e.g. verbal paired associate learning), these intentional encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g. a category exemplar) to a specific stimulus (e.g. a category name) (e.g. Fletcher *et al.*, 1998a, 1998b).

In summary, we suggest that an important factor for understanding the role that the mid-ventrolateral frontal cortex plays in memory and its relationship with more posterior regions (e.g. the medial temporal-lobe system) is the extent to which a volunteer explicitly *intends* to remember or retrieve a given stimulus and the changes in attentional control that may be consequent upon such an intention.

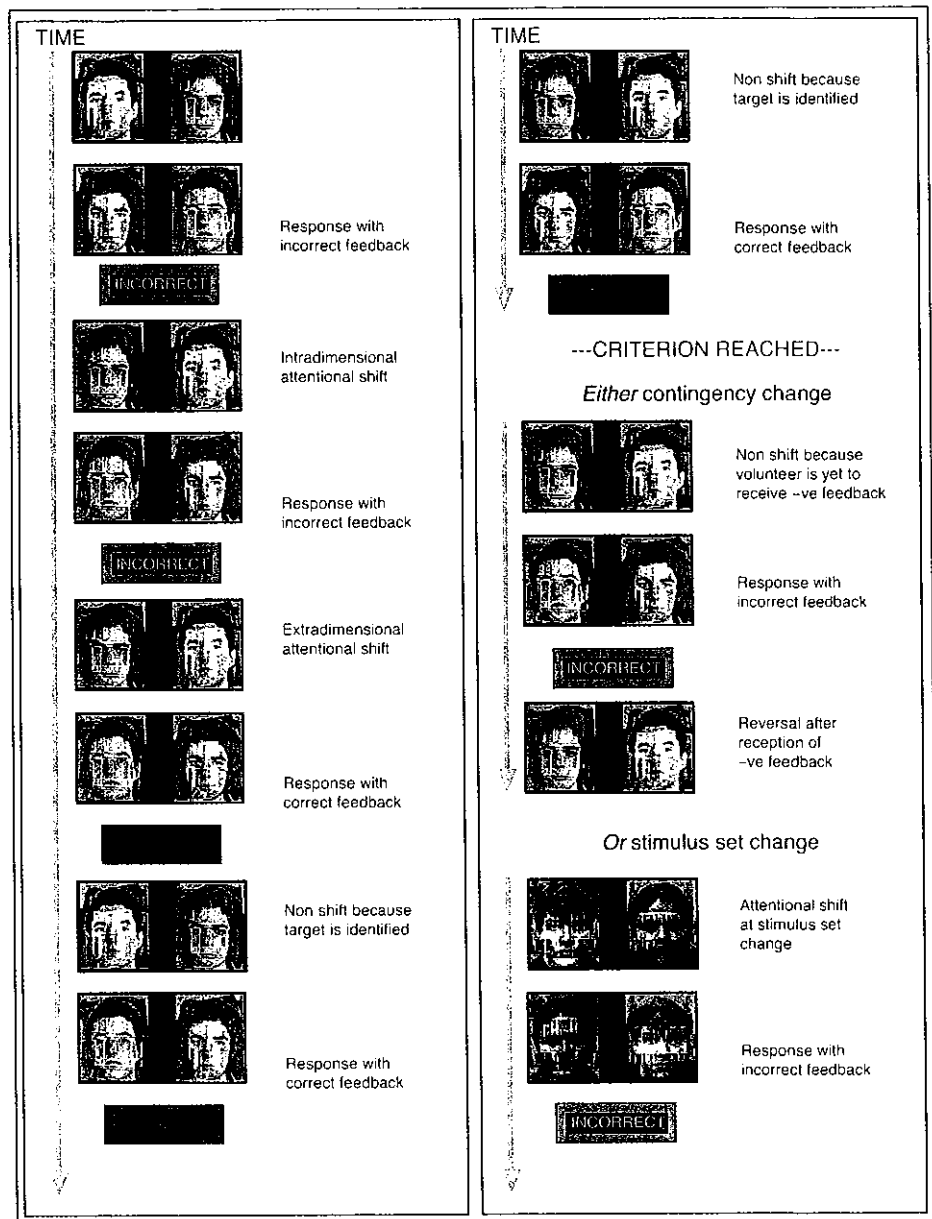
### **The mid-ventrolateral frontal cortex and tasks that do not require memory**

Although all of the studies described above have reported activation in the mid-ventrolateral frontal cortex during tasks that place various demands on memory processes (see Figure 11.2), activity in this region has also been reported frequently during tasks that appear to make no direct demands on memory at all. For example, the mid-ventrolateral frontal cortex has been activated during stimulus selection (Rushworth *et al.*, 1997), when judgements of word meaning are required (Kapur *et al.*, 1994) during reversal learning (Cools *et al.*, 2002), inhibition (Konishi *et al.*, 1999), extra dimensional set-shifting (Nakahara *et al.*, 2002; Hampshire & Owen, 2006) and task switching (Dove *et al.*, 2000). Similarly, patients

with frontal-lobe damage are impaired on many tasks, some of which have no obvious mnemonic component at all (e.g. Milner, 1964; Luria, 1966; Corkin, 1965; Semmes *et al.*, 1963). Whilst each of these tasks, arguably, require memory of some sort (if only to remember the task instructions), it seems unlikely that memory *per se*, or any specific mnemonic process, is the common feature that results in activation of the mid-ventrolateral frontal cortex, or an impairment in the patients with frontal-lobe damage. On the other hand, they do all require the self-initiated, conscious (i.e. intentional) selection of appropriate responses, often in the absence of external cues.

In one recent study, event-related fMRI was used to examine frontal-lobe activation in healthy human volunteers during performance of a probabilistic reversal learning task (Cools *et al.*, 2002). Reversal learning involves the adaptation of behaviour according to changes in stimulus-reward contingencies and places a relatively low load on memory. It is exemplified by visual discrimination tasks where subjects must learn to respond according to the opposite, previously irrelevant, stimulus-reward pairing. Reversal learning is disrupted following lesions of ventral prefrontal cortex in non-human primates (Iversen & Mishkin, 1970; Dias *et al.*, 1996). However, evidence of the same system being involved in reversal performance in humans is limited to two studies in patients with non-selective ventral prefrontal cortex damage (Rolls *et al.*, 1994; Rahman *et al.*, 1999). In the study by Cools *et al.* (2002), volunteers were required to respond to one of two stimuli according to probabilistic feedback; thus switches in the correct response were uncued in the sense that they could not be determined based on the feedback received on any given trial (e.g. the trial immediately prior to a switch). A significant signal change was observed in the right ventrolateral prefrontal cortex on trials when subjects decided to stop responding to the previously relevant stimulus and shifted responding to the newly relevant stimulus. Moreover, the response on the final reversal error, prior to shifting, was not modulated by the number of preceding reversal errors, indicating that error-related activity does not simply accumulate in this network, but rather, corresponds precisely to the exact moment when volunteers *decided to make the shift*. These data indicate that intentional shifting of lower-level stimulus-reward associations is sufficient to activate the ventrolateral prefrontal cortex. The study also concurs well with other, human brain imaging studies that have emphasized a role for the right ventrolateral prefrontal cortex in behavioural inhibition (or intentional stopping) using go-no go tasks (Garavan *et al.*, 1999; Konishi *et al.*, 1999).

Unfortunately in many studies that have used shifting tasks to examine attentional control, multiple discrete cognitive operations have been confounded within the design, making it impossible to define the exact contribution made by the mid-ventrolateral frontal cortex. For example, in the study by Cools *et al.* (2002) described above, volunteers were required to shift attention between two stimuli based on changes in partial reinforcement contingency. The same stimulus set was used repeatedly and consisted of complex stimuli; hence reversals, stimulus change, stimulus-response mapping change, and possibly even dimension change, were all confounded. In another relevant study (Dove *et al.*, 2000), isolation of the multiple components of switching was only achieved



**Figure 11.3** A typical series of trials from the study by Hampshire and Owen, (2006). In this example, the participant initially chooses the face in the left superimposed face/building pair and so indicates left with the button box by pressing the button with right index finger. When the response is made, the stimuli are removed from the screen and reappear after a short interval rearranged with the chosen face on the right of the screen superimposed on the other building; the participant therefore indicates right by pressing button with right middle finger. Because the face-building combinations swap from one trial to the next, the program can compute which item was selected and because (in this example) it is not the target, negative feedback



by confounding stimulus colour change, reversal of rule, and the reversal of response. Similarly, several previous fMRI studies that have used variants of the Wisconsin Card Sorting Test have confounded attentional switches between dimensions with reception of negative feedback, response inhibition, and updating working memory (e.g. Konishi *et al.*, 1998). Most importantly, all of these studies have focused on experimental manipulations (e.g. experimenter imposed shifts) rather than volunteer behaviour during the scanning session.

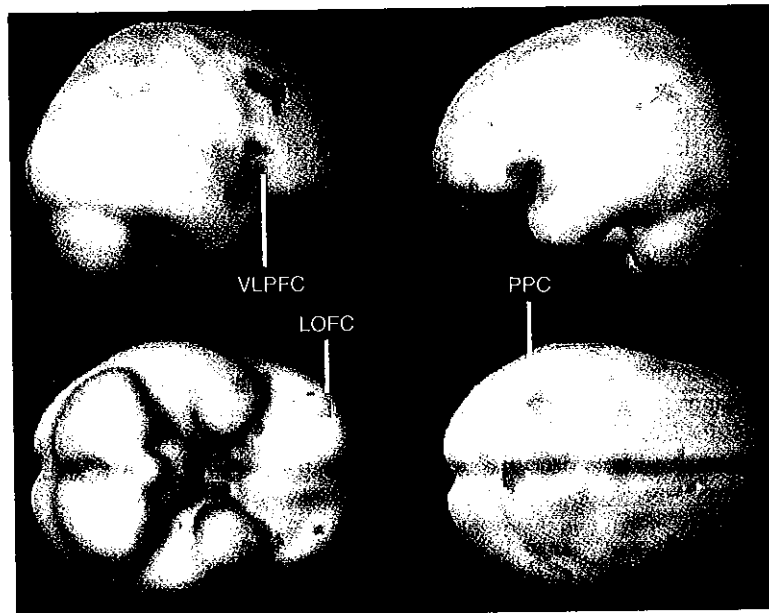
In one recent fMRI study, a novel approach was used in which the responses of the volunteer dictated the pace and order of experimental events (Hampshire and Owen, 2006 – see Figure 11.3 and legend for description). Hence, the focus of attention could be monitored and used to define the events (e.g. attentional shifts), rather than those events being dictated by the experimental design. This approach allowed the volunteers chosen decision-making strategies and attentional shifts to be functionally and behaviourally examined independent of the will of the experimenter. Many stimulus sets were used, each containing stimuli of two distinct types (faces and buildings). Switches of attention between stimuli of the same type (intra-dimensional shifts) and between stimuli of different types (extra-dimensional shifts) could therefore be modelled. Owing to the difficulty of intermixing extra- and intra-dimensional shifts without using unnatural cueing or fixed order event sequences, previous studies have often used blocked designs that allow only limited interpretation of the activation results (e.g. Rogers *et al.*, 2000). In the study by Hampshire and Owen (2006), these transient attentional control functions were intermixed and could therefore be contrasted at the event level in the current trial and error situation (see Figure 11.3). Thus, extra- and intra-dimensional shifts could be compared directly, effectively isolating the extra-dimensional component of shifting from other switch-related processes, such as inhibition of the previously relevant response

← ('INCORRECT') is given. Subsequently the stimuli reappear on the screen and the participant selects the other face (intra-dimensional, ID shift). Following the second response, negative feedback is given and the participant switches to select the building on the right of the screen (extra-dimensional, ED shift). Following the second response to the building, positive feedback ('CORRECT') is given because the participant has correctly identified the target item. When the stimuli reappear on the screen, the participant responds to the same building, as they now know that it is the target (early correct response). They receive positive feedback on the second response, and so continue to select the same building (late correct response). After responding correctly again they receive positive feedback and have now reached the criterion of six correct responses in a row. One of two things then happens; either a new stimulus set is presented, in which case the participant starts searching for the new target (set change). Alternatively, the reward contingency changes, in which case the participant responds twice more to the same building (because they have no way of knowing that anything has changed) before receiving negative feedback. They must then inhibit their responses to the recently rewarded target object, and start trying to identify which of the other three possible items has become the target (reversal). It is important to note that the extra- and intra-dimensional shift events, along with the feedback, do not always occur in the sequence shown because the order in which the stimuli are tested is determined entirely by the choices made by participants.

(Nakahara *et al.*, 2002). The novel partial feedback paradigm also enabled switch events and feedback events to be modelled separately, allowing regions involved in abstract reward processing and/or the implementation of attentional control to be measured independently.

The behavioural data demonstrated that moving attention between stimulus dimensions caused more errors than moving attention between stimuli of the same type. Since all target changes could logically be solved within the same number of trials, these differences must reflect the various strategies employed by the volunteers to solve the task. The main question for the imaging data, therefore, was whether this component of attentional control (extra-dimensional shifting) would be associated with any specific neural substrate. Accordingly, when shifts in the focus of attention between stimulus types (extra-dimensional shifts) were directly compared with shifts within stimulus type (intra-dimensional shifts), significant activation was observed only in the mid-ventrolateral frontal cortex (Figure 11.4).

This result clarifies and extends several previous imaging studies of set-shifting behaviour. For example, Nakahara *et al.* (2002) reported previously that the ventrolateral frontal cortex is involved in extra-dimensional shifting in both humans and macaques using a modified version of the Wisconsin Card Sorting Test. However, in that study, multiple processes were confounded in the set shift itself leading the authors to interpret the observed ventrolateral frontal cortex activity as 'related to inhibition of the previous



**Figure 11.4** Adapted from Hampshire and Owen (2006). Results for the extra-dimensional shift component (green), and the reversal component (red) FDR corrected for the whole brain mass at  $p = 0.05$ . Extra-dimensional shifting was specifically associated with activity in the mid-ventrolateral frontal cortex. VLPFC = ventrolateral frontal cortex. LOFC = lateral orbitofrontal cortex. PPC = posterior parietal cortex.

relevant response'. The results of the study by Hampshire and Owen (2006) demonstrate that this is unlikely to have been the case. Thus, during reversals, where inhibition is maximal, there was no activation in the mid-ventrolateral frontal cortex compared to several other components of the task (see Figure 11.4). In addition, this region was not significantly activated when intra-dimensional shifting was compared to non-shifting trials.

On the basis of these findings, it was suggested that the commonly observed increase in reaction time for extra-dimensional shifting reflects the time taken for the ventrolateral frontal cortex to bias attentional processing between competing stimulus dimensions (Hampshire & Owen, 2006). Such attentional biasing, or 'tuning', while relevant to many components of set shifting, is likely to be maximal when a complete reconfiguration of the attentional set is required, as is the case during a shift from one dimension to another (competing) dimension (Figure 11.4).

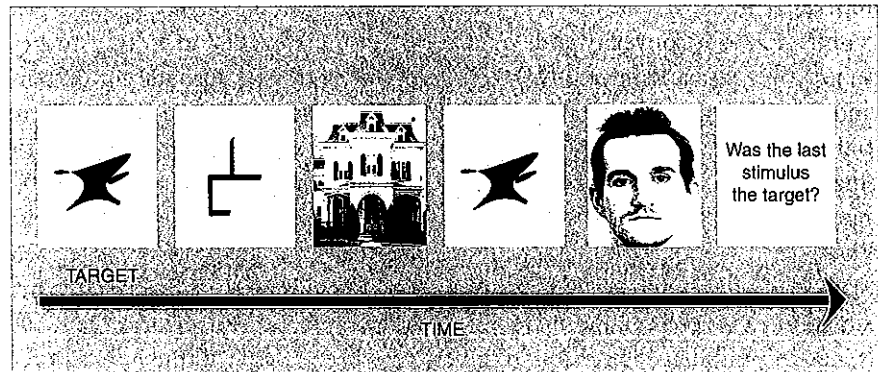
### The mid-ventrolateral frontal cortex and attentional control

In the two previous sections, we have reviewed evidence suggesting that the mid-ventrolateral frontal cortex plays an important role in intended thoughts and actions, whether that be in the active encoding and retrieval requirements of many memory tasks, or in the need to actively (or wilfully) shift attention between competing components of set-shifting tasks.

Broadly speaking, the findings from lesion and electrophysiological studies in the monkey also suggest that the mid-ventrolateral frontal cortex makes a polymodal contribution to a variety of different tasks that require the initiation and execution of intended actions. In the macaque, the mid-ventrolateral frontal cortex lies below the sulcus principalis on the inferior convexity and comprises areas 12 or 47/12 and 45 (Carmicheal & Price, 1994; Petrides & Pandya, 1994). Lesions of the ventrolateral frontal cortex, but not the more dorsal cortex surrounding the *sulcus principalis*, cause impairments in non-spatial delayed-matching-to-sample for single items (Mishkin & Manning, 1978; Passingham, 1975), spatial and non-spatial delayed alternation (Mishkin *et al.*, 1969), the learning of arbitrary stimulus-response associations (Gaffan, 1994; Petrides, 1994; Murray & Wise, 1997) switching attention to behaviourally relevant aspects of the world (e.g. Dias *et al.*, 1996), and even impair object matching when the sample and the match are simultaneously present and there is no delay component (Rushworth *et al.*, 1997). Thus, once a simultaneous version of the task has been relearned, the imposition of a delay between sample and match poses no more of a problem for a monkey with a ventrolateral frontal lesion than it does prior to surgery (Rushworth *et al.*, 1997). Electrophysiological data from the monkey also support a role for this region in the initiation of a variety of explicit cognitive processes. For example, Sakagami and Niki (1994) trained monkeys to either make or withhold a response depending on which stimulus they were shown. On some blocks of trials the relevant dimension of the stimulus was its colour, on other trials it was its position or shape. Ventrolateral neurons appeared to encode the stimulus dimension of current interest to the monkey. Similarly, Rao *et al.* (1997) identified neurons ventral to the principal sulcus, that encoded either, or both, the location and the identity of stimuli presented in a novel delayed response procedure.

Remarkably, some neurons adapted (or 'tune') flexibly as the emphasis of the task changed during its various stages. Thus, once a target object's identity was no longer relevant many of the 'what-and-where' cells no longer coded for object identity but switched to code for object location. This finding suggests that the response of ventrolateral prefrontal 'memory cells' is flexible, i.e. they can code different stimulus attributes at different times according to task demands. In other words, they will respond to a stimulus, irrespective of the modality and whenever there is an explicit requirement and an associated intention to do so. In categorisation tasks, similar properties have been described for lateral frontal neurons; e.g. Freedman *et al.* (2001) identified neurons within the monkey lateral frontal cortex that tune to respond selectively to just those categories that are currently relevant, whilst becoming unresponsive to those same categories when the task demands change.

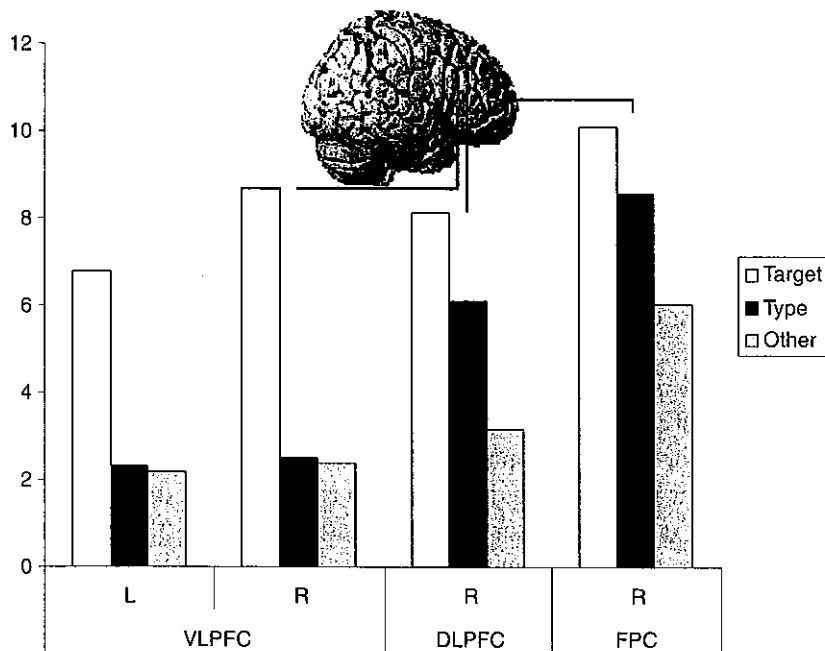
We have recently investigated whether regions of the human frontal lobe can also be shown to selectively adapt to represent currently relevant information during a simple attentional task – monitoring for a target item in a series of non-targets (Hampshire, Duncan, & Owen, 2007). Volunteers were instructed to simply look for a previously defined target item (e.g. a particular face) within sequences of non-target items. Non-targets are drawn from either the same category (e.g. another face) or a different category (e.g. a building) as the current target item, allowing categorical similarity to be used as a



**Figure 11.5** Adapted from Hampshire *et al.* (2007). Volunteers looked for the presentation of a target item within sequences of visually displayed non-target items. At the beginning of a sequence, the current target item appeared with the word 'target'. Sequence lengths were varied from 1 to 8 stimuli in a row, and the target could be presented at one, many, or none of those positions. At the end of each sequence the question 'Was the last stimulus the target?' appeared on the screen and the volunteer was required to respond yes or no, using a button box. Target and non-target items were taken from a pool of stimuli, consisting of pictures from each of four distinct categories: faces, buildings, abstract line figures, and abstract shapes. The stimuli monitored could therefore be categorised according to whether they were the target item, non-targets from the same category as the target item, or non-targets from one of the other three categories.

metric for comparing how selective the neural response in different frontal and non-frontal sub-regions actually is (Figure 11.5).

Using fMRI, we searched the brain for regions that followed either a tightly tuned profile, responding selectively to just the current target item, or a more widely tuned profile, responding to all stimuli from the same category as that target. The results demonstrated that the mid-ventrolateral frontal cortex, bilaterally, followed a tightly tuned response function; thus, activation was tightly tuned to the presentation of just the target stimulus, with no significant differences between responses to non-targets from the same or different categories as the target (Figure 11.6). In contrast, both the mid-dorsolateral frontal cortex and the posterior parietal cortex followed a more widely tuned response function, responding to all stimuli from the current target category, regardless of whether it was the actual target that was presented or not (Figure 11.6). These results confirm that, even in a simple target detection task, the role of the mid-ventrolateral frontal cortex can be dissociated from other frontal and parietal regions, according to their differential responses to targets and target category non-targets. More importantly, they suggest that the mid-ventrolateral frontal cortex acts specifically by biasing or 'tuning' attentional processing to the representations that are most relevant to the task at hand. Thus, activation within this region will be maximal whenever an intended thought or action requires a discrete (or 'tight') focus of attention, either on a specific stimulus, or on a particular



**Figure 11.6** Adapted from Hampshire *et al.* (2007). Activation levels in the frontal cortex for targets, target category non-targets (labelled 'type') and non-target category non-targets (labelled 'other'). Unlike other areas, the mid-ventrolateral frontal cortex is tightly tuned to the target with little activity in response to same type or other distractors.

aspect of the task in hand. Such a requirement is, of course, central to many memory tasks in which the memoranda need to be attended to, either for intentional encoding or for active retrieval, but is also an important component of many non-memory tasks that require that some stimuli are the targets of attention, while others are ignored (e.g. many attentional set-shifting tasks). In this context, it is perhaps not surprising that the ventrolateral frontal cortex is particularly active during extra dimensional shifting (Hampshire & Owen, 2006) given that the focus of attention needs to be shifted entirely, i.e. from one stimulus of a particular dimension to an entirely different stimulus from an unrelated dimension (see Figure 11.4).

## Conclusions

In summary, the studies reviewed here demonstrate how finely tuned experiments in both humans and in non-human primates, which are guided by psychological observations and theories, can sharpen our view of both the functional architecture and the neural bases of specific cognitive processes. For example, a wealth of data exists from neuroimaging to suggest that the mid-ventrolateral frontal cortex plays a crucial role in intended thoughts and actions across multiple cognitive domains. Crucially, the tests that were used to probe those cognitive domains were derived largely from predictions based on psychological theories and models. On the other hand, the neuroimaging data feed back into the psychological models by revealing hidden processes (e.g. fMRI events that correspond to the BOLD response in a particular task) or intervening variables within the observed behaviour. For example, in one of the neuroimaging studies described above (Hampshire & Owen, 2006 – see Figure 11.3), it was shown that the brain regions that contribute to shifting behaviour continue to be involved beyond the point at which the stimulus ceases to be novel – suggesting that there may be parallel systems, within the frontal-lobe system that remain involved, but become redundant, with familiarity. In that case, the fMRI data analysis was driven by internal events that can not be observed directly and therefore, would be impossible to predict based on psychological theories alone. Indeed, the findings are not obviously predicted by the results of lesion studies in humans or monkeys either.

The neuroimaging data have also revealed a mechanism of action for the mid-ventrolateral frontal cortex in mnemonic and attentional processes; this region appears to operate by biasing or 'tuning' attentional processing between competing representations in modality-specific posterior regions in order to maintain their relevance to current behavioural goals. Such a view is anatomically plausible given the strong bi-directional connections between many posterior cortical association areas and the mid-ventrolateral frontal region, which, in turn, is closely interconnected with the entire lateral prefrontal cortex (Petrides, 1994). Moreover, a frontal module with such properties has been proposed recently (O'Reilly *et al.*, 2002; Frank *et al.*, 2004; see also, Dehaene *et al.*, 1998), although in those computational models the critical region was defined rather more generally as the 'lateral prefrontal cortex'. Flexible tuning of task relevant variables within the mid-ventrolateral frontal cortex would be consistent with accounts of prefrontal function

that emphasise its importance in switching (Cools *et al.*, 2002; Konishi *et al.*, 1999; Nakahara *et al.*, 2002; Dove *et al.*, 2000; Hampshire & Owen, 2006) and the 'top-down' modulation of attention (e.g. Owen *et al.*, 1991, 1993; Knight, 1994; Desimone & Duncan, 1995; Dias *et al.*, 1996). Moreover, compromising such a function would be expected to affect a wide variety of tasks, but particularly any behaviour (e.g. an action or a thought), that derives from the subject's plans and intentions (Petrides, 1994).

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