R E V I E W

R.E. Passingham · I. Toni · M.F.S. Rushworth

Specialisation within the prefrontal cortex: the ventral prefrontal cortex and associative learning

Abstract This paper provides evidence that the ventral prefrontal cortex plays a role in the learning of tasks in which subjects must learn to associate visual cues and responses. Imaging with both positron-emission tomography (PET) and functional magnetic-resonance imaging (fMRI) reveals learning-related increases in activity when normal subjects learn visual associative tasks. Evidence is also presented from an event-related fMRI study that activity in this area is time-locked both to the presentation of the visual stimuli and also to the time of the motor response. Finally, it is shown in a study of monkeys that removal of the ventral prefrontal area 12 (including 45 A) impairs the ability of monkeys to relearn a visual associative task (visual matching), even though there were no demands on working memory. It is, therefore, proposed that the ventral prefrontal cortex constitutes part of the circuitry via which associations are formed between visual cues and the actions or choices that they specify. On the basis of the existing anatomical and electrophysiological data, it is argued that the prefrontal cortex is the only area that can represent cues, responses and outcomes.

Key words PET · fMRI · Ventral frontal cortex · Motor learning · Associative learning

Introduction

It has often been proposed that the prefrontal cortex is involved in decision making and in the selection of actions (Damasio 1991; Frith et al. 1991; Frith 2000;

R.E. Passingham (✉) · M.F.S. Rushworth
Department of Experimental Psychology, University of Oxford,
South Parks Road, Oxford OX1 3UD, UK
e-mail: dick.passingham@psy.ox.ac.uk
Fax: 441 1865 310447

I. Toni
Wellcome Department of Cognitive Neurology,
Institute of Neurology, University College London,
12 Queen Square, WC1N 3BG, UK

Passingham 1993, 1997). However, strictly speaking, it is the animal that selects, and not one area of the brain. It is, therefore, necessary to specify more precisely the operations that are performed by the prefrontal cortex. Hypotheses concerning these operations have been mainly based on data concerning the dorsal prefrontal cortex and, in particular, Brodmann area 46. Goldman-Rakic (1987, 1998) and Fuster (1997) stress the importance of "working memory" or "active memory" in response selection. By contrast, Shallice (1982; Shallice and Burgess 1998) argues that the prefrontal cortex can be regarded as a "supervisory attentional system", and Baddeley and Della Sala (1998) identify this with the "central executive" of working memory.

The present account redresses the balance by considering the ventral prefrontal cortex. In the macaque brain, this lies ventral to sulcus principalis and, in the human brain, it lies ventral to the inferior frontal sulcus. It comprises the inferior prefrontal convexity (areas 45 A, 12/47) and the orbital surface (11, 13, 14) (Petrides and Pandya 1995). This paper studies the functions of the ventral prefrontal cortex using functional brain imaging in humans and the lesion method in macaques.

The learning of visuo-motor associations

Positron emission tomography

We required subjects to select between actions, moving one finger given stimulus A, another finger given stimulus B, and so on for the four fingers of the right hand (Passingham et al. 1998; Toni and Passingham 1999). This is a visuo-motor associative task. Since the appropriate movement is conditional on the stimulus presented, a task of this sort is often also referred to as a "visuo-motor conditional task" (Passingham 1993). The association between the stimulus and the appropriate movement is entirely arbitrary, and it must therefore be learned or acquired.

Using positron emission tomography(PET), we scanned human subjects while they learned such a visuo-motor con-

Fig. 1A–D Learning-related changes: baseline control (*grey*), motor sequence task (*white*), visuo-motor conditional task (*black*). The data are shown for four scans for each task. *rCBF* Relative cerebral blood flow. Data from Toni and Passingham (1999). **A** Lingual gyrus (MNI coordinate = 16, –60, –10). **B** Inferior frontal gyrus (36, 16, 20). **C** Caudate (–12, 8, 18); **D** Subiculum/ parahippocampal gyrus (–24, –26, –8)
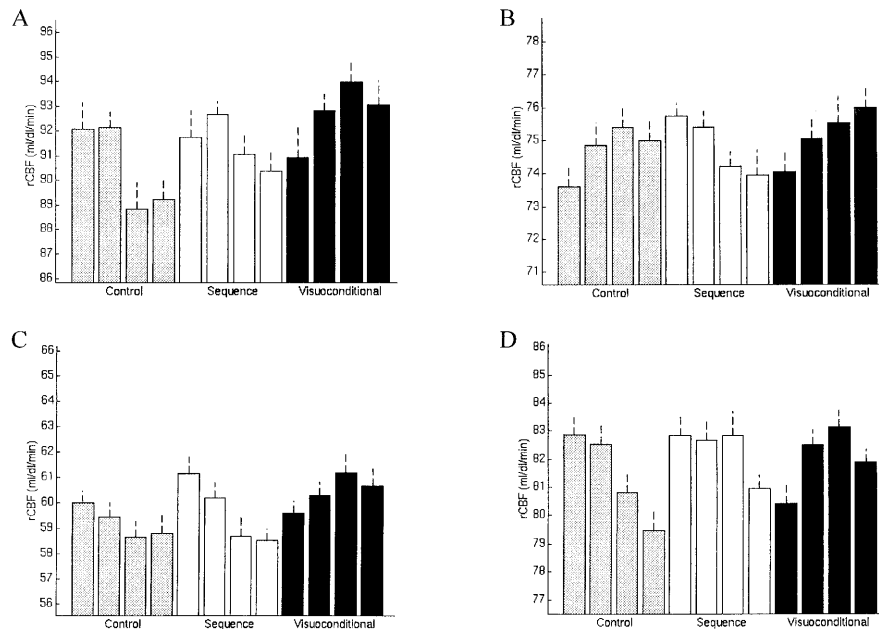
ditional task by trial and error (Toni and Passingham 1999). There were four sessions in which they learned, by trial and error, which finger to press given each of four nonsense figures (VMC). In another condition, the subjects learned a motor-sequence task, eight-moves long (SEQ); here, the nonsense figures served to pace performance, but not to specify *which* finger should be moved. Finally, in a baseline condition (BASE), the subjects were presented with a different set of nonsense figures, but no response was required. Comparison of the visuo-motor with the motor sequence condition allowed us to look for learning-related changes that were specific to the learning of visuo-motor transformations. Learning-related changes were assessed by investigating where there were differential changes in activation across the four sessions as the subjects learned.

As previously reported (Passingham et al. 1998), when we looked for interactions between the changes over time for the visuo-motor conditional task and the baseline condition (VMC vs. BASE), we found a learning-related change in the ventral temporal cortex (lingual gyrus) (Fig. 1A). We take this change to reflect the process of learning the identity of the visual stimuli. When we compared visuo-motor conditional learning with the learning of a sequence (VMC vs. SEQ), we found learning-related increases in the inferior prefrontal gyrus; as is shown in Fig. 1B, there was an increase in activation over time for the visuo-motor task, but a decrease for the motor-sequence task. We also found activation in the inferior prefrontal gyrus in a related study in which we scanned subjects while they performed a visuo-motor conditional task that they had already learned (Passingham et al. 1998).

Removal of the ventral prefrontal cortex in monkeys very severely impairs the learning of visuo-motor conditional tasks (Murray and Wise 1997; Murray et al. 2000),

and it is known that this area derives its visual input from the infero-temporal cortex (Webster et al. 1994; Pandya and Yeterian 1998). Both the infero-temporal cortex (van Hoesen et al. 1981) and the ventral prefrontal cortex (Selemon and Goldman-Rakic 1985) also send subcortical projections to the caudate nucleus. We also found a learning-related increase in the caudate nucleus for the visuo-motor task (Fig. 1C) (Toni and Passingham 1999). Lesions in the nuclei of the ventral thalamus, to which the basal ganglia project, have been shown to severely impair the retention of a visuo-motor conditional task (Canavan et al. 1989).

There was also a learning-related increase in the parahippocampal gyrus (VMC vs BASE) (Fig. 1D). The peak lay on the borders between the subiculum and the parahippocampal gyrus. Lesions of hippocampus and parahippocampal gyrus have also been shown to severely impair the learning of visuo-motor conditional tasks (Murray and Wise 1996).

Functional magnetic resonance imaging

In the PET study described above (Toni and Passingham 1999), there were only four data points during learning. Using functional magnetic resonance imaging (fMRI), it is possible to scan for much longer during learning and, thus, to produce continuous curves for activity during learning (e.g. Toni et al. 1998). In a recent study, we scanned subjects while they learned a visuo-motor conditional task by trial and error (Toni et al. 1999a). In another condition, the subjects performed a pre-learned visuo-motor task. Here, the nonsense figures contained arrowheads: if the arrowhead pointed to the left, the subject moved the first finger; if the arrowhead pointed up and to the left, the subject moved the second finger;

A)

B)
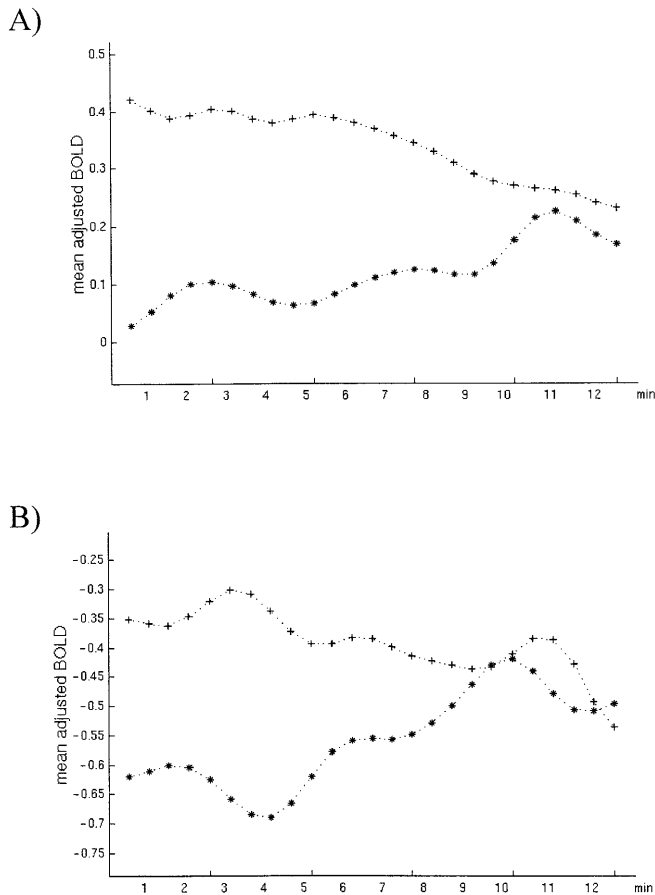
Fig. 2A, B Curves showing change in blood oxygen-level detection (*BOLD*) signal (mean adjusted) during learning of a visuo-motor conditional task (*stars*) and performance of a pre-learned visuo-motor task (*crosses*). Minutes during learning are plotted on the abscissa. Data from a study by Toni et al. (1999a). **A** Scans for infero-temporal cortex (MNI coordinate = –58, –54, –6); **B** Scans for ventral prefrontal cortex (–52, 40, –4)

and so on. Thus, in this control condition, the subjects also attended to visual stimuli and made movements on the basis of visual cues. This design allowed us to compare the *learning* of visuo-motor associations with the performance of a visuo-motor task in which the association had been pre-learned. Figure 2 shows that there were learning-related increases in the infero-temporal cortex (Fig. 2A) and in the inferior frontal gyrus (Fig. 2B), as well as in the orbitofrontal cortex. For the pre-learned motor task, there was a decrease in activation with time.

Representation of cue, response and outcome

To learn a visuo-motor conditional task, the subject has to associate the success of a particular response with the specific cue that is presented (Fig. 3). Response 1 is only successful (correct) in the presence of cue A. Here, we review evidence that prefrontal cortex can represent cues, responses and outcomes.
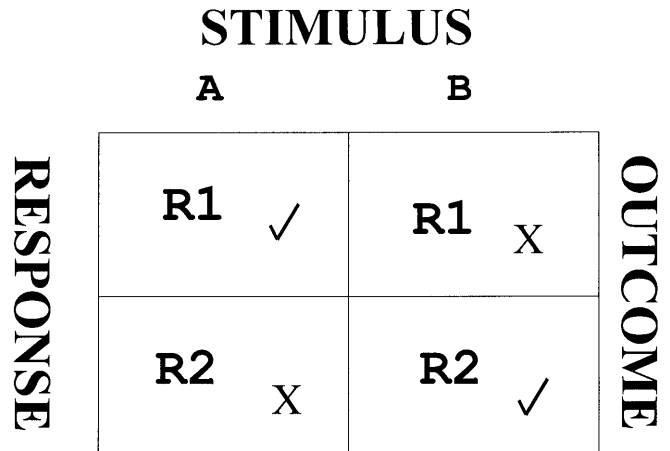
Fig. 3 The association of cues (*A* and *B*), responses (*R1* and *R2*) and outcomes (correct, incorrect) in the learning of a visuo-motor conditional task

There are two indications that cues can be represented in the ventral prefrontal cortex. First, it can be seen from Fig. 1A that, during learning, there was an increase of activation in the inferior frontal gyrus not only in the visuo-motor learning condition, but also over the four sessions of the baseline condition. In the latter condition, four new nonsense figures were repeatedly presented, one at a time, and thus the subjects had the opportunity to learn to identify which figure was presented on any trial. The learning-related increase in this area for the visuo-motor condition may, therefore, also be related to the learned identification of the figures. It is not suggested that this area is involved in the process via which stimuli are recognised as *familiar*, but rather in the process via which stimuli are *categorised* as the A, B, C or D figure. There are also cells in the inferior prefrontal convexity that respond to visual stimuli even when no explicit response is required (Wilson et al. 1993; Scalaidhe et al. 1997).

There is another way of showing that there is activity in the ventral prefrontal cortex that is related to the presentation of the cue. In a related study using event-related fMRI, we plotted the evoked hemodynamic responses when subjects selected a finger on the basis of visual cues (visuo-motor conditional task) (Toni et al. 1999b). Random delays were introduced between the presentation of the instruction cue and an auditory cue that triggered the response. This allowed us to align the evoked hemodyamic response either to the presentation of the instruction cue or to the presentation of the trigger cue. The response in the infero-temporal cortex could be shown to be statistically associated with the presentation of the instruction cue, but not with the response (Fig. 4A). Figure 4B shows the data for trials with a long delay (12.8 s); if the data are plotted for short delays, there is overlap between the evoked hemodynamic responses to the instruction cue and trigger stimulus. It will be seen that, in the inferior frontal gyrus, there was also a cue-related response.

There is also evidence that responses can be represented in the prefrontal cortex. First, it can be seen from Fig. 4B that, in the inferior frontal gyrus, there is also an evoked hemodynamic response that is time locked to the response. Movement-related activity has also been reported in the inferior prefrontal convexity in monkeys (Di Pellegrino and Wise 1991). We also found a second prefrontal peak in the frontal polar cortex (Fig. 4C), and here the movement-related activity started early before the tone, building up towards the time at which the movement was performed. It is not clear whether the peak should be classified as lying in dorsal or ventral prefrontal cortex. Pre-movement activity has also been reported for single cells in the dorsal prefrontal cortex (Fuster 1973; Kubota and Funahashi 1982; Funahashi et al. 1991). Other imaging studies have shown that the dorsal prefrontal cortex is activated when subjects select between finger movements (Frith et al. 1991; Jueptner et al. 1997) or prepare to make finger movements (Krams et al. 1998).

Finally, it can be shown using brain imaging that outcomes are represented in the prefrontal cortex. Elliott et al. (1997) report activation of the ventromedial frontal cortex when subjects are given either positive or negative feedback; the subjects were required to guess, and the feedback was unrelated to the actual guesses they made. The orbito-frontal cortex is also activated when subjects are scanned while they await negative outcomes: Chua et al. (1998) scanned subjects while they expected electric shocks and found activation in the orbito-frontal cortex that varied as a function of the degree of anxiety the different subjects felt. Cells have also been recorded in the inferior prefrontal convexity and orbital frontal cortex that respond to cues predicting a specific reward (reward A rather than reward B) (Watanabe 1996; Rolls 1998; Tremblay and Schultz 1999).

The level of representation

If two-dimensional shapes are to be associated with specific actions, both the stimuli and the actions must be represented at a high level, since there is no direct spatial correspondence between them. Wise et al. (1996) cites such associations as examples of "cross-domain mapping". A high-level representation of the response may differ little from the high-level representation of the cue. Thus, prefrontal cortex may specify the response by its target, irrespective of how that target can be achieved. It is, however, not clear how the prefrontal cortex can influence movement. Desimone and Duncan (1995) have suggested that the ventral prefrontal cortex may act to set
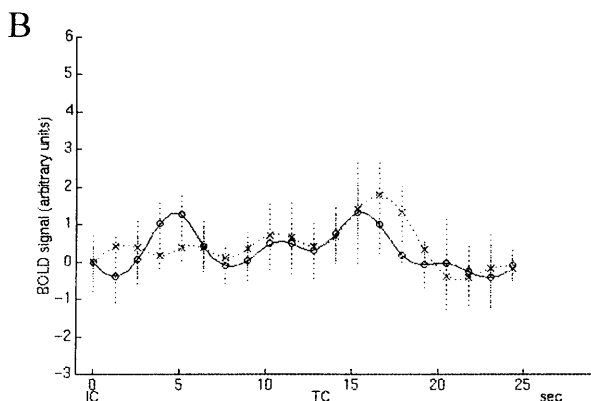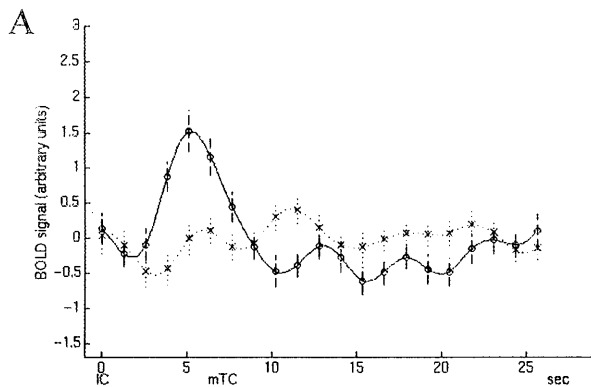
Fig. 4A–C Evoked hemodynamic responses. The ordinate shows the relative blood oxygen-level detection (*BOLD*) signal. The abscissa shows time during a trial in seconds. *IC* Presentation of instruction cue, *mTc* mean time of presentation of trigger cue, *TC* presentation of trigger cue. Data from Toni et al. (1999b). **A** Data for infero-temporal cortex (MNI coordinate = 52, –56, –20). The *solid line* shows the evoked hemodynamic response when the data are aligned to the time of presentation of the instruction cue. The *dotted line* shows the lack of an evoked hemodynamic response when the data are aligned to the time of presentation of the trigger cue. **B** Data for the inferior prefrontal cortex (*solid line*) (–30, 28, 12) and motor cortex (*dotted line*) (–36, –22, 60). The data are shown only for trials with a delay of 12.8 s. There is an evoked hemodynamic response for ventral prefrontal cortex at the time of the instruction cue and at the time of the movement. For motor cortex, there is only a response at the time of the movement. **C** Data for the frontal polar cortex (*solid line*) (34, 58, 20) and motor cortex (*dotted line*) (–36, –22, 60). The data are shown only for trials with a delay of 12.8 s. The hemodynamic response for the frontal cortex rises before the time of presentation of the trigger
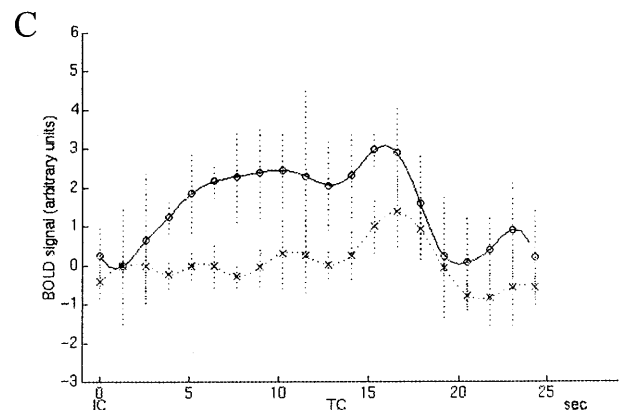
up an "attentional template" for objects and their unique features in the infero-temporal cortex. This acts to "highlight" the cues that are behaviourally significant and to bias competition in favour of the representation of one stimulus. It is possible that the prefrontal cortex selects movements in the same way, by biasing competition between the representations of movement in the premotor areas (Frith 2000).

The role of the ventral prefrontal cortex is not restricted to the learning of visuo-motor associations. Monkeys with lesions of the inferior prefrontal convexity are severely impaired in relearning a visual matching task, in which they must choose A rather than B if the sample is A (Rushworth et al. 1997). Disconnection of the inferotemporal and prefrontal cortex also severely impairs the learning of associations between one visual stimulus and another (Eacott and Gaffan 1992), between an auditory stimulus and a visual stimulus (Gaffan and Harrison 1991) and between presentation of a reward and choice of a visual stimulus (Parker and Gaffan 1998). Hasegawa et al. (1998) taught monkeys to associate two visual stimuli and reported that, if the cue was presented to one hemisphere, the anterior callosum must be intact if the other hemisphere is to select the correct response. The ventral prefrontal cortex is also activated when human subjects either encode (Dolan and Fletcher 1997) or retrieve (Rugg et al. 1996) verbal paired-associates and when they categorise items such as tools (Vandenberghe et al. 1996).

Associations

The fact that cues, responses and outcomes can be represented in the prefrontal cortex does not show that the *associations* between these are also explicitly represented in the prefrontal cortex. Figure 4B shows that there is a cue-related and a movement-related response in the inferior frontal gyrus; but the hemodynamic responses represent the activity of a whole population of cells, and there may be separate subpopulations representing *only* the cue *or* the response. However, Asaad et al. (1998) have shown that single cells in the dorsal and ventrolateral prefrontal cortex can code a specific cue-response association. These authors trained monkeys to look to the left or right, depending on the identity of an instruction cue. They report that many of the task-related cells coded a specific cue-response relation. For example, a cell might fire when the monkey looked to the left given cue A, but not when it looked to the right given A; at the same time, the same cell might fire less or not at all if the monkey was taught to look to the left given cue B.

This leaves open the questions of where these associations are first formed and where they are stored. There are interconnections between and within the ventrolateral, orbital and dorsal sectors of the prefrontal cortex (Barbas 1988; Pandya and Yeterian 1998). It could thus be argued that associations can be formed by interconnections *within* the prefrontal cortex. To learn a visual

conditional task, it is necessary to associate the success of a specific response with the presentation of a specific cue (Fig. 2). It has been argued that representations of the cue, response and reward are available to the prefrontal cortex.

These associations may be learned in interaction with the basal ganglia and the hippocampal system. There were learning-related increases in the caudate nucleus (Fig. 1B) and parahippocampal gyrus (Fig. 1C) that were specific for the establishment of visuo-motor associations. Several authors have proposed that the basal ganglia are involved in procedural motor learning and, more specifically, in the process via which the contexts of the movements are learned (Hikosaka 1993; Passingham 1993; Dominey et al. 1995; Houk and Wise 1995). The nigral dopamine cells sends projections to the same medium spiny neurones in the striatum on which the cortical afferents terminate (Groves et al. 1995), and it has been shown that these synapses are modifiable (Calabresi et al. 1996). Furthermore, changes have been shown in the firing of the nigral dopamine cells (Hollerman and Schultz 1998) and of the striatal cells (Kawagoe et al. 1998; Tremblay et al. 1998) when monkeys are reinforced for making specific responses. The association between cue and response may be reinforced by the dopamine system at the level of the striatum. It is important to note that no assumption need be made that there is an interaction between the prefrontal and premotor loops (Alexander et al. 1991). If both the cue and the response can be represented in the prefrontal cortex, the association can be established by projections onto striatal cells within a prefrontal-striatal loop.

There is evidence that the hippocampal system is also involved in the acquisition of the association. Lesions that include both the hippocampus and parahippocampal gyrus severely impair the learning of visual conditional tasks, while leaving unimpaired the retention of such tasks if learned before surgery (Murray and Wise 1996). Similarly, transection of the fornix impairs the ability of monkeys to learn a visuo-spatial conditional task (Rupniak and Gaffan 1987). Furthermore, the parahippocampal gyrus is activated when human subjects encode verbal paired associates in episodic memory (Dolan and Fletcher 1997). There are suggestions that the hippocampal system may be involved in the process by which the context of episodic memories is established (Dore et al. 1998; Parker and Gaffan 1998). Further work is needed to directly compare the contribution of the basal ganglia and hippocampal system with the learning of visual conditional tasks. Furthermore, studies need to be conducted to identify the pathways that are involved in overlearned performance.

Working memory

It could be argued that the ventral prefrontal cortex is involved not in the association of the cue and the response, but in the working-memory. Though the cue is available
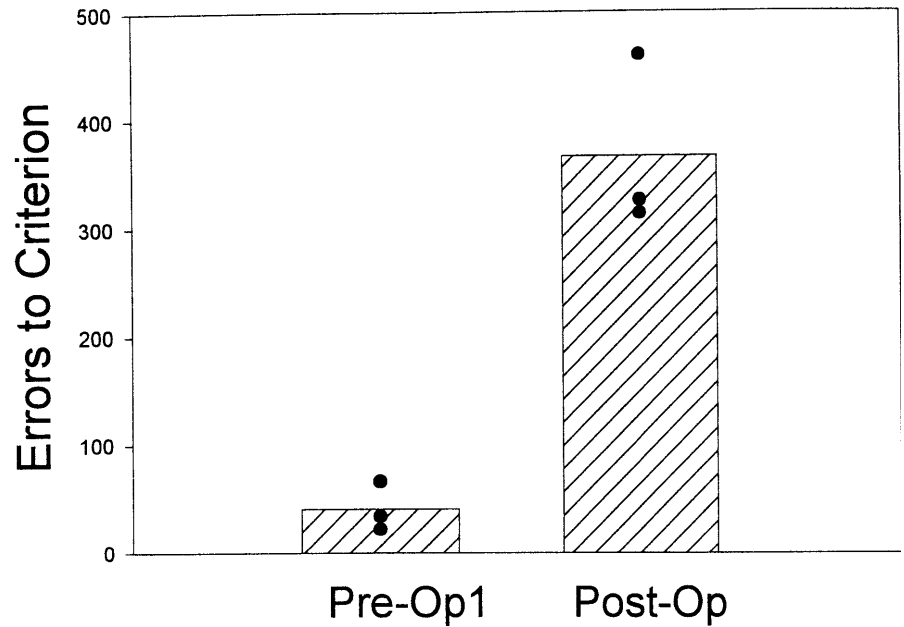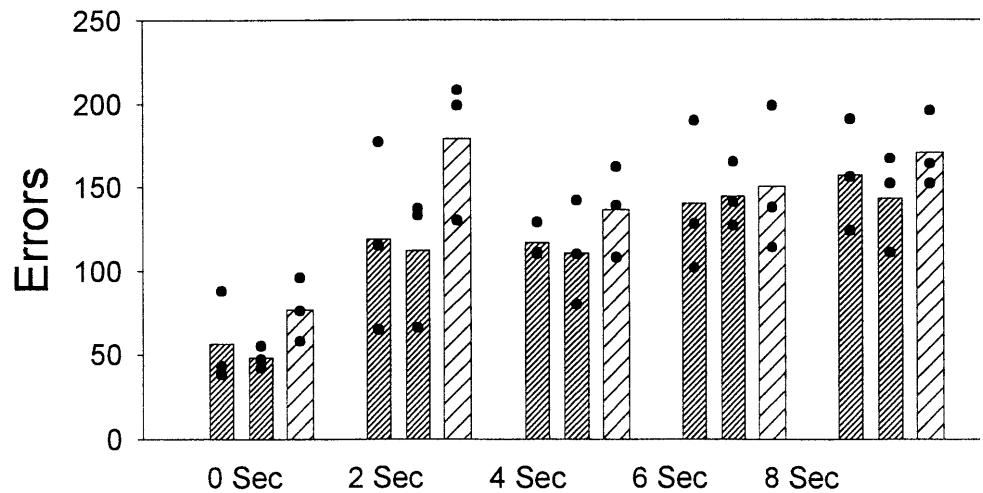
at the time of response, it might be supposed that, nonetheless, subjects first remember the cue, before deciding on the appropriate response.

It has long been known that monkeys with bilateral lesions in dorsal prefrontal area 46 are impaired on delayed-response tasks, but not impaired if the same responses are required without a delay (Goldman and Rosvold 1970; Funahashi et al. 1993). Rushworth et al. (1997) therefore assessed the ability of monkeys with lesions of the inferior prefrontal convexity to remember across delays. The monkeys were trained on a visual matching task. After surgery, they were severely impaired, even when the sample was present at the same time that the choice was made (Fig. 5A). The animals were, however, able to relearn the task with extended training. They were then tested with delays interposed

between the presentation of the cue and the time of response, and they were able to perform as well as they had done pre-operatively (Fig. 5B). It cannot, therefore, be argued that the impairment of the animals on the simultaneous condition was due to a working-memory impairment. This experiment (Rushworth et al. 1997) makes two points. First, the ventral prefrontal cortex is not essential for working memory. Second, there is a difference in specialisation between the ventral and dorsal prefrontal cortex, since lesions of the dorsal prefrontal cortex do not impair visual matching (Passingham 1975; Mishkin and Manning 1978).

The connected brain

There are two findings from single-unit studies that might be thought to challenge the first of these conclusions. First, on a delayed-response task, it is possible to record continuous cell activity during the delay period not only in area 46, but also in the inferior prefrontal convexity (area 12) (Rosenkilde 1981; Rao et al. 1997). However, White and Wise (1999) have recorded cell activity on a visuo-motor conditional task with no working memory requirement, and they were able to record task-specific activity in the prefrontal cortex. It is true that there are cells in the ventral prefrontal cortex which respond differentially when a stimulus is presented for the second time after a delay filled with other stimuli (Chelazzi et al. 1993). But the results of the study by Rushworth et al. (1997) suggest that the change in activity could reflect the comparison that is made, and that it may not be crucial that the comparison be made between the stimuli that are presented at different times.

There are also single-unit studies which appear to challenge the conclusion that there is specialisation between the ventral and dorsal prefrontal cortex. For example, in a visuo-motor conditional task, White and Wise (1999) recorded task-related cells in the dorsolateral as well as the ventrolateral prefrontal cortex (caudal third). In the studies by Rao et al. (1997) and Asaad et al. (1998), cell activity was recorded on conditional tasks both in area 46 and in the ventrolateral prefrontal cortex below. One possible explanation for the difference between the results of lesions and recording studies relies on the fact that there are strong interconnections between the dorsal and ventral prefrontal cortex (Barbas 1988; Pandya and Yeterian 1998). Both cell recording and functional brain-imaging studies are conducted in a "connected brain", that is one with intact interconnections. Thus, it is not possible to distinguish whether the activity of a cell in the dorsal prefrontal cortex depends on the activity of a cell in the ventral prefrontal cortex, and vice versa. In a lesion study, one of the areas is removed, and behavioural tests demonstrate whether that area is essential for the task. In other words, in the interconnected frontal lobe, the activity of a cell in one sector may be *derived* from the other. In a lesion study, one of the areas is removed, and behavioural tests demonstrate

whether that area is essential for the task. After a lesion of, say, the ventral prefrontal cortex, the activity of the cells in the dorsal prefrontal cortex can no longer be derived from the activity in the ventral prefrontal cortex. If this explanation is correct, it should be possible to demonstrate a change in the pattern of activity in one area when the other is removed or temporarily inactivated.

Specialisation of ventral and dorsal prefrontal cortex

There have been two views as to the specialisation of the dorsal and ventral prefrontal cortex. The first is that they perform the same operations, but for different inputs (Goldman-Rakic 1998). The second is that the ventral and dorsal prefrontal cortex perform different operations (Owen et al. 1996; Owen 1997; Petrides 1998). The data presented in this paper are consistent with the second of these views.

That there may be differences in specialisation is suggested by the pattern of anatomical connections. The dorsal area 46 and the ventral areas 12/47 and 45 A differ in their inputs and outputs. The inferior prefrontal convexity and orbital prefrontal cortex receives inputs from all sensory modalities. The ventral prefrontal cortex derives visual information from the infero-temporal cortex (Webster et al. 1994; Pandya and Yeterian 1998), auditory information from superior temporal cortex (Pandya and Yeterian 1998) and somatic information from SII and 7b (Cavada and Goldman-Rakic 1989; Preuss and Goldman-Rakic 1989; Carmichael and Price 1995); and the orbital prefrontal cortex derives information about taste from the insula and smell from the pyriform cortex (Rolls 1998). There are also interconnections between the ventral and orbital prefrontal cortex (Barbas and Pandya 1989), and both are connected with the amygdala (Aggleton et al. 1980; Porrino et al. 1981; Amaral and Price 1984; Barbas and De Olmos 1990). In both ventrolateral and orbital prefrontal cortex, there are cells that respond to cues predicting a specific reward (reward A rather than reward B) (Watanabe 1996; Rolls 1998; Schultz and Tremblay 1998).

The dorsal prefrontal cortex, on the other hand, derives its visual input from inferior parietal cortex in the dorsal visual system and is also connected with somatic area parietal 7b. There are motor outputs from area 46 to the dorsal and ventral premotor cortex (Dum and Strick 1997; Matelli et al. 1986) and to the pre-SMA and cingulate motor area CMAr (Lu et al. 1994). There are also outputs from area 46 to the superior colliculi (Goldman and Nauta 1976; Fries 1984) and to the cerebellum via the pons (Schmahmann and Pandya 1997). There are no projections to the pons from the ventral prefrontal area 12 (Schmahmann and Pandya 1997), and it is disputed whether the origin of the projections to the ventral premotor cortex is restricted to the ventral bank of sulcus principalis (area 46) (Matelli et al. 1986; Luppino et al. 1998) or includes the ventral convexity cortex (area 12) (Pandya and Yeterian 1998).
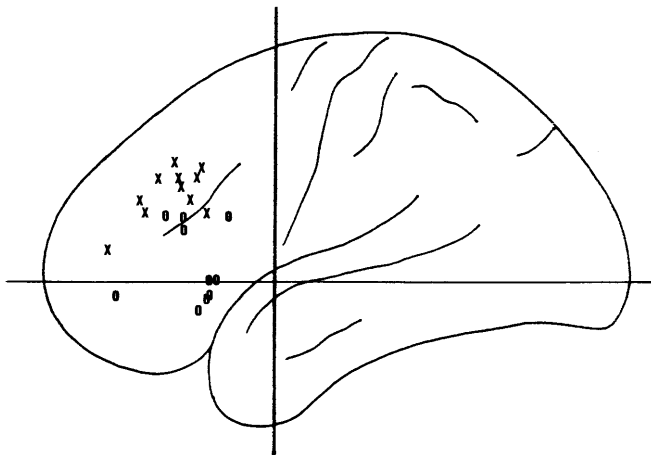
Fig. 6 A comparison of the peaks for visual conditional tasks (*0*) and free-selection and motor-preparation tasks (*X*), plotted on the Talairach and Tournoux (1988) brain. Some of the studies normalised the brains using the Talairach and Tournoux (1988) template and others using the MNI template (Montreal Neurological Institute); this introduces minor errors when the peaks for MNI data are plotted on the Talairach and Tournoux (1988) brain. Data from Paus et al. (1993), Deiber et al. (1997), Jueptner et al. (1997), Krams et al. (1998), Spence et al. (1998), Toni et al. (1999b) and Rushworth et al. (in preparation)

These anatomical differences underlie the functional specialisation of the ventral and dorsal prefrontal cortex. The ventral prefrontal cortex receives information concerning the identity of a visual stimulus, since it is the infero-temporal cortex that analyses the shape or colour that identifies an object (Ungerleider and Mishkin 1982; Milner and Goodale 1997). It is the inferior prefrontal cortex that is activated when subjects categorise items by making semantic judgements about them (Vandenberghe et al. 1996). By contrast, the dorsal prefrontal cortex receives an input from the inferior parietal cortex in the dorsal visual system. Milner and Goodale (1997) have reviewed evidence that suggests that parietal cortex operates on sensory information for the purposes of action. This includes the generation of both hand and eye movements (Snyder et al. 1998) as well as the direction of covert attention, where subjects prepare to make eye movements, but do not actually make them (Nobre et al. 1997, 1998).

This functional difference between the ventral and dorsal prefrontal cortex is highlighted by contrasting the activations on two types of task. In the first, visual cues are presented that specify the appropriate response (visual conditional task). In the second, the subject must either arbitrarily select between responses ("free selection") (Deiber et al. 1991; Frith et al. 1991; Jueptner et al. 1997) or are required to attend while they prepare to move a finger (Krams et al. 1998). Figure 6 shows that there is a difference between the peaks of activation. They tend to lie more ventrally for performance of visual conditional tasks and more dorsally for the tasks on which subjects must represent actions to themselves.
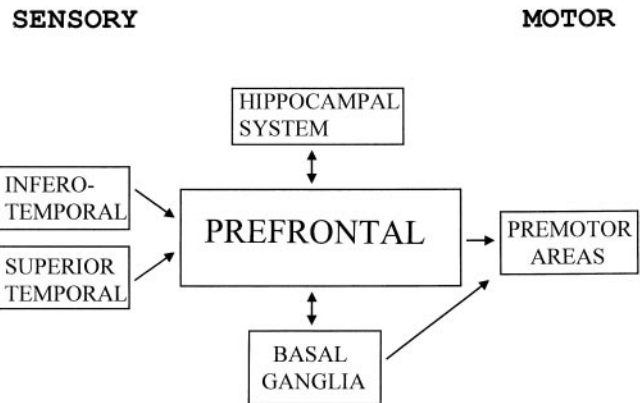
Fig. 7 Anatomical connections of the prefrontal cortex showing that it lies at the top of the sensory hierarchy and at the top of the motor hierarchy

Conclusions

It has been argued that the prefrontal cortex has an associative role that can be missed by the concentration in the literature on the functions of the dorsal prefrontal cortex. Both Passingham (1993) and Petrides (1987) have previously argued for a role of the prefrontal cortex in conditional learning, and Murray et al. (2000) also argue that the prefrontal cortex is involved in the process by which rules are learned that govern the production of responses on the basis of visual cues. White and Wise (1999) have demonstrated that there are cells in the ventrolateral and dorsolateral prefrontal cortex that show a different pattern of activity, depending on whether the rule concerns the association between a visual pattern and an eye movement or the association between a spatial location and an eye movement.

The prefrontal cortex is a position that associates high-level representations of cues and actions. As also noted by Fuster (1997), the prefrontal cortex lies at the top of the sensory hierarchy and at the top of the motor hierarchy (Fig. 7). The question arises why these associations are not learned by a direct interaction between the infero-temporal cortex and the premotor areas. As far as we know, there are no direct projections from the infero-temporal cortex to premotor area 6 (Boussaoud et al. 1996, and pers. comm.). The behavioural relevance of a visual stimulus can only be determined by detecting the association of a successful response with the presence of that stimulus. This means that there must be associations between the visual stimuli, the responses and the outcomes. While infero-temporal cortex has information about visual stimuli and premotor cortex can represent actions, *only* the prefrontal cortex can represent stimuli, actions and outcomes.

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