Functional Imaging

of

Response Selection

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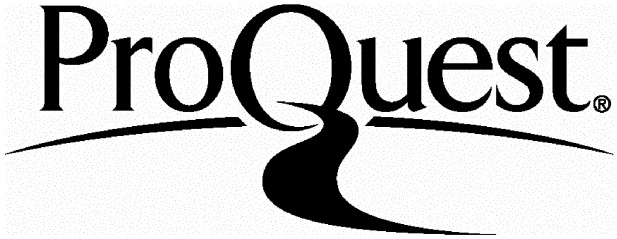

Abstract

The functions of the prefrontal cortex remain controversial. Electrophysiological and lesion studies in monkeys have emphasised a role in working memory. In contrast, human functional neuroimaging studies and neuropsychology have emphasised a role in executive processes and volition. An alternative interpretation of the role of the prefrontal cortex is proposed in this thesis: that the prefrontal cortex mediates the attentional selection of sensory, mnemonic and motor representations in non-prefrontal cortex. This hypothesis is tested in a series of functional imaging experiments.

In the first two experiments (chapters 4 and 5), event-related functional magnetic resonance imaging (fMRI) was used to re-examine the role of the prefrontal cortex in spatial and spatio-temporal working memory. Maintenance of information in memory was associated with activation of posterior prefrontal cortex (area 8). In contrast, the selection of an item from several remembered items was associated with activation of the middle and anterior parts of the prefrontal cortex (including area 46).

To test the generalisation of 'selection' as a function of prefrontal cortex, experiment three (chapter 6) required subjects to select either a finger to move, or a colour from a multicolour display. Free selection was associated with activation of the prefrontal cortex (area 46) bilaterally, regardless of sensory or motor modality.

The selection of voluntary actions has been proposed to depend on top-down modulation of motor regions by prefrontal cortex. The fourth and fifth experiments used structural equation modelling of fMRI time -series to measure the effective connectivity among prefrontal, premotor and parietal cortex. In young (chapter 7) and old (chapter 8) normal subjects, attention to action specifically enhanced coupling

between prefrontal and premotor regions. This effect was not seen in patients with Parkinson's disease (chapter 8).

Lastly, positron emission tomography was used to study planning in the Tower of London task, a common clinical measure of prefrontal function. Several variants of the task were developed, to distinguish the neural basis of the task's multiple cognitive components (chapter 9). The prefrontal cortex was activated in association with generation, selection or memory for moves, rather than planning towards a specified goal.

The results support a generalised role in attentional selection of neuronal representations, whether stimuli, actions, or remembered items. The hypothesised attentional selection of responses is consistent with the activation of prefrontal cortex in working memory tasks and during attention to voluntary action. This role is compatible with the neurophysiological properties of individual neurons in the prefrontal cortex and the results of neuroimaging and lesion studies.

Copyright

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Chapter 1

Functional imaging of response selection

"The removal of the frontal lobes causes no motor paralysis, or other evident physiological effects, but causes a form of mental degradation, which may be reduced in the ultimate analysis to the loss of the faculty of attention"

David Ferrier, 1878

In 'The localisation of cerebral disease'

The challenge of the prefrontal cortex

In 1876 the British neurologist David Ferrier argued for the localisation of brain function (Ferrier, 1878), and his systematic review began with the frontal lobes. However, disorders of the frontal lobes remained one of the most complex problems in neurology one hundred years later (Luria, 1969). Attempts to define the role of the prefrontal cortex based on clinical observation of affected patients were hampered by the variety of clinical syndromes, from apathetic akinesia to antisocial disinhibition.

Recent advances in our understanding of the frontal lobes have been fuelled by developments in neurology and other neurosciences, particularly neuropsychology,

neurophysiology and functional neuroimaging. However, these neuroscientific disciplines have evolved with distinct conceptual and linguistic frameworks, which can lead to confusion (Toga and Mazziotta, 1995). It has not always been clear for example how to relate the 'attentional deficits' following focal lesions in patients (Luria, 1969) to the regional activations identified by neuroimaging of 'attention' in normal humans (Coull *et al.*, 1998: Buchel *et al*, 1997) or to the 'attentional modulation' of the function of neurons and synapses in the homologous regions in non-human primates (Desimone, 1999; Tomita *et al.*, 1999).

A common framework for understanding the functions of the prefrontal cortex must consider the **anatomy** of the prefrontal cortex, in humans and non-human primates. The principal patterns of cytoarchitecture and interconnections of the prefrontal cortex are discussed in the first part of this chapter. A common framework should also be able to use the **basic properties** of neurons in the prefrontal cortex to explain the regional activations identified by functional neuroimaging and the consequences of lesions here. The electrophysiological properties of neurons are introduced in the subsequent sections, first in delayed response tasks and later during more complex learning and selection paradigms. The common framework should be applicable to the experimental **paradigms** commonly used to study prefrontal cortical function in patients or animals with focal lesions, or in functional imaging studies. Close attention will be paid to the details of individual paradigms. Small differences in task instructions or parameters will be shown to critically affect the component cognitive processes and the demands on the prefrontal cortex.

Such a framework would help to resolve some of the current controversies concerning the prefrontal cortex, and generate specific testable **hypotheses**. In this

chapter I will review the neurophysiological, neuroimaging and neuropsychological evidence for the influential 'working memory' hypothesis of prefrontal cortical function. However, I will then present evidence for an alternative role in response selection and the control of action. Response selection is consistent with working memory functions, and in the last two sections I will discuss the emergence of an integrated theory, including the proposed mechanism of 'attentional selection' underlying response selection and working memory. In the last section, I will introduce the specific issues that form the basis of the functional imaging experiments in chapters four to nine, testing the 'attentional selection' hypothesis.

Functional anatomy of the prefrontal cortex

Gross anatomy of the prefrontal cortex

The central sulcus marks the posterior boundary of the frontal lobe, illustrated for the human brain in figure 1.1a. In the human brain, the pre-central sulcus runs approximately parallel to the central sulcus, but is often discontinuous, and it is variable from person to person (Toga and Mazziotta, 1995). The central and precentral sulci delineate the precentral regions. Anterior to the pre-central region lies the prefrontal cortex. The lateral convexity of the prefrontal cortex is divided by the inferior and superior frontal sulci, into inferior, middle and superior frontal gyri. These sulci do not extend to the frontal pole.

In monkeys, the gross anatomy is different, as illustrated in figure 1.2a. The lateral convexity is divided in half by the arcuate sulcus. Behind the arcuate sulcus is the pre-central region, and in front of it lies the prefrontal cortex. This is itself divided

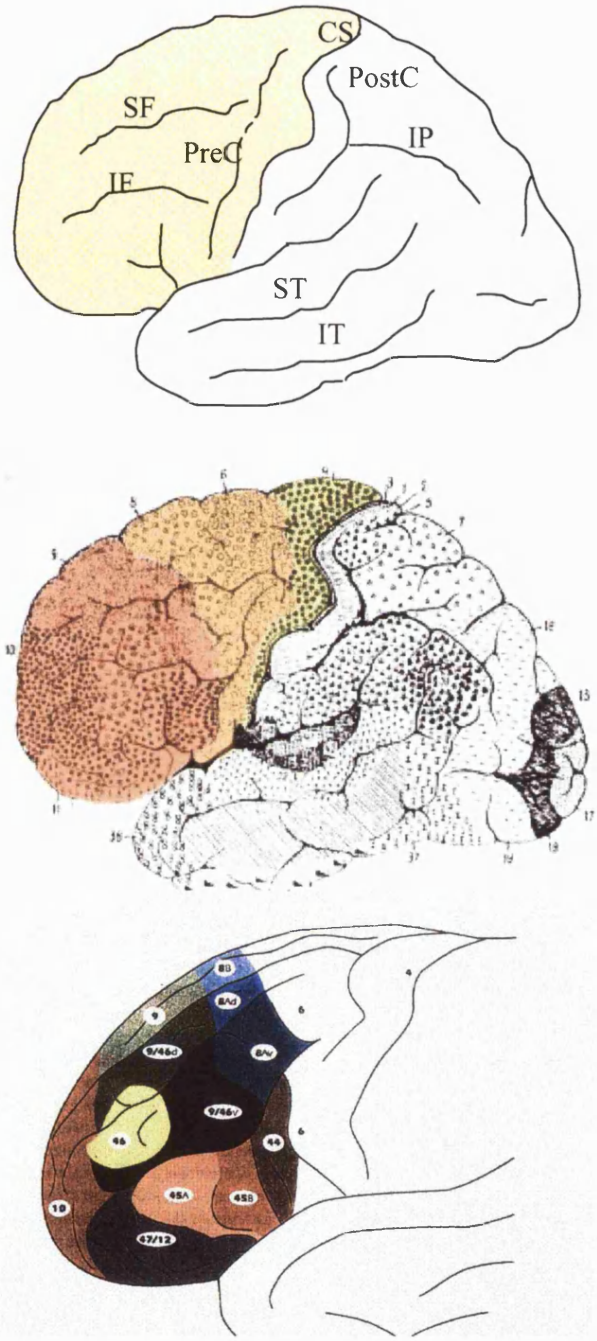


Figure 1.1, The human frontal lobe. (a) showing major sulcal and gyral landmarks, redrawn from Brodmann (1909), with the frontal lobe in yellow, SF=superior frontal sulcus, IF=inferior frontal sulcus, PreC=precentral sulcus, CS=central sulcus, PostC=post-central sulcus, IP=intraparietal sulcus, ST=superior temporal sulcus and IT=inferior temporal sulcus. (b) showing Brodmann's 1909 outline of the cytoarchitecturally distinct regions, with motor cortex in yellow, prefrontal cortex in red, and intermediate areas 6 and 8 in orange (© Smith-Gordon ltd, London) (c) the more recent revision of the cytoarchitectural regions by Petrides and Pandya (1994) (© Elsevier Science).

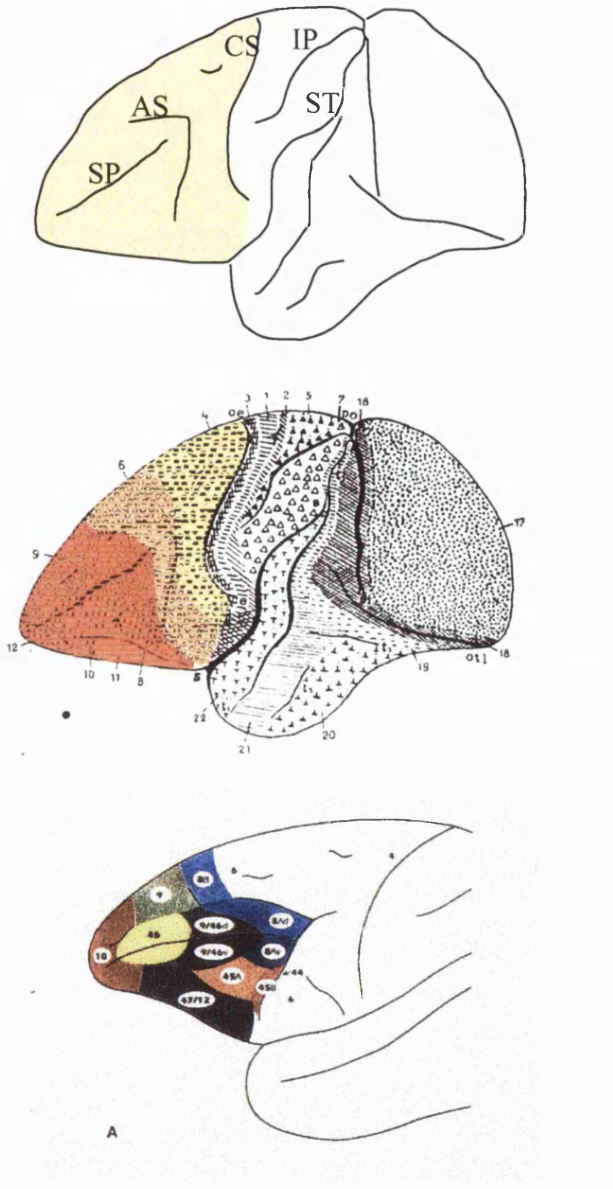


Figure 1.2, The macaque frontal lobe. (a) showing major sulcal landmarks, redrawn from Brodmann (1909), with the frontal lobe in yellow, SP=sulcus principalis, AS=arcuate sulcus, CS=central sulcus, IP=intraparietal sulcus, ST=superior temporal sulcus. (b) showing Brodmann's 1909 outline of the cytoarchitecturally distinct regions, with motor cortex in yellow, prefrontal cortex in red, and intermediate areas 6 and 8 in orange. (© Smith-Gordon ltd, London) (c) the more recent revision of the cytoarchitectural regions by Petrides and Pandya (1994) (© Elsevier Science).

into two parts by the sulcus principalis. The tissue in sulcus principalis and the convexity above forms the dorsal lateral prefrontal cortex: the tissue on the convexity below the sulcus principalis forms the ventral lateral prefrontal cortex. The medial surface of the frontal lobe is divided by the cingulate sulcus in humans and macaques, and often by an additional paracingulate sulcus in humans. The inferior surface of the frontal cortex lies over the orbit in both species, divided by the orbitofrontal sulcus.

Confusion may arise over the use of the terms dorsolateral prefrontal cortex (often abbreviated to DLPFC or DPFC) and ventrolateral prefrontal cortex (often abbreviated to VLPFC or VPFC)(Fuster, 1997; Passingham, 1993) For example, the 'dorsolateral prefrontal cortex' has been variously interpreted as (1) the whole lateral surface of the monkey prefrontal cortex, distinguished from the medial and orbital surfaces, (2) only the prefrontal cortex that lies above the sulcus principalis in monkeys, (3) the middle and superior frontal gyri in humans, (4) the area of specific cytoarchitectural regions (see below), or (5) the approximate extent of those cytoarchitectural regions in standard anatomic space.

To avoid this confusion, I will refer to specific regions by their gyral, sulcal or cytoarchitectural anatomy where possible. For regional summaries, I will adopt the terminology used by Murray and Wise (Murray *et al.*, 2000). The region of monkey prefrontal cortex on the lateral convexity in and above the sulcus principalis, excluding the anterior bank of the arcuate sulcus, will be called PFd. The human analogue will be taken as the middle and superior frontal gyri, excluding the posterior part. The region below the sulcus principalis, again excluding the anterior bank of the arcuate sulcus, will be termed PFv. The human analogue will be taken as the middle and anterior parts of the inferior frontal gyrus. The orbital surface will be termed PFo.

Cytoarchitectural parcellation of the prefrontal cortex

The pre-central region is characterised by the absence of an inner granular layer. It includes Brodmann's cytoarchitectural area 4 with pyramidal cells, and area 6 without pyramidal cells (Brodmann, 1909) (also known as FA and FB, (Economo and Koskinas 1925). In the monkey, area 6 extends anteriorly to the arcuate sulcus. In humans, the inferior part of area 6 extends to the pre-central sulcus, and the dorsal part extends 1-2 cm anterior to it.

The prefrontal cortex is characterised by an inner granular layer. This cortex is evolutionarily and ontogenetically late to develop (Brodmann, 1909; Paus *et al.*, 1999; Rilling and Insel, 1999; Steen *et al.*, 1997) and contains many anatomically distinct regions (Brodmann, 1909; Petrides and Pandya, 1995; Rajkowska and Goldman-Rakic, 1995). Brodmann identified thirteen cytoarchitecturally distinct areas in the human brain: 8, 9 and 46 dorsally, areas 11, 44, 45, 47 ventrally, 24, 25, 31, 32, 33 medially and a polar region 10, as shown in figure 1.1b (Brodmann, 1909).

However, Brodmann noted great difficulty in parcellation of the prefrontal cortex, due to the indistinct boundaries between cytoarchitecturally distinct areas. There was coarse homology with the brains of monkeys, although several important differences were noted. For example, he found no clear structural homologues to areas 44,45 and 47, and the polar area 12 was of uncertain significance. Area 46 was not initially identified in the macaque brain by Brodmann, although Walker (1940) and subsequent authors have included it (Petrides and Pandya, 1995; Petrides and Pandya, 1999).

To add to the confusion, the numerical designations were not always the same even for comparable areas. For example, human area 47 and monkey area 12 are topographically and cytoarchitecturally very similar (Petrides and Pandya, 1995).

Brodmann described area 8 as a long strip, wide in its medial and dorsal lateral parts, tapering out ventrally with indistinct borders. In the monkey it lies along the anterior bank of the arcuate sulcus. In humans, it occupies the posterior part of the superior and middle frontal gyri. Area 9 was extensive, from the callosomarginal sulcus medially, to the inferior frontal sulcus on the lateral surface. Area 46 was smaller, with indistinct boundaries, occupying the middle third of the middle frontal gyrus, and anteriormost part of the inferior frontal gyrus. It was bounded dorsally and caudally by area 9.

The cytoarchitecture of the human prefrontal cortex has been revised recently, using single and multiple brains (Petrides and Pandya, 1995; Petrides and Pandya, 1999; Sarkissov *et al.*, 1955) and normalised to standard anatomic space (Rajkowska and Goldman-Rakic, 1995; Talairach and Tournoux, 1988), using the numerical parcellation scheme proposed by Brodmann. Particular attention will be paid to the dorsal areas 8, 9 and 46, because of their role in response selection.

Area 8 was confirmed as occupying the dorsal lateral surface, occupying the posterior part of the middle and superior frontal gyri (Petrides and Pandya, 1995; Petrides and Pandya, 1999; Rajkowska and Goldman-Rakic, 1995; Sarkissov *et al.*, 1955). Petrides and Pandya identified two clear subdivisions, 8A and 8B, but the extent of area 8 as a whole was the same.

The more recent studies revealed greater variation in the extent of areas 9 and 46. Whereas Brodmann (1909) and Sarkissov (1955) identified area 9 as extending

across the middle frontal gyrus, caudal to area 46, this was not confirmed by Petrides and Pandya (1995,1999) or Rajkowska and Goldman-Rakic (1995). The part of middle frontal gyrus previously labelled area 9 was found to be cytoarchitecturally intermediate between 9 and 46. Petrides and Pandya (1995,1999) therefore coined the term 'area 9/46' (see figure 1.1c and 1.2c). Note that this refers to a definite region of intermediate architecture. In contrast, some neuroimaging studies report activations in 'area 9/46' to indicate uncertainty over the location. Rajkowska and Goldman-Rakic (1995) also reported a transitional zone at the inferior-caudal margin of area 9, over the middle frontal gyrus. In the monkey, area 9 occupied only the dorsal part of the dorsal lateral convexity, and did not extend to the sulcus principalis.

Area 46 proper occupies the middle part of the middle frontal gyrus in humans (Petrides and Pandya, 1995; Petrides and Pandya, 1999; Rajkowska and Goldman-Rakic, 1995; Sarkissov *et al.*, 1955). In some cases it extends into either the inferior or superior frontal sulcus (Rajkowska and Goldman-Rakic, 1995). In the monkey, area 46 occupies the middle third of the sulcus principalis. Beyond this, it has intermediate cytoarchitecture with neighbouring areas 9 and 10. This restriction of area 46 to the banks of the middle third of the sulcus principalis will be most significant when reviewing the effects of focal frontal cortical lesions.

Area 10 is located over the pole in both humans and monkeys. Area 47 occupies the middle and anterior thirds of the inferior frontal gyrus, extending infero-medially onto the orbital surface. It is bounded dorso-caudally by area 45. Area 24 lies on the medial surface, extending from area 6 caudally, around the genu and rostrum of the corpus callosum, to merge inferiorly with area 25. Area 32 runs along the paracingulate gyrus, surrounding area 24 and itself enveloped by areas 8, 9 and 10.

Intracortical anatomical connectivity of the frontal cortex

Since Monakow's demonstration (Monakow, 1904) of retrograde degeneration of the thalamus following frontal lobe lesions, there has been an explosion in methods available for determining the interconnections of the prefrontal cortex. These include the invasive methods of autoradiography, axonal transport of tracers, fluorescent dyes, immunohistochemistry, transynaptic carriage of viral tracers, and more recently non-invasive tractography by magnetic resonance imaging and transcranial magnetic stimulation. This section cannot offer a complete survey of this literature but it will emphasise some of the important features of the organisation of frontal lobe connectivity.

Three systems of organisation can be readily appreciated from studies of non-human primate connectivity. **First**, regions have prominent connections with near neighbours, weaker connections with more distal association cortex, and few connections with the primary motor or sensory cortex (Fuster, 1997). There are in addition frequent reciprocal connections. **Second**, the inputs to the prefrontal cortex are segregated into broad dorsal and ventral streams (Goodale and Milner, 1992; Milner and Goodale, 1993). **Third**, the homuncular topography evident in areas 1,2,3,4 and 6 is notably not continued into prefrontal cortex (Passingham, 1993).

The premotor region 6 includes several regions distinguished by their patterns of cortical connectivity. The dorsal lateral region (known as area 6D (Barbas and Pandya, 1987) or PMd (Wise *et al.*, 1997)), receives rich innervation from lateral parietal areas 5 and MIP, which in turn receive inputs from dorsal extrastriate regions (Wise *et al.*, 1997). The ventral lateral region (known as area 6V (Barbas and Pandya, 1987) or PMv) receives prominent inputs from ventral parietal area 7b (Cavada and

Goldman-Rakic, 1989; Petrides and Pandya, 1984). The medial premotor region (also known as the supplementary motor area, SMA (Passingham, 1993) or 6M (Barbas and Pandya, 1987) receives major inputs from medial parietal area 5 (Dum and Strick, 1991). Thus, parallel connections seem preserved so far within anterior-posterior connections of the dorsal brain. Within area 6 there are whole body maps, arranged vertically and horizontally respectively (Kurata, 1991; Luppino *et al.*, 1993; Luppino *et al.*, 1991; Luppino *et al.*, 1990), with connections from the posterior parts of area 6 to the homuncular equivalent regions of primary motor cortex (area 4) (Luppino *et al.*, 1991). The anterior parts are connected reciprocally with prefrontal areas 9 and 46 (Barbas, 1988; Barbas and Pandya, 1987; Barbas and Pandya, 1989; Lu *et al.*, 1994) without homuncular organisation.

The prefrontal area 8 receives extensive inputs from the inferior intraparietal cortex (LIP) (Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1984), but unlike premotor area 6 there are no inputs from area 5. The dorsomedial part of area 8 in monkeys also receives inputs from ventral intraparietal cortex (Huerta *et al.*, 1987). There are extensive reciprocal connections with areas 9 and 46 (Barbas, 1988; Barbas and Pandya, 1989). Area 8 represents an exception to the separate streaming of information in dorsal and ventral structures. In addition to parietal inputs, there are also connections from the superior temporal cortex (Barbas and Mesulam, 1981; Petrides and Pandya, 1988) and regions of the infero-temporal cortex more typically considered to be part of the ventral stream (Barbas, 1988; Barbas and Mesulam, 1981).

Areas 9 and 46 of PFd themselves are closely interconnected (Barbas, 1988; Barbas and Pandya, 1989), and are similar in their connectivity with other cortical

regions. They both receive inputs from parietal areas. Indeed, there is a remarkable preservation of the topological segmentation of the cortical origins of these projections and the sub-regions to which they project (Cavada and Goldman-Rakic, 1989). Moreover, the recipient sub-regions are not continuous with one another but are interspersed by cortical columns in receipt of projections from contralateral homologous cortex (Goldman-Rakic and Schwartz, 1982; Schwartz and Goldman-Rakic, 1984). The caudal part of the sulcus principalis, area 9/46, also receives inputs from superior temporal cortex and V5 of the infero-temporal cortex (Petrides and Pandya, 1988; Seltzer and Pandya, 1989).

Areas 9 and 46 both project to the anterior parts of the premotor area 6 and to the posterior prefrontal area 8 (Barbas, 1988; Barbas and Pandya, 1987; Barbas and Pandya, 1989; Huerta *et al.*, 1987; Rizzolatti *et al.*, 1998), but not to area 4, the primary motor cortex. These connections with premotor area 6 include the medial 'pre-supplementary motor area', as well as the lateral premotor area (Muakkassa and Strick, 1979; Selemon and Goldman-Rakic, 1988). The prefrontal cortex is therefore only able to initiate or influence actions indirectly, through a series of connections via anterior premotor areas to posterior premotor areas and finally to the motor cortex itself.

In contrast with the prominent interconnections amongst the regions of PFd and parietal cortex, the regions of PFv and PFo are closely interconnected with the temporal lobe, the hypothalamus and amygdala. The uncinate fasciculus carries connections between PFv and the temporal lobes, (Ungerleider *et al.*, 1989). This includes connections from auditory association cortex in the superior temporal cortex, visual association cortex along infero-temporal cortex, secondary somatosensory

cortex SII, and regions of the operculum and insula associated with taste and smell (Barbas, 1988; Seltzer and Pandya, 1989). These sensory pathways are relatively independent until they reach the prefrontal cortex. Integration through secondary projections within PFv makes this region anatomically suited to the convergence of multimodal sensory information. The interconnections with the temporal lobe are both direct and via the thalamus (Barbas and Blatt, 1995; Barbas and De Olmos, 1990; Barbas *et al.*, 1991; Watanabe *et al.*, 1991).

The diverse connectivity of the prefrontal cortex is important when considering its possible functions. Prefrontal cortical regions receive input from all sensory modalities, such that cells here may in principal be responsive to changes in the environment and body state. There are interconnections with the limbic system, and hippocampus, so that cells may in principal be responsive to learned information, rewards and intended goals. PFd is also interconnected with premotor cortex (area 6) and the eye fields (area 8), and therefore can in principal influence behaviour via control of the limbs, the eyes or voice. The homuncular organisation of sensory and motor cortex is not present in the prefrontal cortex, suggesting an integration of information from all body parts and ability to influence any part of the motor system.

The integration of information in the prefrontal cortex suggests a role in adapting responses to changing stimuli, or responding according to remembered information, in order to achieve the current goals. PFv and PFo do not send significant projections to primary motor cortex or PMd. So although there may be integration of sensory information here, there are few direct connections to effector motor output regions. Integrated information in PFv and PFo may influence action by direct interconnections with PFd, or through convergence with connections of PFd and

premotor cortex within cortical-subcortical circuits. These cortical-subcortical circuits are considered in the next section.

Subcortical connections of the frontal cortex

Most of the cerebral cortex projects to the striatum, in a highly organised pattern. Alexander et al (Alexander *et al.*, 1990; Alexander *et al.*, 1986) proposed multiple polysynaptic circuits from the cortex via the striatum, and the thalamus back to the cortex. These parallel cortical-striatal-thalamic-cortical circuits have been well defined for the dorsal areas 6, 8, 9, and 46. There is also increasing evidence for equivalent circuits for PFv and PFo (see Fuster, 1997 and Passingham, 1993)).

PFd and the premotor cortex project to the caudate nucleus and the putamen. There is relative preservation of the topological organisation, such that PFd projects to a central strip of the caudate, and the premotor cortex projects to a more lateral strip and the putamen (Kunzle, 1978; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991). The central strip of the caudate projects to the substantia nigra pars reticulata (Parent *et al.*, 1984) and the lateral striatum strip projects to the globus pallidum. These two target areas in turn project to the thalamus, to the ventral-anterior (VA) and ventral-lateral (VL) nuclei respectively (Ilinsky *et al.*, 1985; Schell and Strick, 1984). The VA and VL nuclei project back to the cortex, to the prefrontal and premotor cortex respectively. (Barbas *et al.*, 1991; Ilinsky *et al.*, 1985; Schell and Strick, 1984). The frontal eye field of area 8 also has a distinct loop, via the caudate, to the substantia nigra, then to the VAmc nucleus of the thalamus and back to prefrontal cortex including area 8 (Barbas *et al.*, 1991; Ilinsky *et al.*, 1985; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991).

Within each of these re-entrant loops, there exists the possibility of convergence of information, as fibres from interconnected cortical regions tend to project to neighbouring regions of the striatum and thalamus. However, the anatomical convergence is often limited, suggesting parallel, rather than fully integrated loops (Kitano *et al.*, 1998; Middleton and Strick, 1997; Middleton and Strick, 2000b; Selemon and Goldman-Rakic, 1985). Moreover, the functional properties of neurons are similar in neurons along each loop, and distinct from those of neurons in other loops (Middleton and Strick, 2000a).

A distinct set of cortico-subcortical loops exists from the frontal cortex, via the pontine nuclei to the cerebellum and back from the dentate nuclei via the thalamus to the cortex. These are most prominent for the motor and premotor cortex. As for the cortical-striatal-thalamic loops, there are specific parallel cortical-cerebellar-thalamic loops. For example, in prefrontal cortex, only the dorsal parts of area 46, and area 9 receive inputs from the VL nucleus of the thalamus, which is the target of cerebellar afferents from the dentate nucleus. Ventral area 46, and area 12 (area 47) do not receive such inputs from VL (Middleton and Strick, 2001). In contrast, the premotor cortex receives inputs from the pons via the ventral lateral nuclei of the thalamus, VLc, VPLo and area X (Schell and Strick, 1984).

It remains controversial whether or not there is extensive overlap between these parallel cortical-cerebellar-thalamic loops (Middleton and Strick, 2000a; Passingham, 1993; Ramnani and Miall, 2001). The results of transynaptic retrograde neuronal tracers (Middleton and Strick, 2001) suggests that the prefrontal-cerebellar-thalamic circuits are largely segregated and parallel. It is also unclear to what extent there is convergence between the cortical-striatal-thalamic loops and cortical-

cerebellar-thalamic loops. Some anatomical convergence has been demonstrated in premotor cortex, with cortical columns receiving inputs from those parts of the thalamus connected to the striatum, and parts connected to the cerebellum (Darian-Smith *et al.*, 1990; Wiesendanger and Wiesendanger, 1985).

The functional significance of the cortical-subcortical loops is not clear. With convergence among loops, information from widespread regions of cortex might be integrated at subcortical levels, prior to feedback to specialised cortical sub-regions. For example, partial convergence in the striatum of the cortico-striatal projections from PFv and the premotor cortex would enable PFv to influence action in the absence of direct connections to dorsal premotor cortex. Without convergence, such loops may still enable changes in cortical neuronal properties or activation patterns, such as stabilising the sustained neuronal firing described in more detail in the next section.

Sustained neuronal firing in prefrontal cortex

A conceptual framework for understanding the roles of the prefrontal cortex must take into account the properties of individual neurons, and not be restricted to a 'systems' level analysis based on lesions or functional neuroimaging studies. Although the rate, pattern and synchronisation of neuronal firing are all separable modes of coding and integrating information (Friston, 1997), prefrontal neuronal firing patterns are most often represented by their firing rate, during single unit microelectrode recording.

Delayed response tasks

Much of our understanding of the functions of the prefrontal cortex has come from recording during monkey performance of the delayed response task or variations on it (Chafee and Goldman-Rakic, 1998; Fuster *et al.*, 2000; Fuster, 1973; Fuster and Alexander, 1971; Niki, 1974; Niki and Watanabe, 1976). Variant tasks include delayed non-match to sample and conditional delayed response tasks. Although these tasks are not equivalent in their cognitive demands (or susceptibility to lesions), they share certain features.

Delayed response tasks all involve a temporal separation between an initial stimulus and the response, illustrated in figure 1.3. The initial cue may be in any sensory modality, and the response may be made with the limbs, eyes or mouth. However, the response depends on the initial stimulus of that trial. Usually, the initial stimulus is obscured during the delay. This may be by an opaque screen coming down between the monkey and the object stimulus array, or the computer monitor becoming blank. Typically, the delay is a few seconds long.

The critical feature of the delayed response task is that if the monkey is to make a correct response after the delay, it must be based on an **internal representation** of the initial stimulus. That is to say, the response cannot be made according to cues present at the time of response. Often, the monkey is required to change its position in a cage or fixate on a fiducial marker to prevent responses based on sustained postures or maintained gaze. Such sustained postures or gaze might provide sensory cues at the time of response that would obviate the need for maintaining an internal representation of the stimulus.

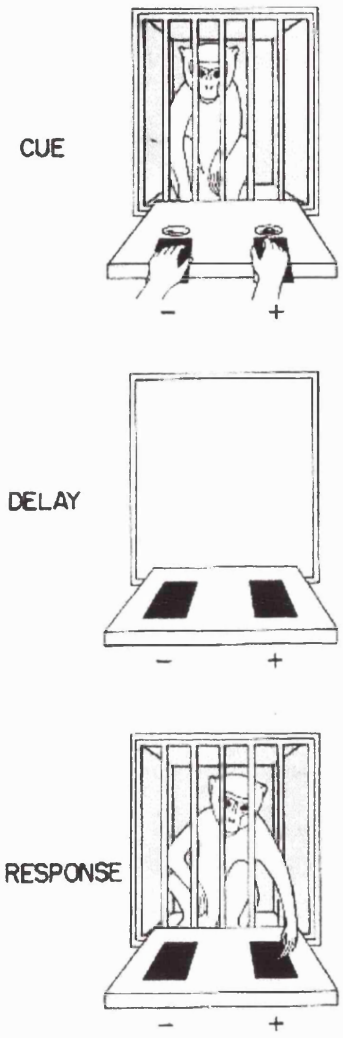


Figure 1.3. The delayed response task used by Goldman-Rakic (1987, ©American Physiological society). A monkey is shown the placement of a reward peanut at a specific location. A screen then obscures the view of the locations for several seconds. In the final stage, the monkey may choose freely one of the locations to receive the reward. Successful performance depends on the maintenance of an internal representation of the rewarded location for the current trial, throughout the delay period.

In the prefrontal cortex, there are neurons which exhibit sustained firing during the delay period of delayed response tasks. These were initially labelled 'memory cells' (Fuster and Alexander, 1971), and were thought to be the neural basis of short term memory. These cells may continue firing throughout delays up to 60 seconds (Fuster and Alexander, 1971). Many of these cells also respond to the initial stimulus and/or the response (Funahashi *et al.*, 1989; Fuster, 1973; Kojima and Goldman-Rakic, 1982).

However, sustained firing is not unique to the prefrontal cortex, and similar firing patterns may be found in many areas that are interconnected with the prefrontal cortex, including premotor cortex (Weinrich *et al.*, 1984), parietal cortex (Chafee and Goldman-Rakic, 1998; Koch and Fuster, 1989), caudate nucleus (Hikosaka *et al.*, 1989) and thalamus (Alexander and Fuster, 1973; Fuster and Alexander, 1973).

Stimulus selectivity

Not all delay related cells respond equally to all stimuli. The sustained firing patterns seen in many prefrontal cells during delayed response tasks appear to be specific to particular stimuli (Funahashi *et al.*, 1989; Funahashi *et al.*, 1993; Kojima and Goldman-Rakic, 1982; Niki, 1974; Niki and Watanabe, 1976; Quintana *et al.*, 1988). Early studies were confined to single modalities of stimuli, and responses were consistently directly related to the stimulus, without being conditional on other cues (c.f. 'contextual coding', p82).

The delay related firing could be specific to a location, colour or object identity in the initial stimulus, provided that it was predictive of the correct (rewarded) response. Unfortunately, in spatial delayed response tasks, the response may be determined from the moment that the stimulus is presented. The sustained

activity could therefore be interpreted as response preparation rather than stimulus representation.

This problem may be overcome by conditional delayed response task. For example, in oculomotor delayed response, a red cue at a position indicates that a delayed saccade is to be made to a location at + 90°from the stimulus, whereas a blue cue indicates that the saccade is to be made to a location at – 90° to the stimulus location. The directional specificity of delay activity can then be correlated to the location of the cue, independently of the intended response. Delay-related activity has been confirmed as related to the initial stimulus (Funahashi *et al.*, 1993; Niki and Watanabe, 1976).

However, such delay-related activity is not static. For example, in a manual spatial delayed response task, the specificity of the stimulus related activity (how well 'tuned' it was to particular locations) increased over time (Sawaguchi and Yamane, 1999a). This spatial tuning is dependent on the activity of prefrontal inhibitory inter-neurons (Rao *et al.*, 2000). These results suggest that stimulus specificity of delay-related activity is based in part on local mutual inhibition, and may mediate dynamic cognitive processes rather than fixed memory traces. Moreover, while some cells maintain the stimulus representation throughout the delay, others change during the delay and become selective for the impending response (Constantinidis *et al.*, 2001).

Distribution of stimulus sensitive delay responsive cells

So far the electrophysiological behaviours of sets of neurons at different locations in the prefrontal cortex have not been distinguished. However, cytoarchitectural differences between regions suggest functional differences that may be characterised by microelectrode recording.

Access to the anterior and ventral regions of the prefrontal cortex for microelectrode recording in monkeys is difficult. The majority of studies have recorded from territory within the bow of the arcuate sulcus, extending at most to mid-sulcus principalis. Therefore, most recordings will have been in area 8 or 9, with few from area 46 in mid sulcus principalis (Hoshi *et al.*, 1998; Hoshi *et al.*, 2000). This will become very important when trying to compare the results of monkey electrophysiology with human neuroimaging.

It has been reported that there are functional differences between delay-related cells in PFv and PFd (Levy and Goldman-Rakic, 2000). Discrete populations have been reported for objects, locations, colour patterns and faces (Goldman-Rakic, 2000; Levy and Goldman-Rakic, 2000; Romo *et al.*, 1999; Scalaidhe *et al.*, 1997; Scalaidhe *et al.*, 1999; Wilson *et al.*, 1993). In these studies, sustained firing during spatial delayed response tasks was associated more frequently with cells in or above the sulcus principalis. However, the majority of recordings are from the posterior third of the sulcus, or lying in the bow of the arcuate sulcus. In contrast, on delayed response tasks based on object features or face identity, more cells in PFv exhibited sustained firing. The selectivity for stimulus type in these regions was found even in animals not trained on delayed response tasks (Scalaidhe *et al.*, 1999).

These data provided seemingly strong evidence for **'domain specificity'** of prefrontal memory cells (Goldman-Rakic, 1998; Levy and Goldman-Rakic, 2000). They were also consistent with the connectivity patterns of prefrontal cortex. PFd is strongly interconnected with parietal cortex and the frontal eye fields, associated with the perception and memory of spatial locations. In contrast, PFv is strongly

interconnected with temporal cortex, associated the perception and identification of objects and faces.

The neurophysiological support for this domain specificity is not conclusive. For example, many neurons in PFd are responsive to non-spatial stimuli (Carlson *et al.*, 1997; Quintana *et al.*, 1988; Rainer *et al.*, 1999; Rao *et al.*, 1997; Tanila *et al.*, 1992). Some authors have argued that the 'domain specificity' is distinct from 'stimulus modality specificity', in that many stimulus modalities may contribute to the spatial or object domain, and that the distinctions are only relative, not absolute (Levy and Goldman-Rakic, 2000). Whether cells can be found that respond to one stimulus type or another does not determine whether that region is necessary for memory during a delay. Lesion studies are required to settle the issue.

Delayed response following prefrontal cortical lesions

Ferrier (1876) made large lesions to the prefrontal lobes of dogs and monkeys, and noted a marked change in behaviour without paralysis or incoordination. However, the observations were made without well-controlled experimental paradigms, and few studies were repeated over the next hundred years (Bianchi, 1895; Franz, 1907; Harlow *et al.*, 1952; Jacobsen, 1936).

Jacobsen (1936) reported that lesions of the prefrontal cortex caused severe impairments on a spatial delayed response task. Again, the lesions were large and included much of PFd and PFv. Nevertheless, performance on this task is critically dependent on the integrity of the prefrontal cortex, rather than parietal, premotor or temporal cortex or the cerebellum, even though these areas may be active during the delay (Dean, 1974; Goldman and Rosvold, 1970; Goldman *et al.*, 1971; Nixon and Passingham, 1999; Pu *et al.*, 1993). More refined lesions have permitted the different

contributions of different prefrontal regions to delayed response performance to be defined.

Many studies have found impairments on monkey delayed response tasks following lesions that included PFd (Bianchi, 1895; Butters *et al.*, 1971; Diamond and Goldman-Rakic, 1989; Franz, 1907; Goldman and Rosvold, 1970; Goldman *et al.*, 1971; Harlow *et al.*, 1952; Hoshi *et al.*, 2000; Jacobsen, 1936; Mishkin and Manning, 1978; Nixon and Passingham, 1999; Passingham, 1975; Passingham, 1978; Passingham, 1985). Cooling of PFd had similar effects (Bauer and Fuster, 1976; Bauer and Fuster, 1978).

Lesions of PFd have an especially deleterious effect on spatial delayed response tasks (Goldman-Rakic, 1987b). However, lesions including just the middle third of the sulcus principalis were necessary and sufficient to cause severe impairments following short delays (Butters and Pandya, 1969; Butters *et al.*, 1971). Lesions in neighbouring PFd, including area 9 lesions, did not cause the same deficit (Goldman *et al.*, 1971).

Transient neurochemical blockade by muscimol injections into the ventral bank of the middle third or the sulcus principalis also severely impaired spatial and object based delayed response (Hoshi *et al.*, 2000). This was despite the sparing of cells in the superior and posterior parts of the sulcus that showed sustained spatial delay-related activity. This suggests that failure of the delayed response was not due to an inability to maintain the items during the delay, but rather an inability to use this maintained information to guide the appropriate response.

Lesions of PFv may impair performance on tasks that require responses after a delay, whether spatial or non-spatial features of the stimuli were relevant (Iversen and

Mishkin, 1970; Passingham, 1975). This occurs when the delay is within a trial, such as the delayed matching to sample, or when the delay occurs between successive trials, such as delayed alternation. However, unlike PFd lesions, PFv lesions produce deficits in performance of matching tasks with a delay (Mishkin and Manning, 1978). However, lesions of PFv including areas 45 and 47/12 also cause a severe impairment on simultaneous colour matching (Passingham, 1975; Rushworth *et al.*, 1997). Furthermore, once learned, increasing the delay was not associated with worsening performance.

Given the profound effect of small lesions of area 46 in monkeys on delayed response performance, it might be expected that large prefrontal lesions in humans would impair working memory. However, there appears to be little effect of prefrontal lesions on some working memory tasks (D'Esposito and Postle, 1999). For example, Owen et al (1990), Canavan et al (1989) and Miotto et al (1996) have all reported that spatial span was not reduced after right or left lesions of the prefrontal cortex. Similarly, digit span may be preserved despite extensive prefrontal lesions (Canavan *et al.*, 1989; D'Esposito and Postle, 2000; Pigott and Milner, 1994). This apparent discrepancy might be due to the task differences, or lesion differences, or species differences.

Lesion differences are not a sufficient explanation. The human lesions were varied, but usually large, and as a group tended to include dorsal prefrontal cortex. Species differences in prefrontal function cannot be ruled out, but task differences can account for much of the apparent discrepancy. Span tasks are not equivalent to the delayed response task. Indeed, if the items are not reported by subjects immediately (as in span tasks) but only after a delay, then patients with frontal lobe damage are

often impaired (Bechara *et al.*, 1998; D'Esposito and Postle, 2000; Miotto *et al.*, 1996; Pigott and Milner, 1994). The effect of delay is exacerbated by distraction during the delay (Ptito *et al.*, 1995). This impairment may in part depend on the manner in which the spatial information is tested: if the items must be recalled after a delay, the deficit is greater than if the items are to be recognised (Ferreira *et al.*, 1998).

The working memory hypothesis

The neurophysiological and lesion data were drawn together by Goldman-Rakic into one of the most influential theories of prefrontal cortical function, that of working memory (Goldman-Rakic, 1998; Goldman-Rakic, 1987b; Goldman-Rakic, 1990; Goldman-Rakic, 1995). The details of the theory have evolved since its first formulation, but three key features were proposed.

First, the prefrontal cortex (PFd and PFv) processes information on-line in the service of a wide range of cognitive functions. This processing is essential for goal-directed behaviour in the absence of external cues to guide the actions of the subject. The delayed response task for example, requires an internal representation of the stimulus to be maintained until the response is made. Because the reward associated with a stimulus varies from trial to trial, neither recognition memory nor fixed stimulus response strategies are sufficient for the task.

Second, this process occurs in many regions of the prefrontal cortex, according to the type of information being processed. For example, PFd processes spatial information while PFv processes non-spatial information.

Third, each of these subdivisions (PFd, PFv) concerned with one working memory domain, integrates the mnemonic, attentional, responsive and perhaps also affective components of the task.

Cognitive models of working memory

The working memory hypothesis put forward by Goldman-Rakic has had a great influence on research into the prefrontal cortex. It has drawn on animal and human studies, using neurophysiological, cognitive and functional imaging techniques, in healthy subjects and following lesions. One additional strength is that it relates neuroanatomical structures to particular functions that had been proposed independently after psychological studies of normal human performance.

Baddeley and Hitch (1974) proposed that working memory had multiple components, in contrast to previous unitary models of 'short-term memory'. Critically, they distinguished temporary storage of information in either a 'phonological loop' or 'visuospatial sketchpad' from the attentional control of working memory resources by a central executive. This is illustrated in figure 1.4i.

The central executive supports manipulation of the information in the temporary storage buffers, necessary for complex cognitive tasks such as reasoning or planning. The fractionation of working memory could be used to explain many effects of concurrent task performance on learning, memory and reasoning (Baddeley and Hitch, 1974). However, the functions of the central executive were not initially proposed to be synonymous with the functions of any given anatomical brain region (Baddeley and Hitch, 1974; Baddeley, 1986).

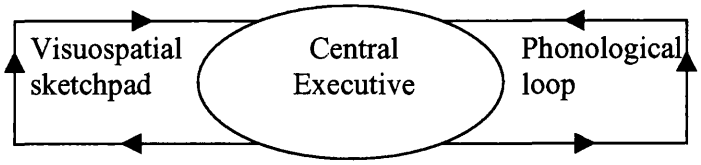
The model does not support the integration of information for complex multimodal representations. Such integration is suggested by the effects of semantics on memory in the phonological loop, or the effects of visual similarity on memory that is dependent on the visuospatial sketchpad. It could be argued that the central executive plays such an integrative role. However, the central executive was defined

partly by its distinction from the memory buffers, having no capacity to hold such complex representations.

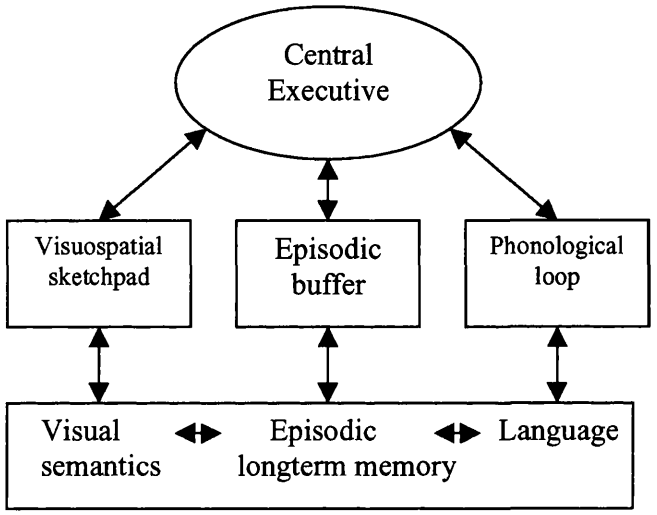
An alternative solution to the problem of integrative working memory is the episodic memory buffer, proposed by Baddeley (2000), and illustrated in figure 1.4ii. This new buffer is proposed to be a multimodal, integrative buffer of limited capacity under the control of the central executive. The representations – or 'episodes' – are integrated across space and modality, and may be extended over time, like episodic memory (Tulving, 1989). However, in Baddeley's model, they are distinct from long-term episodic memory.

Others have proposed that there is separate streaming of information in the central executive. For example, the visuospatial, auditory and feature properties of items in working memory have been proposed to be processed in parallel following sensory presentation (Goldman-Rakic, 1998), as illustrated in figure 1.4iii. However, the restructuring of the central executive in this form was motivated by the neurophysiological and functional imaging properties of prefrontal cortex, rather than cognitive and behavioural phenomena of the type that supported the original model (Goldman-Rakic, 1998). Such parallel processing in the central executive mirrors the 'domain-specificity' of delayed response activity in prefrontal cortical neurons (Goldman-Rakic, 2000; Levy and Goldman-Rakic, 2000; Romo *et al.*, 1999; Scalaidhe *et al.*, 1997; Scalaidhe *et al.*, 1999; Wilson *et al.*, 1993), and does not support the integrative functions demonstrated by neurons in this region (Rao *et al.*, 1997; Wallis *et al.*, 2001)

A



B



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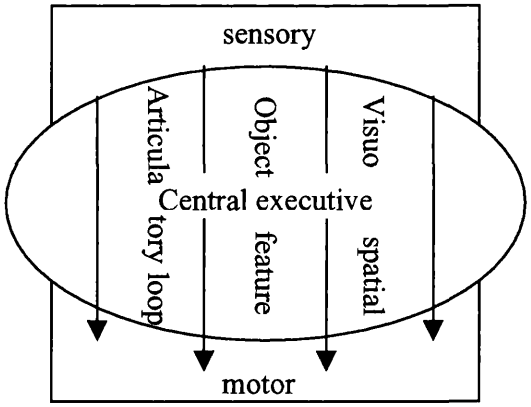


Figure 1.4. Models of working memory, (a) proposed by Baddeley and Hitch (1974, 1986), (b) revised by Baddeley (2000), and (c) elaborated by Goldman-Rakic (1998).

Combined cognitive and anatomic models

The central executive of working memory has been compared to the functions of the frontal lobes (Rabbitt, 1997). This comparison is supported by the neuropsychological evidence for a 'dysexecutive' syndrome following damage to the frontal lobes (Baddeley, 1986); the characterisation of basic properties of neurons suitable for complex executive functions (Miller, 1999); and evidence for the activation of the prefrontal cortex during normal performance of 'executive' tasks (D'Esposito *et al.*, 2000c; Levy and Goldman-Rakic, 2000; Petrides, 2000; Rabbitt, 1997).

Examples of unified structural-functional models include the model of the central executive in working memory proposed by Goldman-Rakic (1998); the computational models of Cohen *et al.* (Cohen *et al.*, 2000; Cohen *et al.*, 1996; Cohen and Servan-Schreiber, 1992); and the supervisory attentional system proposed by Norman and Shallice (Norman and Shallice, 1980; Shallice, 1989). These models will be discussed in more detail below, but they share several potential problems. **First**, that the functional systems of working memory may not map directly to specific neuroanatomical structures. The functions may rather depend on interactions between multiple structures. **Second**, a given structure or region may potentially serve many different functions. A common process may support these different functions, but to identify such a common process requires a more sophisticated functional analysis. **Third**, the crystallisation of structure-function relationships within a model may make it difficult to adapt the model in the light of new information. The existence of a model may potentially bias the interpretation of, or weight given to, new evidence.

Properties of the central executive

If the central executive is principally a function of the prefrontal cortex, then damage to this cortex should produce a recognisable 'dysexecutive' syndrome (Baddeley, 1986). A rich allusory language of executive functions has built up – planning, manipulation, monitoring, reasoning, set-switch – based in part around those tasks that are impaired in patients with frontal lobe damage (Rabbitt, 1997). There is clearly a danger of circular argument.

Baddeley (1998) suggested a number of core properties of the central executive that can operate across a range of sensory and mnemonic inputs. It must be able to **coordinate** the operation of the subsidiary slave systems (see figure 1.4i), and minimise interference between them. The structures mediating the central executive would be expected to be more active during dual-task paradigms, and lesions to those structures would be expected to impair dual task performance. In response to new sensory inputs streaming in, the executive should enable the **selective attention** to one or other stream. Related to this, it must also be able to **switch** this selection. Attentional selection and the switch of attentional set should also be testable with activation or lesion studies. Deficits would result in distractibility and/or perseverative behaviours. Working memory is based not only on sensory inputs, but may include learned information. The executive must therefore have some means to interact with **long-term memory**. Others have suggested that **monitoring** is a fundamental executive process. Although monitoring can also be formulated in terms of selective attention (Petrides, 2000; Petrides, 1995a), it is a term more readily applicable to some experimental paradigms such as the self-ordered pointing task (Petrides, 1995a).

The executive must also be able to create new representations, over and above the perceptual or mnemonic inputs. The episodic buffer proposed by Baddeley (2000) allows for the creation of new cognitive representations under influence from the central executive. However, even before this modification of the model, **manipulation** was proposed as a core process of a central executive, underlying many more complex tasks (D'Esposito *et al.*, 2000c; Petrides, 2000; Petrides, 1994). Manipulation requires the formation of a new representation based on the elements of other perceptual or mnemonic inputs.

The original model of working memory assumed that the actions of the central executive were appropriate to the context or experimental conditions. This implies that the processes of the central executive are **goal directed**. Dysfunction of the executive might then be due to an inappropriate goal or to dysfunction in the processes necessary to achieve a goal.

These properties have been largely tested at a systems level using functional imaging and lesion studies, rather than by neuronal electrophysiology. In the next three sections, I will consider the imaging and lesion evidence for the role of the prefrontal cortex in working memory and response selection, examining whether the prefrontal cortex has the properties of the proposed central executive.

Functional imaging of working memory

Many functional imaging studies have demonstrated activation of the prefrontal cortex during performance of tasks that require working memory. The tasks used have included a simple delayed response; manipulation of remembered items; and monitoring of a sequence of items. The items to be remembered have been visual, auditory, tactile, verbal, visuospatial, or motor, and have been specified either by the

experimenters or self-selected by subjects. Some studies have attempted to differentiate activity at different stages of working memory trials. This diversity of paradigms and methods precludes formal meta-analysis of data, although structured syntheses of results in a common stereotactic framework are possible (D'Esposito *et al.*, 1998; Duncan and Owen, 2000). I will consider the evidence for regional specialisation within the prefrontal cortex and the evidence for differential activity over time within working memory tasks.

Functional distinctions between PFd and PFv

PET and early fMRI studies initially suggested that working memory for spatial locations was associated with activity of the middle frontal gyrus (Baker *et al.*, 1996a; Courtney *et al.*, 1996; McCarthy *et al.*, 1994; Smith *et al.*, 1996; Sweeney *et al.*, 1996). This is consistent with the distribution of spatially selective delay cells in monkey delayed response studies, in the vicinity of the caudal sulcus principalis and anterior to the arcuate sulcus. Moreover, some PET and fMRI studies indicated that working memory for non-spatial items such as objects, letters or words was associated with activation of the inferior frontal gyrus (Adcock *et al.*, 1996; Cohen *et al.*, 1994; Courtney *et al.*, 1996; McCarthy *et al.*, 1996). This distinction between dorsal and ventral prefrontal cortex, according to the type of information to be remembered, is consistent with domain specificity theories of prefrontal cortical functional organisation.

Domain specificity is consistent with the theories of segregated processing of visual information, according to an object's identity ('what') and its location ('where') (Ungerleider and Mishkin, 1982; Ungerleider *et al.*, 1998; Wilson *et al.*, 1993). However, the domain of remembered information does not always account for

the pattern of cortical activity. For example, simple maintenance of spatial material is not always associated with activation of the dorsal prefrontal cortex when compared with sensorimotor control conditions (Courtney *et al.*, 1996; Owen *et al.*, 1996b; Smith *et al.*, 1995). This failure to find predicted activations does not in itself disprove theories of domain specificity.

A more serious blow to the theory of domain specificity comes from PET and fMRI studies that have demonstrated activation of the PFd in non-spatial tasks (Belger *et al.*, 1998; Braver *et al.*, 1997; Cohen *et al.*, 1997; Courtney *et al.*, 1996; Courtney *et al.*, 1997; Jonides *et al.*, 1998a; McCarthy *et al.*, 1996; Petrides *et al.*, 1993a; Smith *et al.*, 1996), and activation of PFv in spatial working memory tasks (Owen *et al.*, 1996a; Owen *et al.*, 1996b). Further, the formal synthesis of peak activations of prefrontal cortex in working memory studies did not reveal a clear distinction between loci for spatial and non-spatial tasks (D'Esposito *et al.*, 1998; Duncan and Owen, 2000). Although all of the tasks used required working memory, they differed in the additional cognitive processes required. Closer analysis of the similarities and differences between these tasks suggested a different functional organisation of the prefrontal cortex.

A difference can be drawn between those tasks that require only the maintenance of information over a delay, and those that require additional processes. Maintenance only tasks include delayed matching to sample, or delayed response tasks in which the responses to be made are based directly on the order and identity (location) of the original stimuli. In other tasks, maintenance may be supplemented by the monitoring of the subject's own responses; the running comparison of current stimuli with previous stimuli; or the manipulation of stimuli prior to response. In

contrast to domain specificity, **'process specificity'** describes the functional organisation of the prefrontal cortex according the presence or absence of these additional processes (D'Esposito *et al.*, 2000c; Petrides, 2000; Petrides, 1995a).

Owen et al (1996) used PET to study a series of spatial working memory paradigms. Subjects were presented with an array of 5 or 8 circles on a screen, and touched five circles in turn according to different conditions. When subjects were required to touch them according to a fixed sequence, there was no activation of PFd (areas 9, 46). Similarly, when they were required to replay a novel sequence of moves indicated by the circles briefly changing colour, there was also no activation of PFd. However, when subjects were asked to manipulate (reorder) the sequence, there was activation of the (right) middle frontal gyrus. Lastly, subjects were asked to touch the circles in sequence without repetition. This required monitoring of their own actions, remembering which positions they had previously touched. This monitoring was also associated with activation of the middle frontal gyrus. Neither the moves, nor memory for five locations, was sufficient to activate the middle frontal gyrus without additional 'executive' processes of monitoring or manipulation.

Evidence for process specificity comes from studies of the self-ordered task (Petrides, 1991a; Petrides, 1994; Petrides, 1995b), in humans and monkeys (see section below: 'Response selection following lesions to PFd and PFv'). In the self-ordered task, subjects are presented with a limited set of stimuli (locations on a screen, objects on a desk etc.). They must choose items one at a time until all have been selected, but without choosing the same item twice. Each selection must "be marked in the subject's mind and simultaneously be considered in relation to the other that still remain to be selected" (Petrides, 1995b).

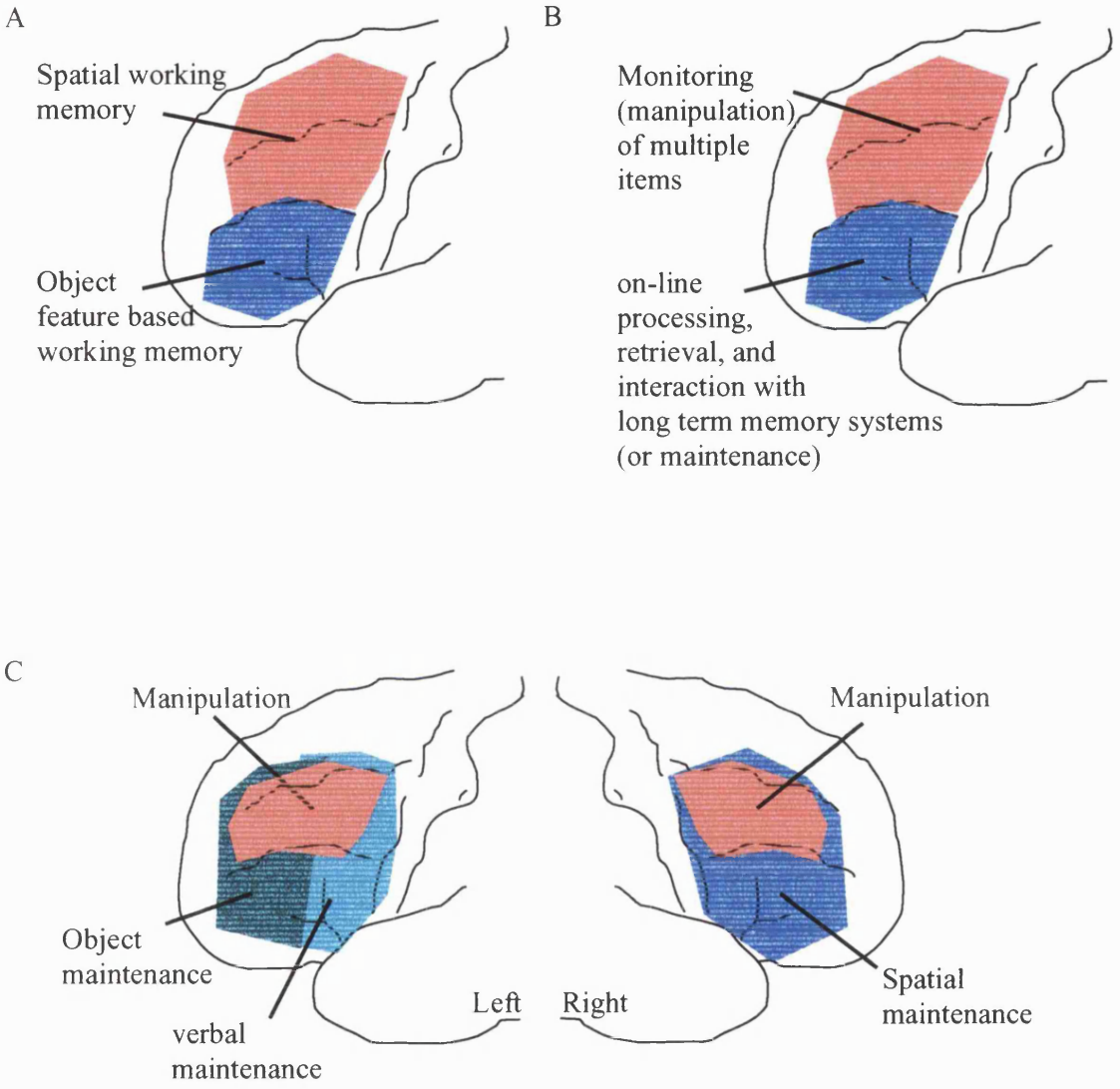


Figure 1.5. Schematic representation of the functional differentiation of the prefrontal cortex according to (a) domain specificity (Goldman-Rakic 1998) (b) process specificity (Petrides 1994, 1995, 2000) (c) a hybrid model of process specificity (D'Esposito et al 1998, 2000),

Performance on the self ordered task has been compared with a visual matching and visual conditional control task (Owen *et al.*, 1996b; Petrides *et al.*, 1993a; Petrides *et al.*, 1993b). Petrides et al (1993) used a set of abstract designs for the three tasks, presented in random locations on each trial. In the self-ordered task, the previous choices needed to be considered when making the current selection, and a new design sought and chosen. In the visual matching task, the subjects needed to search for the specified stimulus. In the conditional task, the subject needed to select and locate the abstract design that had previously been associated with a colour cue stimulus; no monitoring of previous selections was required. The self ordered task was associated with greater activation of PFd than either control task. The conditional task was associated with greater activation of posterior prefrontal area 8, but not areas 9 or 46. Similar results were obtained using numbers (Petrides *et al.*, 1993b) and spatial locations (Owen *et al.*, 1996b) rather than abstract designs.

In the process-specific model put forward by Petrides (1993, 1998), the mid-dorsolateral prefrontal cortex (PFd) mediates the monitoring (or manipulation) of multiple items in working memory. In contrast, the mid-ventrolateral prefrontal cortex (PFv, plus areas 44,45) mediates active or strategic retrieval of information from posterior memory systems. This is illustrated in figure 1.5b. PFv is more activated by free recall of verbal material than paired associate recall (Petrides *et al.*, 1995) or selection from a large rather than a small set (Thompson-Schill *et al.*, 1997). The explicit or controlled nature of the recall was considered important, as distinct from implicit or automatic retrieval processes. Evidence for this came from the comparison of the execution of a visuospatial sequence task when subjects were either ignorant of the operation of a sequence rule (learned implicitly) or were aware of the rule

(explicitly) (Doyon *et al.*, 1996). There was greater activation of PFv under the explicit condition, even though the sequence and performance did not differ.

An alternative process specificity model is suggested by studies of maintenance and 'maintenance-plus' working memory tasks. Maintenance-plus tasks include manipulation of items in memory, and continuous performance tasks such as . the n-back task (below). The role of PFd in monitoring and manipulation is similar to that put forward by Petrides, but there is a subtle shift in the proposed role of PFv (D'Esposito *et al.*, 1999b; D'Esposito *et al.*, 2000c; Postle and D'Esposito, 2000). PFv is proposed to mediate maintenance of information (without manipulation). This has been attributed to Petrides (Jonides *et al.*, 1998a; Levy and Goldman-Rakic, 1999; Levy and Goldman-Rakic, 2000; Smith and Jonides, 1997; Smith and Jonides, 1998), although is distinct from the original proposal of Petrides (1993, 1995, 1998), that PFv interacts with posterior memory systems and supports on–line processing during working memory tasks.

Manipulation of items in working memory includes the reversal of items in a sequence (spatial or non-spatial), or changing the order of a set of letters into alphabetic order. D'Esposito *et al.* (1999b) compared activation of prefrontal cortex during working memory for a five-letter string, with or without manipulating the letters into alphabetic order. Despite considerable variability from subject to subject in activation during the task, there was consistently greater activation associated with manipulation than with simple maintenance, in PFd (D'Esposito *et al.*, 1999b). This difference cannot be attributed to load (2 vs 5 items) or task difficulty, (measured by performance accuracy) (Postle *et al.*, 1999a).

The n-back task is often used to study working memory. The subjects are presented with a series of items one after another. For every stimulus they are asked to indicate whether it repeats one that was presented previously in the series. More specifically, they are asked to indicate when a stimulus is repeated immediately (1-back), after one intervening distractor stimulus (2-back) or after two intervening stimuli (3-back). In addition to the memory load for stimuli, the subjects must remember the temporal order of presentation, associate each item with its order (temporal coding), update the list of recent items, and select or inhibit responses according to the n-back rule.

Owen et al (1999) used PET to compare spatial working memory for five locations and performance of a spatial 2-back task. When compared to a visuomotor control, the spatial span task was associated with activation of PFv but not PFd, contrary to the predictions of the domain specificity model but consistent with those of the process-specificity model. The 2-back task was however associated with activation of the middle frontal gyrus. Direct comparison of the two tasks confirmed the task by regional interactions. Spatial, verbal, object, auditory and face stimuli during the n-back task have also been associated with activation of PFd, for n=2 or n=3 (Braver *et al.*, 1997; Cohen *et al.*, 1994; D'Esposito *et al.*, 1998; Jansma *et al.*, 2000; Martinkauppi *et al.*, 2000; Nystrom *et al.*, 2000; Perlstein *et al.*, 2001; Rama *et al.*, 2001; Schumacher *et al.*, 1996; Smith *et al.*, 1996).

It has been suggested that the type of stimulus does affect the laterality of prefrontal activation, in PFd and especially PFv (Belger *et al.*, 1998; D'Esposito *et al.*, 1998; D'Esposito *et al.*, 1999b; McCarthy *et al.*, 1996). Specifically, the right prefrontal cortex appears to preferentially maintain and manipulate spatial

information, and the left prefrontal cortex appears to preferentially maintain and manipulate verbal and object information. These asymmetries are not absolute, and have been incorporated in to a hybrid model of functional organisation of working memory, outlined in figure 1.5c (D'Esposito *et al.*, 2000c; Postle and D'Esposito, 2000)

Further evidence for process specificity rather than domain specificity comes from the application of transcranial magnetic stimulation (TMS) to induce a temporary disruption of cortical function in otherwise normal adult brains by TMS (Pascual-Leone *et al.*, 1999). In a series of experiments, Oliveri et al (2001) applied bilateral TMS separately to the superior frontal gyrus, middle frontal gyrus, posterior parietal and middle temporal regions. TMS was applied within trials of either a visual-object or visual-spatial n-back working memory task. Disruption of the middle frontal gyrus delayed responses and increased errors on both visual-object and visual-spatial tasks. In contrast, posterior regions were distinguished by modality, with parietal stimulation impairing visual-spatial task performance and temporal stimulation impairing visual-object task performance.

It is possible that domain- and process- specificity both exist in the frontal lobes, and that there is a relative shift from one to the other as one considers more anterior prefrontal cortex. The anterior parts of prefrontal cortex (areas 9, 10, 46, 47) may be distinguished by the processes engaged during working memory. In contrast, more posterior area (areas 6, 8, 44, 45) may be defined by the domain of remembered information. Support for this comes from both functional imaging and TMS studies of humans. The ventral part of these more posterior regions includes Broca's area. This is activated in studies of verbal working memory (non-spatial) (Cohen *et al.*, 1994;

Cohen *et al.*, 1997; Fiez *et al.*, 1996; LaBar *et al.*, 1999; Postle *et al.*, 1999a; Smith and Jonides, 1998; Smith *et al.*, 1996; Smith *et al.*, 1998) as it is in studies using lexical stimuli or verbal responses without a clear working memory component. More dorsally, in the posterior part of the superior frontal sulcus and gyrus, lies area 8. Part of this region is activated in association with both covert spatial attention without working memory load (Gitelman *et al.*, 1999; Nobre *et al.*, 2000; Nobre *et al.*, 1997) and spatial working memory (Courtney *et al.*, 1998b). This part of area 8 is anterior to and distinct from the frontal eye fields (Anderson *et al.*, 1994; Paus, 1996; Petit *et al.*, 1997; Sweeney *et al.*, 1996). In addition, transcranial magnetic stimulation of the posterior superior frontal gyrus impairs performance on the n-back working memory task for spatial but not object items (Oliveri *et al.*, 2001).

Delay related activity

Many of the tasks used to study working memory are complex, with many component cognitive processes. During the n-back task for example, the subjects must remember the temporal order of presentation, associate each item with its order (temporal coding), update the list of recent items, and select or inhibit responses according to the n-back rule. Activity in PFd may relate to any of these processes, alone or in combination. This contrasts with the apparent simplicity of the delayed response tasks first used to demonstrate delay-related activity in monkeys. Functional imaging studies have sought evidence of activity related to maintenance alone of information during a delay period.

The temporal resolution of lesion studies or PET imaging means that one cannot easily distinguish which of the component processes is critical to regional activation. Control conditions can be used to try to adjust for multiple component

processes. For example, the maintenance of several items in memory may occur in the self-ordered task and an externally specified memory task used as control (Petrides *et al.*, 1993b). One could assume that the 'memory load' is the same in both cases, according to the number of items, and that any difference between these tasks is attributable to the self ordered nature of the first task, not the memory load per se. However, this depends on the assumption of pure insertion for subtraction analyses (Frackowiak *et al.*, 1997), or requires a factorial design that may not be possible for the isolation of key task elements.

With the advent of event related fMRI it has been possible to study the activation associated with many components within a trial, separated by only a few seconds. In particular, one can distinguish activity associated with stimulus presentation (perception, encoding, naming etc), maintenance during a delay period (with or without manipulation), and making a response (probe stimulus perception, comparison or recognition, response selection and response execution).

The value of such event related designs was shown by Cohen et al (1997), using n-back tasks. The temporal dynamics of event-related fMRI was exploited to show that *active* maintenance was associated with activation of PFd. However, the delay period required active maintenance, including those processes outlined above. This is very different from the delayed response type tasks that revealed sustained firing in prefrontal neurons in monkeys (Chafee and Goldman-Rakic, 1998; Fuster *et al.*, 2000; Fuster, 1973; Fuster and Alexander, 1971; Niki, 1974; Niki and Watanabe, 1976).

Subsequently, activity in areas PFd has been reported during delay periods in working memory studies of visual, verbal and spatial material even without the need

for manipulation of items (Courtney *et al.*, 1997; D'Esposito *et al.*, 2000c; Postle and D'Esposito, 1999; Rypma and D'Esposito, 1999; Rypma and D'Esposito, 2000; Zarahn *et al.*, 1999). However, even on these simple tasks, there may be cognitive processes engaged during the delay periods in addition to maintenance.

For example, Courtney et al (1997) reported delay-related activation in dorsal prefrontal cortex during working memory for faces. However, their subjects were instructed to rehearse the appearance of the stimuli during the delay periods, keeping the image in mind. Active rehearsal, or voluntarily focusing awareness on an imagined image, may make demands on the executive or attentional processes in addition to maintenance. In tasks using verbal material (D'Esposito *et al.*, 1999a; Rypma and D'Esposito, 1999; Rypma and D'Esposito, 2000), subjects might have verbally encoded, rehearsed or subvocalised the material during the delay in addition to maintenance. Using a simpler paradigm without rehearsal, prefrontal activation was confined to part of the posterior prefrontal cortex, in the superior frontal sulcus that is most likely to be area 8, not areas 9 or 46 (Courtney *et al.*, 1998b).

The anticipated response that is to be based on remembered stimuli may also in part determine the activity during a delay period (Pochon *et al.*, 2001). Pochon et al (2001) used fMRI to study prefrontal activation during a six second delayed in a spatial delayed response task. The subjects were shown a sequence of spatially distributed stimuli. In one condition (match), the subjects were instructed to respond if a probe stimulus matched the original items. There was no delay related activation of PFd. In the other condition (replay), the subjects were required to replay the sequence of moves. This was associated with delay related activation of PFd, even without manipulation of the order or position of items. This difference between replay and

match is consistent with the different sensitivity of 'recall' and 'recognition' to frontal lobe lesions (Ferreira *et al.*, 1998).

Active maintenance has been distinguished previously from passive maintenance in working memory (Fuster, 1997). Active maintenance was not operationally defined, but may require the reorganisation of remembered items (manipulation); encoding the items to make the maintenance less vulnerable to distraction and to improve longer term memory; rehearsal of the mental image of visuospatial stimuli or the sound of letter stimuli or object names. These processes are all components of the working memory system (Goldman-Rakic, 1998), but they do not necessarily share the same neural substrate.

Working memory difficulty

Task difficulty may in part determine prefrontal activation. Difficulty may increase with the number of stimuli, the duration of delay, and the quality of stimuli. Greater activation of prefrontal cortex occurs with increasing number of items (Braver *et al.*, 1997; Cohen *et al.*, 1997; Rypma *et al.*, 1999), particularly at encoding (Rypma and D'Esposito, 1999). Load sensitivity may occur because each item to be remembered is associated with a pool of neurons: the more items, the bigger the pool. Alternatively, once a critical number of items is reached, new cognitive processes may be required for successful maintenance. These new processes could be described as changing passive maintenance of a few items into active maintenance of a larger group.

The use of thresholded statistical images may inadvertently indicate that a critical number of items is needed for prefrontal activation. Failure to identify activation below this threshold could then be a problem of statistical power. However,

parametric modulation of load could in principal distinguish a linear relationship between load and activation from a step function in activity, resulting from new cognitive processes.

Increasing working memory load in the context of the n-back task (Braver *et al.*, 1997) was associated with a monotonic increase in activation of PFd bilaterally. However, the 1-back task requires simple matching to (a previous) sample in successive trials. The 2-back task in contrast requires up-dating of the index of recency for multiple items. The increase in PFd activation may be due to this new process, rather than the extra memory load. Cohen et al (1997) and Jonides et al (1996, 1998) have identified a robust non-linear load-response relationship in PFd during performance of the n-back task. The 0-back and 1-back tasks were associated with minimal activation, whereas both 2-back and 3-back performance were associated with significant and similar activation (Cohen *et al.*, 1997).

There is an additional problem with parametric variation in stimulus number. If a finite stimulus set is used (whether a small pool of faces, locations on a grid or objects) the effects of increasing load are correlated with increasing interference among stimuli. Memory for an item on the current trial may be confounded by the interference effect of memory traces from presentation of that item in recent trials. Such interference between successive trials is significant during the delayed response task in monkeys with PFd lesions (Diamond and Goldman-Rakic, 1989). In the study by Rypma et al (1999), subjects were required to remember 1,3 or 6 letters over 5 second delays in a Sternberg task (Sternberg, 1969). Stimuli were drawn from just the upper case consonants. Although PFd and PFv were both activated in association with 6-letter working memory, the blocked design of the experiment meant that 6-letter

trials were subject to greater interference than 3- or 1-letter trials. The result is that increasing activity of PFd associated with increasing load may not be due to the activity of a larger pool of 'maintenance cells'. The increasing activity may instead be due to additional cognitive processes. Selection between competing responses is one such process.

In monkeys, sustained firing of neurons may occur for delays of one second or one minute (Chafee and Goldman-Rakic, 1998; Fuster *et al.*, 2000; Fuster, 1973; Fuster and Alexander, 1971; Niki, 1974; Niki and Watanabe, 1976). Increasing delay has not been reported to increase the number of delay responsive cells, or their firing rate. Many human imaging studies have used short delays of less than ten seconds. Rypma and D'Esposito (2000) reported activation of PFd during a twelve second delay period for verbal items, but this was only significant early in the delay period and not sustained. Longer delays have been associated with dorsal prefrontal activation during maintenance even without manipulation or rehearsal (Baker *et al.*, 1996b; Fiez *et al.*, 1996). The behavioural data also suggested that the subjects found the memory conditions difficult.

Recognition of stimuli and conditional response tasks may be more difficult if the stimuli are degraded. Degradation of stimulus quality has been studied in the context or working memory (Barch *et al.*, 1997). PFd was active in association with active maintenance over long delays, but did not differ significantly with stimulus degradation.

Summary of functional imaging studies

PFd is frequently activated in working memory tasks, whether verbal, spatial or object stimuli are used. The effects of task difficulty and memory delay length on

activity in PFd remain unclear. However, a distinction can be made between passive maintenance or pure storage (minimal PFd activation) and additional processes in working memory such as monitoring, manipulation or rehearsal (consistent PFd activation).

Limitations of the working memory hypotheses

The working memory hypotheses outlined above have been useful to interpret the sustained firing in prefrontal neurons during memory delays, the failure of delayed response performance following prefrontal lesions, and the common activation of the prefrontal cortex in many human imaging studies. However, there are significant limitations.

First, the PFd and PFv are active in many tasks, including some with minimal working memory demands (Duncan and Owen, 2000).

Second, the effects of disruption of prefrontal cortical function may not be proportional to the working memory demands of the task, but rather the demands on other cognitive processes.

Third, 'manipulation' of remembered items is only a meaningful term for humans. Monkeys may make delayed responses, or learn arbitrary rules for conditional responses, but it is not clear whether monkeys can manipulate novel items in memory. Any theory of human prefrontal cortical function would be strengthened by applicability to non-human primates.

The working memory hypotheses are primarily concerned with the conditions associated with activity of specific regions of the prefrontal cortex, or with the behaviour of individual neurons. Typically, they have not focused on the interactions between the prefrontal cortex and other brain regions. Alternative theories of

prefrontal function place more emphasis on the nature of the interactions between prefrontal cortex and other regions, at a systems level, or in terms of inter-neuronal interactions. Some of these alternatives can nonetheless account for the role of the prefrontal cortex in working memory (Miller and Cohen, 2001).

The selection of action

Free selection

It has already been noted that PFd can be activated during performance of tasks that appear to have minimal working memory demands. When we make a movement, the pattern of cortical activity associated with that same movement may vary greatly under different circumstances. Deiber et al (1991) used PET to study joystick movements, made in response to a tone. The subjects could either choose freely which direction to move in (up, down, left, right), or follow an external instruction that selected one of these four locations, or in a control condition they could only move in a fixed direction (up). When one of four movements was selected, versus control, there was greater activation of the premotor and parietal cortex and the supplementary motor area. However, when the self-selected movements (internally cued) were compared with externally specified movements, there was greater activation of PFd.

Frith et al (1991) performed a similar study, comparing what they termed 'willed' acts (freely selected) and 'routine' acts (specified by the examiner). Responses were made in two modalities: finger movement and speech. Willed action was associated with greater activity in PFd, in either modality. However, fMRI of the same tasks has suggested differences in the location of prefrontal activation foci for

'willed' action compared with 'routine' action in different modalities (Hyder *et al.*, 1997; Phelps *et al.*, 1997). These differences include bilateral PFd activation associated with motor willed action and unilateral left activation associated with verbal willed action (although laterality was not included in the analytical model as a factor, and these laterality effects may be artifacts of thresholded images). In addition, the motor willed action focus lay on the middle frontal gyrus, whereas verbal willed action was associated with multiple foci, in the superior frontal sulcus, middle frontal gyrus and inferior frontal gyrus.

Jahanshahi et al (1995) studied the selection of when to act, rather than which action to make. Self-paced movements (which triggered a tone) were associated with significantly greater activation of left PFd than externally triggered movements (by a tone). By yoking the external trigger tones to the times of self-selected movements, they ensured that the actual number and distribution of moves made was the same in both conditions.

Random number generation can also be regarded as a task of response selection, and has been studied using PET (Jahanshahi *et al.*, 2000). The subjects were asked to generate random numbers between 0 and 9, at different rates. At low rates (up to 1 Hz), random number generation was associated with activation of PFd compared to control, regardless of the rate. At higher rates, there was a decline in the activation of PFd. This reduction in activity at higher rates might seem paradoxical, but behavioural analysis indicated that the pattern of responses had also changed. As the rate increased beyond 1 Hz, the responses became more stereotyped, less random. At these higher rates, the responses were no longer as freely selected, but were determined by recently selected numbers.

The activation of PFd associated with freely selected responses has also been demonstrated for free drawing (versus copying drawings) (Jueptner *et al.*, 1997b), selection of mouth movements (Spence *et al.*, 1998), and as discussed more in the next section, the selection of appropriate words (Buckner *et al.*, 1995; Hyder *et al.*, 1997; Klein *et al.*, 1995; Ojemann *et al.*, 1998; Phelps *et al.*, 1997; Pujol *et al.*, 1996; Thompson-Schill *et al.*, 1998).

Although activation of PFd is a consistent finding, other areas are often associated with the selection of action, including the supplementary area, premotor cortex, and parietal cortex. To understand which of these represents the primary influence on freely selected action requires knowledge of the temporal order of activations. A comparison of PET activations and magnetoencephalographic (MEG) source localisation (Pedersen *et al.*, 1998) confirmed the co-localisation of four frontal foci during finger movement. The high temporal resolution of MEG was used to show that activation proceeded sequentially from the middle frontal gyrus (PFd) through the supplementary motor area and premotor cortex, to the primary motor cortex

It could be argued that activation of PFd during random number generation or finger selection represents working memory. When subjects freely select between actions, they might remember the last few moves and use these so as to try to achieve a random series. Against this argument, Hadland et al (2001) found that rapid rate TMS over the left PFd delays freely-selected responses even when there is no memory load; whereas stimulation has no effect on responses to external stimuli (Hadland *et al.*, 2001). This suggests that PFd plays a genuine role in selection.

Constrained response selection

Many responses are not selected freely, but are constrained by external or internal factors. By 'internal constraints' I mean those imposed by a subject on their own actions. For example, a response set may be limited by limited recall of valid responses, or the development of constraints on responses during trial and error learning. External constraints could include the condition that responses are drawn from a limited response set presented by an experimenter, or by the imposition of a general rule for valid responses.

Early in trial and error learning of motor sequences, subjects may freely select one of many moves (Passingham, 1993; Passingham, 1996), or one of many time-points to make their move. As learning progresses, the experience of feedback will guide subsequent moves, such that by the end of learning a move is no longer freely chosen but determined by its place in the sequence.

Early trial and error learning has been associated with activation of PFd in normal subjects (Jenkins *et al.*, 1994; Jueptner *et al.*, 1997a; Sakai *et al.*, 1998; Shadmehr and Holcomb, 1997; Toni *et al.*, 1998), declining gradually as the sequence is learned. Toni *et al.* (1998) showed this most clearly using fMRI to measure activity during forty minutes of continuous whole brain imaging during the acquisition of a complex 12 move sequence by trial and error. Similar activity has been shown when subjects select the time of responses, during the early phases of trial and error learning of rhythmic motor sequences (Sakai *et al.*, 1999).

In contrast, responses may be selected according a rule imposed by the experimenter. Verbal responses have been most often studied. For example, subjects may be given a concrete noun, and then asked to select a semantically related verb

(verb to noun generation: dog bark, apple eat, etc.). Alternatively, subjects may be asked to complete a word stem (stem completion: psa___ psalm, jou___ journal, etc.). Stem completion and verb to noun generation have often been associated with activation or PFd and/or PFv in functional imaging studies (Desmond *et al.*, 1998; Ojemann *et al.*, 1998; Phelps *et al.*, 1997; Warburton *et al.*, 1996). This lateral prefrontal activation is not sensitive to response feedback (Bagdaiyan and Posner, 1998).

Two studies strongly indicate that it is selection between alternatives that is associated with this prefrontal activation, rather than other aspects of the tasks such as semantic retrieval or working memory. **First**, Thompson-Schill et al (1997) studied a series of semantic decision tasks, and independently varied the number of possible responses. In all three tasks, a single response required either a high or a low degree of selection amongst valid alternatives. Selection between many alternatives was associated with activation of PFv. **Second**, Desmond et al (1998) contrasted stem completion for stems with many possible solutions to select between, with stems that had few correct completions. The middle frontal gyri (areas 9,10 and 46) were more active when there were many solutions to choose between. Activation of PFd during random number generation, sequential movement selection or verbal fluency tasks could have been attributed to working memory for previous moves. However, in the stem completion task used by Desmond et al (1998), only a single response was selected. This suggests that PFd can be activated in association with selection where there are no working memory demands.

Response conflict

In the previous section, I discussed the activation of PFd and PFv when there are several responses to choose among. In the examples given, the different responses were valid competitors, and no response was prepotent. There are situations however, when potential responses are in conflict. For example, if a compound stimulus is presented, one feature of the stimulus might indicate one response, whilst another feature of the same stimulus indicates an alternative response.

The Stroop test (Stroop, 1935) has been used to study response conflict. Typically, names of colours are presented in different coloured typescript. The colour of the ink could be congruent with the written word, e.g. 'red', neutral e.g. 'hat' or incongruent with it, e.g. 'blue'. A subject is asked to speak either the colour of the word, or of the ink. In incongruent trials, there are two possible colour word responses. The correct answer varies according to the initial instructions, whether to name the word colour (blue blue) or ink colour (blue red). The conflict between responses is revealed behaviourally by increased reaction times and error rates on incongruent trials, and residual effects of these errors and incongruities on subsequent trials (MacLeod, 1992).

Functional imaging during performance of the Stroop task reveals activation of lateral frontal regions (Carter *et al.*, 1995; George *et al.*, 1994; Taylor *et al.*, 1997) and the cingulate cortex (Barch *et al.*, 2000; Botvinick *et al.*, 1999; Carter *et al.*, 1999; Carter *et al.*, 1995; Casey *et al.*, 2000; George *et al.*, 1994). These regions are more activated during incongruent trials than congruent or neutral trials (Banich *et al.*, 2000a; Banich *et al.*, 2000b; Zysset *et al.*, 2001). Independent manipulation of the relevant and irrelevant dimensions has suggested some frontal regions are dimension

specific (Banich *et al.*, 2000b). It has been suggested that the imposition of attentional set, during incongruent trials, depends on task relevant information in domain specific regions. However, these domain specific regions were towards the posterior margins of the prefrontal cortex (y=10 to 14mm anterior to the anterior commissure in standard anatomic space).

Banich et al (2000a,b) varied the Stroop task, using the same type of stimuli but asking subjects to identify a predetermined target (e.g. respond if the colour is 'purple'). This separated the effects of stimulus congruity from response conflict. They included the three dimensions of word, colour and object. Therefore the colour dimension was sometimes processed more automatically than the other dimension (object) and sometimes processed less automatically than the other dimension (word). PFd (posterior area 9) was more activated in association with incongruent trials of colour-word pairs when attending to the colour stream, but not when attending to the word stream. Conversely, PFd (posterior area 9) was more activated in association with incongruent trials of colour-object pairs when attending to the object stream, but not when attending to the colour stream. The cingulate cortex was not more active during incongruent trials, in the absence of response conflict or error feedback. These results suggest that the imposition of attentional control of responses is mediated by PFd, whereas the cingulate cortex is active when potential responses are in conflict.

Further support for this hypothesis comes from MacDonald et al (2000), who used fMRI to study a cued Stroop task. In each trial, an instruction cue indicated whether the subsequent compound colour-word stimulus should be responded to according to the colour or the written word. The delay between cue and colour-word stimulus enabled the trial specific configuration and maintenance of attentional set,

necessary for the control of responses if the response was to be based on the colour of the word. This delay was associated with greater activation of PFd (area 9) but not the cingulate cortex, in preparation for colour trials, not word trials. Congruity did not differentiate the activity of PFd. In contrast, the cingulate cortex was active in association with the response, more so on incongruent trials.

Changing response patterns

The same response may be correct in one situation, but incorrect in another: clapping ones hands after hearing a speech is usual in a political meeting but inappropriate after a church sermon. In this example the context or environment indicates which responses are appropriate following particular sensory inputs. However, changing feedback or reward reinforcement may indirectly indicate that the behavioural strategy should change. The established group of behavioural (or cognitive) actions that occur in response to a stimulus is called a 'task set' or 'central set'. The configuration of response dispositions that forms the set is transient: if the context or reinforcement schedule changes, it may be necessary to switch to a new set.

Set shifting is required to perform the Wisconsin Card Sort Test (Grant and Berg, 1948). A subject must sort a card according to the colour, shape or number of items printed on them. The examiner decides the 'rule' (colour, shape or number) by which cards should be sorted. This rule, or context, may be learned either by trial and error according to feedback after each trial, or it may be given explicitly to the subject.

Functional imaging during performance of the Wisconsin Card Sort Test has consistently revealed activation of PFd and PFv, using PET (Berman *et al.*, 1995; Esposito *et al.*, 1999; Goldberg *et al.*, 1998; Nagahama *et al.*, 1996; Ragland *et al.*,

1997), SPECT (Catafau *et al.*, 1998; Tien *et al.*, 1998) and fMRI (Konishi *et al.*, 1999; Mentzel *et al.*, 1998). Activation persists even when the rule change is explicit (Konishi *et al.*, 1999). However, PET and SPECT do not allow the different processes within or between trials to be readily distinguished.

The Wisconsin Card Sort Test is a complex task with many sensory, motor and cognitive components, reflected in the wide network of cortical regions associated with the task. However, at the core lies the need to switch attention from one dimension of the compound stimulus card e.g. colour, to another dimension, e.g. number (Downes *et al.*, 1989; Roberts *et al.*, 1988). Importantly, the change in behaviour is not based on reversing the response to a given stimulus, nor learning a new response to discriminatory features within the same dimension. Rather, it is necessary to transfer attention to features defined by a new dimension.

Rogers et al (2000) used PET to study such intra- and extra-dimensional shifts in a visual discrimination paradigm in normal volunteers. Extra-dimensional shift learning was associated with greater activation of PFd than intra-dimensional shift learning, or simple reversal learning, particularly in the right hemisphere. Learning revised stimulus reward associations following an intra-dimensional shift was not associated with prefrontal activation (compared with performance of a pre-learned discrimination). Similar activations of PFd and PFv have been shown in association with attentional set shifting of rules for hand movements (Omori *et al.*, 1999) and switching between stimulus response mappings in a cycle of switch-repeat trials (Kimberg *et al.*, 2000; Rogers and Monsell, 1995; Rogers *et al.* 2000).

Planning unique responses

Planning is an essential everyday activity. To plan the solution to a problem requires the organisation of complex sequences of actions, especially sensitive to the context specified by the environment and the particular goal. The goal or context may not have been encountered before, so there may be no predetermined response set. In addition, no particular action is specified directly by the goal or circumstances, yet the set of actions that will achieve the goal may be limited even to a single course. To determine the correct response, it is necessary to think ahead and evaluate the consequences of possible actions. In other words to plan is to "model a sequence of actions in preparation for carrying out a particular task" (Shallice, 1982).

A clear operational definition comes from Dehaene and Changeux (1997), who define planning as "the goal-directed, trial-and-error exploration of a tree of alternative moves...When no direct move is available, a move must be generated, tried out, and accepted or rejected depending on its ability to bring the problem closer to a solution". This highlights the key processes required in planning: to be aware of the goal; to generate possible moves; to make moves mentally; to evaluate these moves with respect to the goal; to reject or select moves; and to hold these moves in memory. At least some of these processes may involve regions of the prefrontal cortex.

The 'Tower of Hanoi' and the related 'Tower of London' (TOL) tasks have been used to assess planning. The planning demands and problem-solving strategies suitable for these tasks are well defined (Dehaene and Changeux, 1997; Goel and Grafman, 1995; Ward and Allport, 1997). The Tower of London has a clearer rating scale for problem difficulty (Goel and Grafman, 1995) , and performance on the two

tasks may differ (Humes *et al.*, 1997). In the TOL, subjects are presented with two sets of three balls (start and goal arrays), each on three pegs (Shallice, 1982) or in three pockets (Owen *et al.*, 1990). Subjects must plan how to move the balls on the start array, one at a time, in order to match the goal array.

PET, fMRI and SPECT neuroimaging have been used to study regional activations during TOL performance. Compared to visuomotor controls, planning is consistently associated with activation of the left dorsal prefrontal cortex, (Baker *et al.*, 1996b; Elliott *et al.*, 1997a; Morris *et al.*, 1993; Owen *et al.*, 1998; Owen *et al.*, 1996a). Further, increased prefrontal activation was seen with more difficult problems (Baker *et al.*, 1996b; Owen *et al.*, 1996a), and in subjects who took longer to plan moves or made fewer errors (Morris *et al.*, 1993). Although these studies indicate the network of brain activity required for performance on the TOL, they do not permit an analysis of the contributions of these separate regions to the overall task.

The contribution of working memory to the activation of PFd during performance of the Tower of London has been studied using PET (Owen *et al.*, 1996a). However, the working memory condition in this study depended on memory for externally specified moves, rather than self-selected moves of the type made during planning. In view of the PFd sensitivity to externally specified versus freely selected movement outlined above, it is clearly necessary identify the contribution of selection and memory for self selected moves to overall activity of PFd during planning. This is considered further in chapter 9.

Summary

Activation of PFd, and often also PFv, is found in tasks that require the selection of responses. Selection between multiple possible actions is associated with

greater activation of PFd and PFv. Some of these response selection tasks are confounded by concurrent working memory loads. Others have either no working memory load, or the working memory load may be varied independently of the degree of response selection.

Response selection following lesions to PFd and PFv

Non-human primates

Both monkeys and humans can perform delayed response tasks, delayed matching to sample tasks, and delayed non-matching to sample tasks (see section above, 'Delayed response following prefrontal cortical lesions'). Monkeys can also perform the self-ordered task that requires monitoring of previous responses (Petrides, 1991a), conditional delayed response tasks, and shift cognitive set in tasks analogous to the Wisconsin Card Sort Test (Dias *et al.*, 1996b; Dias *et al.*, 1997). However, manipulation of a series of items in memory (e.g. reorganisation of letters into alphabetic order) is not directly applicable to monkeys. Therefore, the process specificity model of working memory put forward by D'Esposito (1998, 2000) is not directly testable in animals. The closely related model proposed by Petrides (1993,1995, 2000) and Owen (1996) is concerned primarily with monitoring rather than manipulation, and has been tested in monkeys.

Petrides (1991, 1995) trained monkeys to perform the self-ordered task. The monkeys chose from an array of three objects. On the first presentation, they were free to choose any stimulus. After ten seconds, the objects were rearranged and re-presented. The monkey had to choose one of the objects that had not been chosen in the previous trial. The objects were rearranged and represented again, until all the

objects were selected. Monkeys with lesions to PFd (areas 9, 9/46 and 46) performed at chance on all trials. That is to say they were unable to select a response that was dependent on monitoring of previous responses. They were not impaired on a visual conditional associative task that required long term memory for the appropriate response to a cue (Petrides, 1985). Indeed, a double dissociation is present between the effects of two adjacent frontal lesions (PFd vs area 8) and the task that is affected (self-ordered or visual conditional) (Petrides, 1982; Petrides, 1985; Petrides, 1991b).

Monkeys with PFd lesions were also impaired at monitoring externally specified actions, and making a response based on objects not selected by the experimenter (Petrides, 1995b) or based on the order of presentation of the stimuli (Petrides, 1991a). These impairments are not attributable to a simple failure of working memory. These monkeys were still able to perform delayed non-matching for the object they originally chose, if presented amongst novel stimuli (an object recognition test) (Petrides, 1991b).

Petrides (1998) has also shown that the size of the deficit following lesions to PFd depends on the number of items to be monitored, rather than the delay between observation and response. Monkeys with lesions to PFd were impaired at increasing numbers of items (for n>2), but performance was equal after 10-second and 90-second delays. Lesions of area 9 alone (sparing 46), caused only a minor impairment. In contrast, lesions to anterior temporal lobes cased delay sensitive deficits, for all numbers of items. Lesions of area 8 did not impair performance.

Lesions of PFv cause a more widespread impairment of spatial and non-spatial delayed alternation, or delayed matching to sample with repetitive stimuli (Mishkin and Manning, 1978; Passingham, 1975). It has been suggested that PFv plays a role in

retrieval of information from long term memory systems in the temporal lobe, distinct from the monitoring in working memory current responses (Petrides, 1994; Thompson-Schill *et al.*, 1998). This is supported by the deleterious effect of PFv lesions on the learning or performance of learned arbitrary visuomotor associations (Murray *et al.*, 2000) or the selection of contextually appropriate responses (Passingham, 1993).

The Wisconsin Card Sort Test is not applicable to monkeys, but simpler visual discrimination learning tasks that require intra- and extra- dimensional shifts are suitable. Lesions to PFd impair monkey performance following extra-dimensional shifts (Dias *et al.*, 1996a; Dias *et al.*, 1996b; Dias *et al.*, 1997). It could be argued that poor performance on extra-dimensional shift tasks (including the Wisconsin Card Sort Test) is due to poor working memory. For example, the subjects need to remember the instructions for the current trials, and it could be argued that they need to maintain a representation of the information necessary for the next response based on previous responses and feedback.

However, these working memory demands are the same for learning successive reversal shifts, intra-dimensional shifts and extra-dimensional shifts; yet performance is only impaired on the extra-dimensional shifts (Dias *et al.*, 1996a; Dias *et al.*, 1996b; Dias *et al.*, 1997). Similar deficits have been found in patients with structural lesions to PFd (Owen *et al.*, 1991) or functional deficits following degenerative diseases of the frontal lobes and their striatal projections (Downes *et al.*, 1989).

Patient studies

Early reports by Ferrier (1876), Penfield and Evans (1935) and Luria (1969) of the consequences of frontal lobe damage described poverty of judgement and planning, perseveration of behaviour in the face of corrective feedback, distractibility and stimulus driven behaviour. Habitual actions may be unchanged – patients with lesions of the frontal lobes may show no paresis, apraxia or aphasia – but behaviour may not be chosen appropriately or adapted for non-routine situations.

Group studies of patients with lesions to the frontal lobes are problematic. Lesions may vary greatly in their aetiology, spatial extent and rate of development. With the advent of CT and MRI scanning, a lesion can at least be clearly defined. However, if a lesion damages deep white matter tracts a wide area of cortex may be 'disconnected' from other brain structures even if it remains intact. The true extent of dysfunctional cortex would then be underestimated. Also, PFd and PFv are often not damaged independently of each other. Nevertheless, some features of frontal lobe damage are consistently reported.

In previous sections I have discussed the activation of PFd during the self-ordered task developed by Petrides, and the effects of lesions of PFd in monkeys. However, deficits on this test were first shown in patients (Petrides and Milner, 1982). They make errors selecting a response on the basis of objects chosen previously by themselves or by an examiner. Although often discussed in terms of 'monitoring', the deficit is in selecting a single response from several competing options; in the absence external cues or pre-potency of correct responses; in the absence of useful information from long term memory systems such as recency; and in the absence of learned arbitrary stimulus-response associations.

Patients with prefrontal lesions are impaired on other tasks that require selection of responses, whether free selection or from a constrained response set. For example, Johns (1996) studies patients with left and/or right frontal lobectomies (including mainly dorsal frontal cortex). Her subjects were asked to move a joystick in one of four directions, in response to a pacing cue, so as to build up a random sequence of movements. Randomness was assessed by comparing the actual frequencies of pairs of movement (up-up, up-left etc.) with the frequencies expected in a truly random series. Randomness was reduced in the patient group compared with controls, with more stereotyped sequences of movements. The patients were not impaired on a control task in which joystick movements were specified by the examiner.

Temporary 'lesions' induced by transcranial magnetic stimulation over the dorsal lateral prefrontal cortex also impair random number generation (Jahanshahi and Dirnberger, 1999; Jahanshahi *et al.*, 1998). In particular, the randomness of responses is changed, with reduced inhibition of repetitions, and increased counting.

Selection of verbal responses is often constrained by a rule. Efficiency of verbal response selection (fluency) is measured by the number of responses within a specified time period (say 60 seconds) or known maximal response set. Neurosurgical, ischaemic, and traumatic lesions to the left frontal lobe often show impairments in word fluency. This includes letter fluency (words beginning with a given letter)(Johns, 1996; Levin *et al.*, 2001; Stuss *et al.*, 1998); phonemic fluency (words rhyming with a cue word) (Jurado *et al.*, 2000); and semantic fluency (words belonging to a particular category) (Johns, 1996; Jones-Gotman and Milner, 1977;

Tucha *et al.*, 1999). However these deficits do not always occur, even after large and bilateral lesions (Jurado *et al.*, 2000),

The deficits are more marked if the semantic category of response is shifted. For example, the responses might be semantically different, but share a common homophone ('mark' and 'insect' both related to 'tick') (Warrington, 2000). The shift between category has been proposed as the principal deficit here, rather than fluency within any given category. Even within an apparently simple category (like words beginning with 's'), normal subjects impose structure on their serial responses (giving animals beginning with 's' followed by foods beginning with 's' etc.). This ability to move from one sub-category to another increases the overall fluency, and is an example of voluntary shifting of response set. Set-shifting is impaired in patients with damage to the frontal lobe (see below), and it could be argued that the resulting disorganisation of response strategies underlies poor fluency (Gershberg and Shimamura, 1995; Stuss *et al.*, 1996).

However, a deficit in selection of one response out of many possibilities may occur even without category shifting. For example, Thompson–Schill et al (1998) studied verb to noun generation in patients with frontal lobe lesions. The patients were not always impaired at semantic retrieval, but they were impaired when the probe noun was associated with many potential verb answers. A single item needed to be selected from amongst many possible alternative responses (Thompson-Schill *et al.*, 1998).

Set shifting may be impaired following surgical or degenerative lesions to the frontal lobe. Patients with frontal lobe damage typically show behavioural rigidity on the Wisconsin Card Sort Test. The impairment is not because the patients cannot

understand, remember or apply a sorting rule. These patients (with lesions including PFd) are able to sort cards according to a rule, but they are severely impaired at switching to a new rule (Drewe, 1974; Johns, 1996; Nelson, 1976; Stuss *et al.*, 1983). The impairment is greater following lesions to PFd than other frontal regions (Johns, 1996), or posterior cortical lesions (Drewe, 1974; Nelson, 1976), and may occur even if the tester tells the patient when the rule has changed. In addition, the poor performance on the Wisconsin Card Sort Test is correlated with metabolic activity of the right PFd following head injury (Lombardi *et al.*, 1999). However, deficits in performance on the Wisconsin Card Sort test are not obligatory following prefrontal cortical lesions (Anderson *et al.*, 1991; Eslinger and Damasio, 1985; Heck and Bryer, 1986), nor are they specific to frontal damage (Anderson *et al.*, 1991; Herman *et al.*, 1988).

One consequence of the inability to switch set is that prepotent responses will occur in preference to contextually appropriate responses. Where no response is prepotent, an irrelevant environmental stimulus may trigger response pertaining to that stimulus, even if the response is also irrelevant to the task or context. Distractibility and stimulus driven behaviour has been long described in patients with frontal lobe damage (Ferrier, 1878; Luria, 1969). Stimulus driven inappropriate behaviour may be dramatically demonstrated by utilisation behaviours (Lhermitte, 1983).

More formal evidence of the inability to suppress prepotent responses comes from the Stroop task (Stroop, 1935). Damage to PFd and PFv may impair performance on the Stroop task (Golden, 1976; Vendrell *et al.*, 1995). Even when the

need to switch set is cued, or predictable, patients may still be impaired (Rogers and Monsell, 1995; Rogers *et al.*, 1998; Stablum *et al.*, 1994).

Despite the behavioural rigidity evident on tasks like the Wisconsin Card Sort Test, patients with lesions to PFd also exhibit greater distractibility. For example, they are unable to sustain attention to stimuli if they were presented at a monotonous slow rate (Wilkins *et al.*, 1987). The essential role of PFd and PFv in suppression of responses to irrelevant distractors has been shown clearly by Barcelo and Knight (2000). Patients with lesions to PFd and PFv were more distracted by a novel stimulus in a visual detection task. However, despite being distracted by a novel stimulus, when a novel stimulus heralded a subsequent target, patients were not able to benefit from its predictive value (Barcelo *et al.*, 2000a).

Impaired planning has also been reported in patients with lesions involving the prefrontal cortex. For example, performance on the Tower of London task is impaired following neurosurgical (Johns, 1996; Owen *et al.*, 1990; Shallice, 1982) or neurodegenerative (Owen *et al.*, 1998) damage. Planning deficits may not be evident during performance of clinical measures of planning, such as the Tower of London. This may be because these tests, or the test environment, are highly structured. Patients with frontal lobe damage may have greater difficulty with 'real-world' tasks of organisation of behaviour (Burgess *et al.*, 1996).

Summary

Studies of patients with damage to the frontal lobes, and animals with well defined lesions of PFd, reveal impairments of response selection in the self-ordered task, free or constrained selection both motor and verbal responses, and set-shifting.

These deficits are not attributable to a simple inability to maintain information during a delay until a response is to be made, or the sensorimotor aspects of the response.

Attentional control of action

Norman and Shallice (1980) proposed a cognitive model for the control and selection of action, later elaborated by Shallice (1982, 1989, 1998). Like the cognitive model of working memory (Baddeley and Hitch, 1974), the model was based on a functional analysis of cognitive and behavioural phenomena, but has subsequently been closely associated with the prefrontal cortex (Shallice, 1989). The model emphasised the difference between 'automatic' and 'controlled' action. Automatic behaviour may be loosely considered to be behaviour that does not require attention, or awareness for its expression. A clearer operational definition is that automatic behaviour does not make demands on limited processing resources e.g. attention, and can therefore be performed without interfering with other tasks (Cohen *et al.*, 1990; Shiffrin and Schneider, 1977).

The supervisory attentional system

Norman and Shallice (1980) proposed that for habitual actions in familiar circumstances, the constituent movements were represented within a schema. This is illustrated in figure 1.6. The schema can be activated without execution of the action. Activation may occur by preparation or imagination of a movement, or by sensory inputs that are habitual antecedents ('triggers') to the action. However, if the schema is further activated, beyond its threshold, its action is executed. Different schemas may have elements in common (e.g. the shared movement of a limb) and similar

perceptual precipitants (e.g. an amber traffic light). Indeed, many schemas may be selected at once if they do not conflict.

Multiple schemas may be necessary for complex cooperative tasks (e.g. the complex set of actions following a green traffic light). To coordinate multiple schemas it is necessary to avoid simultaneous activation of schemas of opposite effect; to minimise co-activation of schemas that draw upon common structures of operations; and to ensure the sequence of activation of schemas results in the intended overall action. This process of coordination has been termed contention scheduling. Contention scheduling was proposed to be stabilised by lateral inhibition between schemas. Lateral inhibition between effector representations or between percept representations has been a recurrent theme in subsequent models of cortical function (Desimone and Duncan, 1995; Miller and Cohen, 2001).

The automatic execution of appropriate actions is not always possible (e.g. in novel situations). Even in familiar situations, automatic execution may be ill advised, (e.g. if the consequences of error are extremely serious) or we may voluntarily attend to or control our actions with a sense of 'will'. Actions under these three very different circumstances have in common the deliberate attentional control of our responses.

Norman and Shallice (1980) proposed that a **'supervisory attentional system'** biases the activation of schemas. The result of this bias may be selection (therefore execution) or inhibition of a schema. The modulatory influence of the supervisory attentional system may critically affect the final actions carried out, but it does not

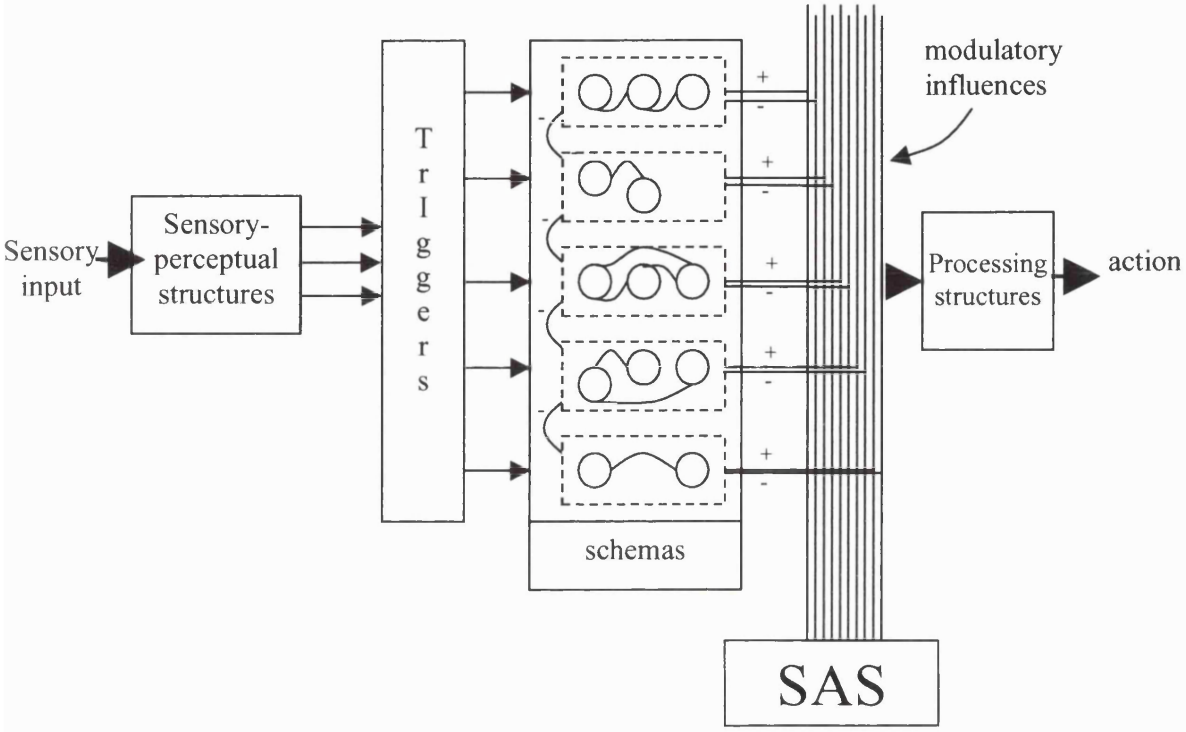


Figure 1.6. The supervisory attentional system (SAS) redrawn from Norman and Shallice (1980). Perceptual inputs may trigger activation of schemas: if the activation exceeds a threshold, the action represented by the selected schema is executed. Multiple schemas are mutually inhibitory. The activation of schemas may be enhanced or diminished by the modulatory influence of the supervisory attentional system.

represent an on or off switch for schemas. Activation bias has also been a recurrent theme in models of cortical function (Desimone and Duncan, 1995; Miller, 1999; Miller and Cohen, 2001), for representations of actions, percepts or memory.

If several schemas are activated, because several actions are possible in a situation for instance, then the supervisory attentional system will select among multiple schemas such that only one schema action is executed. The supervisory attentional system will have exerted a differential effect between schemas. In the presence of lateral inhibition between schemas, there may be no net increase in activation in the pool of schemas. If a situation has one prepotent response, then effect of the supervisory attentional system will be to increase overall activation in the schema pool.

Anatomical substrate of the supervisory attentional system

There is convergence between the properties of supervisory attentional system and the properties of the frontal lobes, including PFd, PFv and the cingulate cortex (Posner and DiGirolamo, 1998; Shallice, 1989). Baddeley (1986) introduced the term 'dysexecutive' syndrome to describe a combination of impaired responses to novelty, distractibility, poor planning, and the breakdown of control of appropriate behaviour.

The dysexecutive syndrome was neither homogenous, nor explicitly linked to the prefrontal cortex. However, such a syndrome would be expected from the dysfunction of the supervisory attention system, evident in situations when contention scheduling is not able to sculpt an appropriate complex action.

Contention scheduling will be inadequate in novel situations, when distractors are irrelevant to a task, or when a habitual response ceases to be correct. This will include the Stroop test, mis-cued conditional response tasks and the Wisconsin Card

Sort Test. In the previous sections, it is clear that PFd, and cingulate cortex, play a critical role in these tasks, They are activated during performance in normal subjects, and lesions impair patient performance.

Contention scheduling can also only apply to formed schemas, for learned actions. It will therefore not be sufficient for planning or problem solving in novel situations. As described in the previous sections, planning is consistently associated with activation of the PFd in normal subjects, and impaired following lesions in patients.

Even when contention scheduling is adequate, motivational or other factors may support activation of the supervisory attentional system, for wilful attention to action (Norman and Shallice, 1980). Willed action, or the free selection of motor and verbal responses, is again associated with activation of the PFd and PFv in healthy subjects.

Summary

The functional analysis of voluntary action suggests a supervisory attentional system for the control of action when 'contention scheduling' of responses was not adequate or appropriate. The properties of the supervisory attentional system are similar to those of the proposed central executive of working memory. Both the supervisory attentional system and the central executive appear to be dependent on the integrity of frontal regions, although neither should be regarded simply as the function of a single brain region.

Contextual coding

The central executive and the supervisory attentional system are taxed when the subject is presented with novel situations. An appropriate response cannot be selected on the basis of a fixed stimulus response association. General rules, based on the context, must be implemented to respond to the novel stimulus. Is there evidence that cells in the prefrontal cortex can modify responses or encode the general rules? In the next two sections, I will return to focus on the properties of neurons in PFd, and show how these have given rise to a new systems level understanding of the frontal lobes.

A previous section reviewed the fact that cells in the prefrontal cortex are in receipt of multiple sensory afferents. It was suggested that they are selective for specific stimuli, or stimuli defined by their sensory modality. Recall that PFd is closely interconnected with sensory association cortex in parietal, occipital and temporal cortex (Barbas, 1988; Barbas and Pandya, 1989; Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1988; Seltzer and Pandya, 1989). PFv and PFo are also closely interconnected with non-frontal association cortex, particularly in the temporal lobe, and the amygdala. (Barbas, 1988; Barbas and Blatt, 1995; Barbas and De Olmos, 1990; Barbas *et al.*, 1991; Seltzer and Pandya, 1989; Watanabe *et al.*, 1991). Stimulus selectivity during delayed response tasks was demonstrated early in prefrontal cortical research (Funahashi *et al.*, 1989; Funahashi *et al.*, 1993; Kojima and Goldman-Rakic, 1982; Niki, 1974; Niki and Watanabe, 1976; Quintana *et al.*, 1988).

However, the stimulus selectivity is not inherent but is learned through experience. Activity in stimulus responsive cells develops gradually, and is modulated

by the expected reward. For example, Watanabe (1990, 1992) trained monkeys to discriminate between auditory and visual cues that were followed by a juice reward on some but not all trials. Cells in caudal PFd were responsive to specific cues, but only when these were expected to be followed by reward. Further back in area 8, cells that were not initially responsive to specific objects developed stimulus specific activity as the animal learned to make eye movements conditional on the specific stimuli (Bichot *et al.*, 1996).

The selectivity profile of cells in the sulcus principalis also evolves over time. For example, the location specificity of the stimulus related cells can increase over time (Sawaguchi and Yamane, 1999a). Moreover, while some cells maintain a stimulus representation throughout the delay, others change during the delay and become selective for the impending response (Constantinidis *et al.*, 2001).

Stimulus specificity is not restricted to simple features within a single sensory domain. Neurons in PFd and PFv may become selective for specific conjunctions of features. It is particularly interesting that object identity and location may be conjointly coded by a single cell. These two domains are often considered to be processed separately along dorsal and ventral 'streams' from the visual cortex (Ungerleider and Mishkin, 1982).

Rao et al (1997) demonstrated integration of 'what' and 'where' information in PFd. They trained monkeys to remember first an object and then its location in two steps. Monkeys were first presented with an object, then after a delay, with two objects. One of the later objects matched the original stimulus, but in a new location. The monkey was required to remember the location of the match, and saccade to this location to receive reward. About half of the stimulus responsive cells in PFd were

responsive to the conjunction of an object and its location. The location memory fields (analogous to visual fields, but for remembered locations) were approximately 9^{o} in radial diameter, and distributed across central and peripheral locations (Rainer *et al.*, 1998). The 'what and where' conjoint selectivity may be further dependant on the temporal order in a sequence of stimuli (Funahashi *et al.*, 1997).

Some cells in PFd show greater activity when the object and/or location predicts reward, but at the time of response rather than during a delay period. Cells in PFd have been identified that are active in association with a specific stimulus, at the time when a response is made to that stimulus, in conditions that predict that reaching to that stimulus will lead to a reward (Hoshi *et al.*, 1998). Other cells in this region are sensitive to the nature of the expected reward (Hikosaka and Watanabe, 2000).

Stimuli may be presented in different contexts. The context may be present throughout a trial as part of a compound stimulus. Alternatively, the context may be indicated by an initial 'instruction' cue. The context governed by the instruction cue must itself be remembered throughout the trial. Under context C1, stimulus S1 indicates that response R1 will be rewarded, whereas under context C2, the same stimulus S1 indicates response R2 will be rewarded.

The context is therefore defined by a rule that determines conditional stimulus response associations. Cellular activity in PFd may reflect this context. Asaad et al (2000) trained monkeys to perform delayed matching to sample, spatial delayed response, and a conditional visuomotor response (associative) task. The activity of half of the cells adjacent to the sulcus principalis was rule dependent. That is, the same cell may be spatially tuned in the spatial delayed response task and tuned to

object features in the delayed matching to sample task. White and Wise (1999) have shown similar rule-dependent behaviour in cells of PFd (White and Wise, 1999).

If cells show differential stimulus sensitivity according to context or rules, they might be able to encode the rule itself without reference to particular stimuli. Activity specific to the abstracted rule has only recently been demonstrated (Wallis *et al.*, 2001). Wallis et al (2001) trained monkeys to compare two successive visual stimuli, and respond if they were matched according to an arbitrary rule. The rule for a current trial was visually cued. Neuronal activity was recorded when the monkeys performed the rule based comparison using novel stimuli. Neuronal activity could be defined as sensitive to the stimuli, the response or the rule, or some combination of these factors. The commonest type of cell in area 46 was responsive to the rule applicable to the current trial, and not to a stimulus or response per se.

Summary

Cells in PFd and PFv can encode different specific stimuli and the conjunction of stimulus attributes. They may modulate this stimulus related activity according to the context or rule that determined whether the stimulus is predictive of reward. They may even encode the abstracted rule itself, independent of any particular stimulus. Models of prefrontal cortical function have even equated this region with contextual representation (Cohen *et al.*, 2000; Cohen *et al.*, 1996; Cohen and Servan-Schreiber, 1992), as illustrated in figure 1.7.

These cells are potentially able to control voluntary action to obtain reward. However, it remains to be shown how such voluntary action can be controlled, or how the best response is selected. An account of the role of the prefrontal cortex in

response selection must also consider the 'effector' mechanisms by which the specific response is selected. This is considered in the next section.

Attentional selection

Attentional selection

The neural substrate of cognitive control has been better characterised within the visual system than the motor system, but the role of the prefrontal cortex may be common to both domains. An analogy will be drawn between a stimulus that is perceived or attended to out of a complex visual scene; a single item that is chosen out of several that are remembered; and one action that is made out of several possible actions. Each stimulus, memory or action will be associated with a particular set of neuronal activations, distributed spatially over a neuronal population and over time. This distributed neuronal activation will be called the neuronal representation of the stimulus, memory or action.

When we look at a crowded visual scene, there will be many such neuronal representations. With limited resources, not all stimuli can be analysed, or be used to determine behaviour. The corresponding representations must compete for analysis. Those representations that are preferentially analysed are said to be 'attended to'.

If one object in the crowd is brighter, louder or more mobile, it will 'stand out' or 'command attention'. The control of our attention in this case by the intrinsic properties of the object is called 'bottom-up' control. Alternatively, we may attend to one object voluntarily, perhaps because our goal is to notice a change in the object. Such voluntary or goal-oriented control of attention to is termed 'top-down'. Real world situations involve a combination of these processes. For example, when

crossing the road, we attend to a car moving towards us rather than away from us both because it is more salient and because we voluntarily lookout for such a potential hazard.

In the inferotemporal and prestriate cortex, neurons can be identified for which the activity represents a particular stimulus, or location of the stimulus in the visual field (Ungerleider and Mishkin, 1982). These neurons are part of the distributed neuronal representation of those stimuli or locations. These representations are competitive, suppressing alternative representations (Chelazzi *et al.*, 1998; Chelazzi *et al.*, 1993; Desimone, 1998; Reynolds *et al.*, 1999).

In monkeys, a stimulus or location will be preferentially attended to if it is associated with reward, or indicates a response that is expected to be rewarded. Attention to a stimulus has been proposed to 'bias' the activity of these competing representations (Desimone and Duncan, 1995).

Attentional bias may be seen as a lateral shift in a stimulus-response curve. For example, cells in prestriate regions V4 were identified that responded to single stimuli across a range of luminance contrasts (Reynolds *et al.*, 2000). The firing rate changed with luminance, giving a non-linear luminance-response curve. The same stimuli were next presented together with a distractor and the monkey was required to choose between them. When the same stimulus was predictive of reward, its luminance response curve changed, increasing responsiveness at low luminance by over 50%, but less so at high luminance. A second type of bias changes the gain or slope in dose-response curves (Desimone, 1998; Desimone and Duncan, 1995) and a third type of bias is a shift in the baseline activity of cells. A shift in baseline activity

of stimulus specific neurones in inferotemporal cortex is revealed when its associated stimulus is absent but expected (Chelazzi *et al.*, 1993; Kastner *et al.*, 1999).

These forms of bias may occur together to produce 'top-down' control of early visual processing. The effects of bias will be enhanced if the stimulus representations exhibit mutual inhibition (Chelazzi *et al.*, 1998). The result is that the relevant representation is selected above alternative representations, enabling further processing and responses to the task relevant stimulus.

The term '**attentional selection**' summarises the mechanism and consequence of this top-down modulation of representations (Miller, 2000; Miller, 1999). The biased competition model put forward by Desimone and Duncan (1995) was not explicit about the anatomical origin of the bias. However, the bias must come from areas that are able to integrate the stimuli present and the behavioural relevance of those stimuli in the current experimental context, and be interconnected with the visual cortex. The prefrontal cortex meets these requirements.

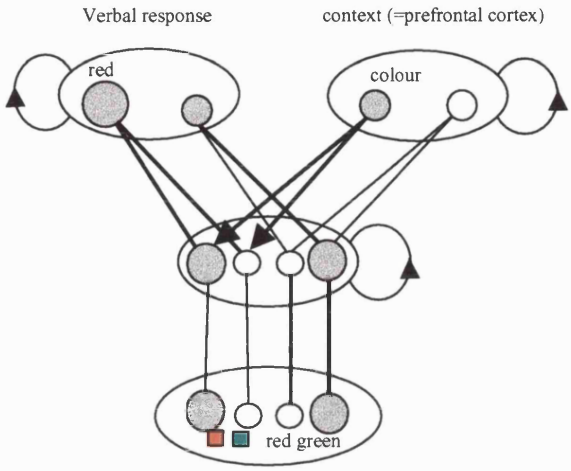
However, the mechanism of attentional selection of neuronal representations may be a general phenomenon applicable to sensory stimuli, thoughts, memories or actions (Miller, 2000). Functional imaging of humans has demonstrated attentional modulation of posterior cortical function in the visual system (Brefczynski and DeYoe, 1999; Hopfinger *et al.*, 2000; Kastner *et al.*, 1999; Rees *et al.*, 1997) and auditory system (Alho *et al.*, 1999). However, there is indirect evidence for a generalisation of attentional selection beyond the sensory domain to motor and cognitive function

In parallel with the development of biased competition models, Cohen et al (1992, 1996, 2000) have been developing computational models of cognitive control.

Two of these are illustrated in figure 1.7. In the Stroop test (Stroop, 1935), and the mis-cued stimulus-response task used by Gehring and Knight (2000), stimuli are associated with particular responses. However, a given stimulus indicates a different response in different contexts. One response may be prepotent across many contexts. The prefrontal cortex is proposed to represent the context, and exert a modulatory influence on the stimulus-response mappings. The prefrontal cortex does not act like a switch, turning a response on or off, but rather it biases the stimulus response associations to guide the selection of one response rather than another. The mechanism has been termed 'guided activation' (Miller and Cohen, 2001). The imposition of bias is more important when responses conflict. The anterior cingulate has been proposed to mediate the detection of conflict (Cohen *et al.*, 2000) and increase the bias exerted by the prefrontal cortex.

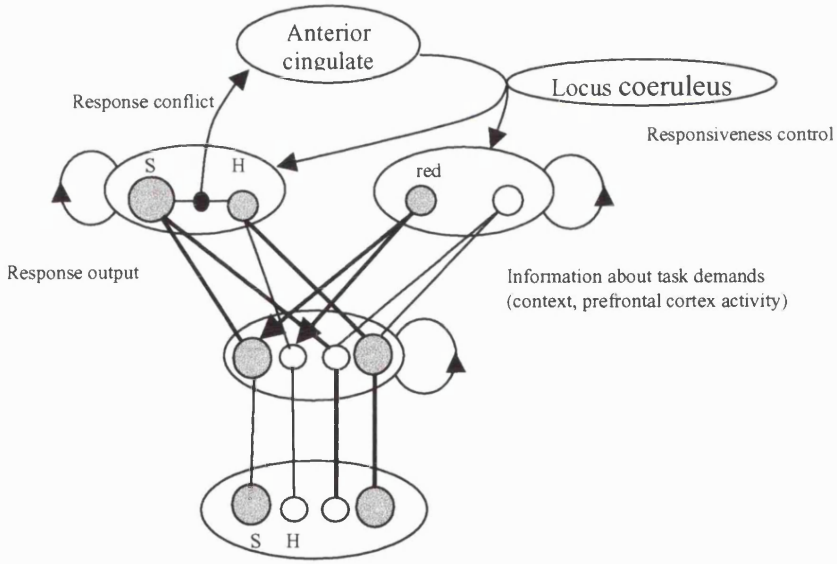
These models have been used effectively to simulate the stimulus response behaviours in the Stroop task, a monitoring task, and stimulus-delay-response activity in working memory paradigms (Cohen *et al.*, 1996; Cohen *et al.*, 1990; Cohen and Servan-Schreiber, 1992). With additional assumptions about the regulatory or gating role of monoamines, the authors have also simulated the effects of schizophrenia on task performance (Braver *et al.*, 1999; Cohen and Servan-Schreiber, 1993). The introduction of gating mechanisms between stimulus, response and context modules in a 'noisy' neuronal system may allow for the system to learn and control behaviours without invoking a higher system (or homunculus) to 'control the controller' (Miller and Cohen, 2001; Monsell and Driver, 2000).

A



Stimulus: 'green'

B



Stimulus: S/H

Figure 1.7. Models of the prefrontal cortex, and its relationship to the sensory inputs, effector mechanisms and cingulate cortex, as used to describe cognitive control in conditional response tasks like (a) the Stroop task and CPT task (Cohen and Servan-Schreiber 1992, Cohen, Braver, O'Reilly 1996) and (b) the mis-cued S-R task (Gehring and Knight 2000; Cohen, Botvinick, Carter 2000).

This suggests that a bias function leading to selection of a response is neurobiologically plausible. The prefrontal cortex would be expected to be active when the subject selects between competing responses to a stimulus; when distractor stimuli must be prevented from eliciting responses; or when the goals of a task are such that a non-automatic or non-prepotent response is required. Although the biased competition model (Desimone and Duncan, 1995) arose from studies of visual attention, and the guided activation model (Miller and Cohen, 2001) arose from studies of motor response selection, the mechanism and functional role of the prefrontal cortex is strikingly similar. What remains to be shown is evidence of bias effects of prefrontal cortical activity on remote visual, motor or mnemonic areas.

Remote effects of the prefrontal cortex

I have presented evidence for attentional bias of visual cortical areas, and circumstantial evidence for a role of the prefrontal cortex in this bias. However, there is direct evidence of modulatory fronto-temporal and fronto-occipital connections, at least in the visual sensory and mnemonic domains.

Fuster et al (1985) trained monkeys to perform a delayed response type task. Cooling of the lateral prefrontal cortex temporarily and reversibly disrupts its function. Fuster et al (1985) recorded from microelectrodes in infero-temporal cortex, and identified many cells for which the delay related activity was colour specific. Simultaneous cooling around the sulcus principalis lead to a reduction in delay related activity and colour specificity in many of these cells. Behavioural changes during task performance also suggested that prefrontal to inferotemporal modulatory influence was functionally important (Fuster *et al.*, 1985).

Chafee and Goldman-Rakic (2000) cooled the lateral prefrontal cortex and recorded from parietal neurons during an oculomotor delayed response task. Three quarters of neurons changes their activity during cue- delay- and response- periods of the task. However, both increase and diminished activity was seen, consistent with a reduction in bias to a system of mutually inhibitory neurons.(Chafee and Goldman-Rakic, 2000).

Modulatory influences from the prefrontal cortex to the temporal cortex have been demonstrated directly in the recall of visual images (Tomita *et al.*, 1999). Tomita et al (1999) identified visual-object sensitive neurons in the inferotemporal cortex of monkeys. Object specificity was preserved even after interhemispheric disconnection, even for objects placed in the ipselateral hemifield. The information must have reached the inferotemporal cortex by an indirect route, with sufficient strength to produce object sensitive neuronal activity. Secondary surgery to disconnect the prefrontal cortex showed that the indirect route had been via the prefrontal cortex. The ipselateral prefrontal cortex had been able to bias activity in inferotemporal neurons, sufficient to recreate the response of that neuron to a (absent) visual stimulus.

There is also direct evidence from human studies. Barcelo and Knight (2000) studied patients with unilateral prefrontal lesions, measuring event-related cortical potentials during a visual discrimination task. Stimuli were presented in either hemifield. Prefrontal damage reduced the ERP response to targets in the visual cortex, but only when they were presented in the contralateral hemifield. These electrophysiological abnormalities were matched by impaired visual discrimination, reinforcing the functional significance of modulatory inputs from prefrontal cortex.

Summary

With interconnections between PFd, PFv and PFo, neurons in the prefrontal cortex are able to integrate sensory information about oneself and the external world, learned association between events, and 'internal' goals in order to direct ones actions appropriately. The integration of this information allows the selection of contextually appropriate responses. The response is likely to be selected by 'attentional selection', the top-down bias of the activity of non-prefrontal neurons that represents an action. Attentional selection has been clearly demonstrated in the sensory domain, but computational models and functional imaging data suggest that a similar mechanism mediates response selection.

Experiments in this thesis

The electrophysiological, lesion and functional imaging data indicate that prefrontal cortex clearly plays an important role in working memory, even simple delayed response type tasks. However, this region is activated in many non-memory tasks, particularly the selection of responses. How can the response selection hypothesis be reconciled with the extensive working memory literature? It is possible that it is the response selection inherent in working memory paradigms that underlies the prefrontal cortical activation. This possibility is tested using fMRI, described in chapters 4 and 5.

Attentional selection has been proposed as a generic mechanism of prefrontal function. Although based largely on evidence from studies of visual attention, the same mechanisms are proposed to apply to motor representations. The generalisation of prefrontal selection to motor and sensory modalities is discussed and tested using fMRI in chapter 6.

Activity related to attentional selection would be expected in both the prefrontal cortex (the source of top-down modulatory influences) and the sensory or motor regions (the target). Coincident activity due to top-down influences may be measured using fMRI as 'effective connectivity' between regions. Chapters 7 and 8 assess this connectivity in normal subjects, and ask whether motor abnormalities in Parkinson's disease may be attributable to abnormal prefrontal interactions with the motor system.

The evolution of our understanding of the prefrontal cortex has other clinical implications. It may change our interpretation of patient deficits, and their problems with clinical tests of 'frontal lobe function'. On such test, the Tower of London Task, is assessed in chapter 9, in normal subjects.

Chapter 2

Methods: functional imaging and Statistical Parametric Mapping

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Introduction

The experiments reported in this thesis are based on two neuroimaging techniques: magnetic resonance imaging (MRI) and positron emission tomography (PET). Both of these techniques exploit the relationship between neuronal activity and regional blood flow. This chapter will describe this neurovascular coupling, the principles of PET and MRI data acquisition, and the processing of data prior to analysis. These two techniques are part of a larger family now used to characterise brain structure and activity (Orrison *et al.*, 1995; Toga and Mazziotta, 1995), that also includes event-related electrophysiological potentials (ERP); magnetoencephalography (MEG); magnetic resonance spectroscopy (MRS); and single photon emission computed tomography (SPECT).

Neuronal activity, aerobic metabolism and regional cerebral blood flow

Neuronal activity and glucose metabolism

Figure 2.1 summarises a chain of events from neuronal activity through increased metabolic demands to increased regional blood flow and PET or fMRI measures. There remain controversies at each link of this chain, although a near-linear

monotonic relationship exists between the initial events and outcome measures under physiological conditions (Logothetis *et al.*, 2001).

Under physiological conditions, the brain is wholly dependent on glucose metabolism for energy. At rest, approximately 90% of cerebral glucose metabolism is used for oxidative metabolism, via synthesis of adenosine triphosphate during glycolysis. Direct stimulation of neuronal activity is associated with a linear increase in glucose metabolism (Kennedy *et al.*, 1975; Yarowsky *et al.*, 1983). Neuronal activity includes events at the synapses, axon and soma. In specialised regions of the nervous system where soma and axon terminals are clearly separable, glucose metabolism is associated with activity in axon terminals, not the soma (Kadekaro *et al.*, 1985; Schwartz *et al.*, 1979).

If axon terminals exert the dominant metabolic demands, one can ask whether the pre- and post- synaptic events are equally important, and whether excitatory or inhibitory synapses are equally contributory to metabolic demand? In the brainstem and spinal cord, comparisons of antidromic and orthodromic stimulation (Kadekaro *et al.*, 1985; Kadekaro *et al.*, 1987; Nudo and Masterton, 1986) clearly suggest that the increase in glucose metabolism (measured by 2-deoxy-glucose labelling techniques) is more associated with presynaptic activity than post synaptic activity.

Neurovascular coupling

In animal models, glucose metabolism and blood flow may also be measured simultaneously by double-label autoradiography. Blood flow and glucose metabolism are tightly coupled at rest (Baron *et al.*, 1982; Lear *et al.*, 1981) and after reduction of metabolic activity following muscimol injection (Kelly and McCulloch, 1983).

Positron emission tomography in humans using multiple isotopes has confirmed that local cerebral glucose metabolism, oxygen extraction and local blood flow are again tightly coupled at rest (Fox *et al.*, 1988; Frackowiak *et al.*, 1980a; Frackowiak *et al.*, 1980b; Lebrun-Grandie *et al.*, 1983). Under physiological stimulation, the increase in glucose metabolism remains coupled with regional blood flow, although both are increased by more than the increase in oxygen metabolism (Fox *et al.*, 1988). It has therefore been suggested that physiological activation of neurons is more dependent on glucose metabolism to pyruvate and then to lactate (Fox *et al.*, 1988; Magistretti and Pellerin, 1999).

Direct measurement of blood flow by Doppler flowmetry with simultaneous recording of extracellular field potentials suggests that presynaptic neuronal activity is the dominant cause of increased blood flow (Akgoren *et al.*, 1996; Mathiesen *et al.*, 1998). Moreover, it is the excitatory glutamatergic synapses, rather than inhibitory GABAergic synapses, which are most influential on the blood flow. However, the glutamatergic excitation may be to inhibitory interneurons, rather than principal cells such as Purkinje cells in the cerebellum. Magnetic resonance spectroscopic recording in animals and humans also suggests that glutamate neurotransmission in cortical synapses is linearly associated with glucose oxidative metabolism (Sibson *et al.*, 1997; Sibson *et al.*, 1998).

The mediators of this neurovascular coupling are poorly understood. The local synthesis and diffusion of vasoactive substances such as nitric oxide is certainly a contributory mechanism (Akgoren *et al.*, 1996; Mathiesen *et al.*, 1998). However, direct cellular coupling between the neuropil and capillary bed by astrocytes has also been suggested (Magistretti and Pellerin, 1999).

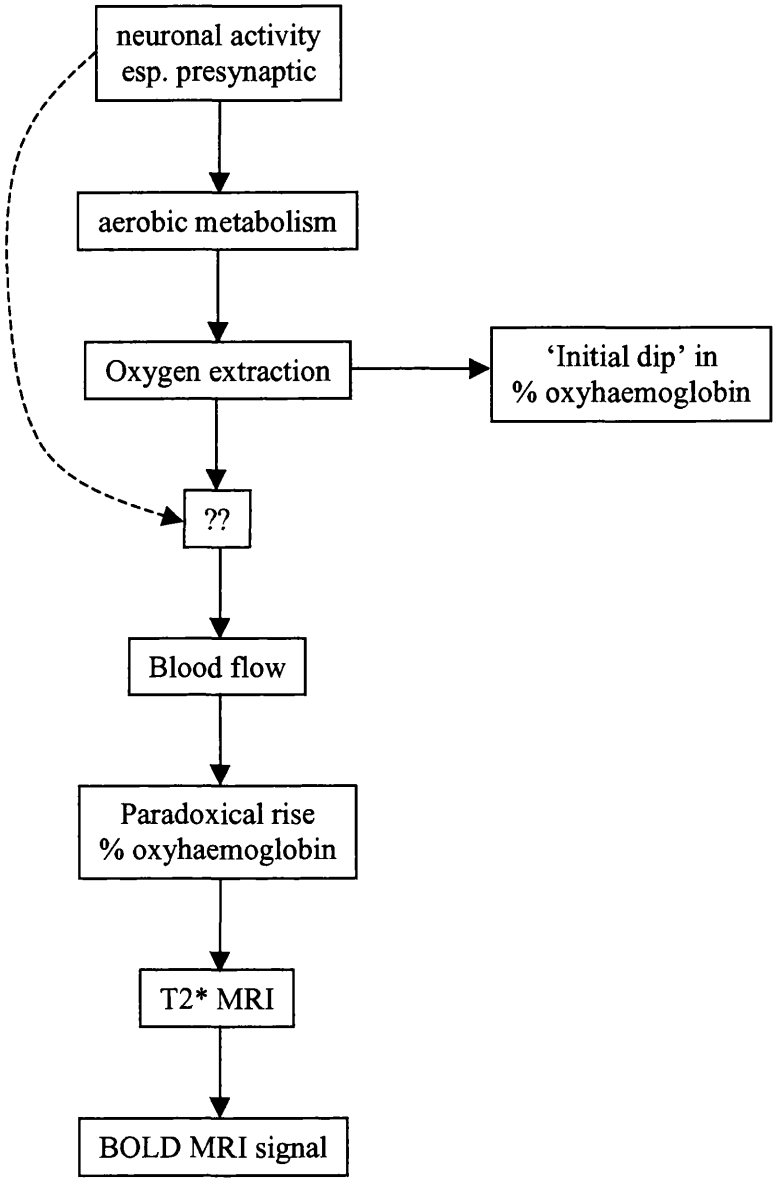


Figure 2.1. A schematic representation of the chain of events from neuronal activation through to the physiological measures used for functional neuroimaging.

PET imaging

Water diffuses readily across the blood brain barrier and cerebral cellular barriers. Following an injection of radio-labelled $H_2{}^{15}O$, the distribution of radioactivity will therefore be governed by the delivery to local tissues by blood flow (regional perfusion). The ^{15}O disintegrates with a half-life of approximately two minutes, to produce a pair of 511 keV annihilation photons. The paired photons can be detected as simultaneous counts on paired photomultipliers.

Many photomultipliers are arranged around the subject's head, to detect paired photons emitted in any direction. If just one of an opposing pair of photomultipliers is activated, then it is unlikely to be due to a photon produced by positron annihilation. In addition, electronic collimation is used to determine whether coincident counts are likely to have come from the same initial positron annihilation in the subject's head.

The subject's head and head restraints will attenuate the emitted photons. An estimation of attenuation is made from a transmission scan. The transmission scan uses an external gallium-germanium source of positrons, which rotates around the subject's head. In the absence of attenuation, the photomultipliers opposite the source would detect the same number of counts each. Computed tomography can estimate the attenuation likely to reduce the signal from any point of emission in the head (Orrison *et al.*, 1995). The intensity of emission from any position in the head, indicating the focal concentration of isotope proportionate to blood flow, can be reconstructed by computed tomography.

At the functional imaging laboratory of the Wellcome Department of Cognitive Neurology, UCL, ^{15}O was generated by a cyclotron next to the imaging suite. A water generator was used to produce $H_2{}^{15}O$, which was injected intravenously

as a bolus suspended in normal saline. The circulation of blood resulted in a delay of 30-60 seconds before a sharp rise in synchronous photomultiplier counts was detected. Cumulative data were acquired for the next 90 seconds.

The cumulative signal from each brain region (voxel) is proportional to the weighted mean blood flow during the scanning period. It is a weighted mean, biased towards the first half of the scanning window, because of the rapid decay of $H_2{}^{15}O$, and distribution throughout body tissues. The absolute number of counts may vary from subject to subject, and from scan to scan. Subject-specific ANCOVA was used with these counts in order to detect condition specific differences in regional cerebral blood flow independent of global flow (Friston *et al.*, 1990b)

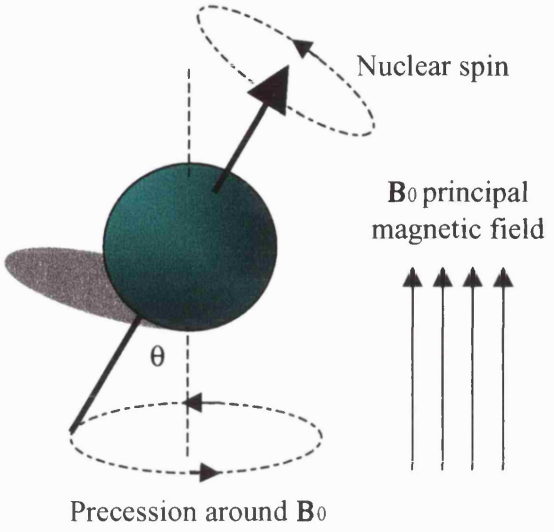
The subjects rested in the scanner for eight minutes between the scanning windows, to permit the radiation to return to baseline. With twelve scans acquired, a total dose less than 5 mSv per subject was given, in accordance with the licence granted by Administration of Radioactive Substances Advisory Committee (ARSAC, UK).

BOLD fMRI imaging

Origin of MRI signal

It has taken over fifty years for functional magnetic resonance imaging (fMRI) evolve from basic principles of nuclear magnetic resonance (NMR)(Bloch *et al.*, 1946; Purcell *et al.*, 1945) to a standard non-invasive neuroimaging tool. Landmark events during this evolution include the topographic imaging of the human body in 1973 (Lauterbur, 1973), the first NMR images of the structure of the human brain (Holland *et al.*, 1980), and demonstration of the use of NMR to measure regional

A



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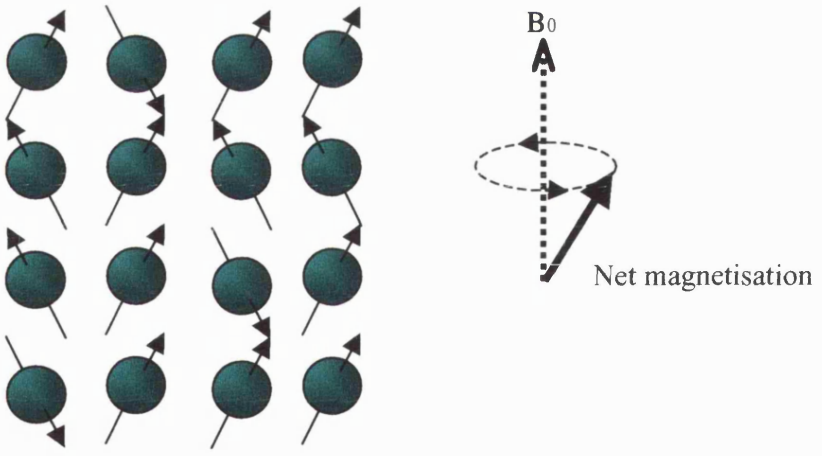


Figure 2.2. (a) Nuclear spin causes the nuclei to align themselves to a magnetic field $\mathbf{B}_0$, The axis of spin is not identical to $\mathbf{B}_0$, indicated by the angular deviation θ. The axis of spin will itself precess around $\mathbf{B}_0$, at the Larmor frequency. (b) For different protons, the spin may differ by phase, or by aligning parallel or anti-parallel to $\mathbf{B}_0$. The net magnetisation is the instantaneous sum of magnetisation of all the individual protons.

brain activity based on intrinsic contrast properties of blood (Kwong *et al.*, 1992; Ogawa *et al.*, 1990; Turner *et al.*, 1991).

Both structural and functional MRI depend on the property of certain nuclei called 'spin'. Nuclei with an odd number of protons and/or neutrons, including protons of hydrogen atoms in water, will have spin. The rotation of a positively charged nucleus induces a local magnetic field with North-South polarity along the 'spin axis', shown in figure 2.2a.

In the presence of an external magnetic field, the nuclei will align themselves to the magnetic field, like a compass needle to the earth's magnetic field. The alignment is not perfect, and the axis of spin will itself precess around the direction of the magnetic field, just as a spinning top precesses around the earth's gravitational field, illustrated in figure 2.2a. The precessional frequency, ω_0, is governed by the strength of the magnetic field, B_o, and a gyromagnetic constant for each type of nucleus, γ, where

$$\omega_0 = \gamma B_o$$

This frequency is also known as the Larmor frequency. For hydrogen in water molecules, $\gamma \sim 4000$ Hz/G, so that at 2- Tesla magnetic field strength $\omega_0 \sim 85$ MHz.

Net magnetisation

The spinning nucleus may be aligned parallel to the magnetic field (a low energy state) or antiparallel to it (a higher energy state). For individual nuclei, intermediate states are not possible. The quantum of energy required to change a proton from parallel to antiparallel (or released by the opposite conversion) depends on the field strength. The energy is small, even at 2-Tesla, and thermal energy at room

temperature is sufficient to move protons from the parallel to antiparallel state. The proportion in each state is given by the Boltzmann relation,

Parallel/antiparallel = $\exp(\gamma hB_o/KT)$

Where h is Planck's constant, K is Boltzmann's constant and T the absolute temperature. The sum of all spins will give a net magnetisation for a group of protons. The net magnetisation will include a component along the applied magnetic field (longitudinal magnetisation) and a component transverse to the applied field (transverse magnetisation). This is illustrated in figure 2.2b.

The net magnetisation may be changed by transferring energy to the protons, by an applied radio-frequency pulse. This is called excitation. Efficient transfer will occur when the applied frequency matches the Larmor frequency, ω_0. The applied radiofrequency pulse generates its own weak magnetic field B1, usually perpendicular to the Bo. The net magnetisation will precess around this weak field (with different Larmor frequency, $\omega_1 = \gamma B_1$). By careful control of the strength and duration of the radiofrequency pulse, the angular deviation of the net magnetisation may be controlled. For example, with enough energy, the net magnetisation of a group of protons may be inverted, to an angular deviation of 180°.

T1 and T2 relaxation

After excitation, the net magnetisation gradually returns to precession around the original magnetic field, B_o. As they return to equilibrium, with a greater proportion of protons in the lower energy state, energy is given off to neighbouring molecules (spin-lattice relaxation) or neighbouring spinning nuclei (spin-spin relaxation).

Spin–lattice relaxation is governed by the 'T1' time constant. The longitudinal magnetisation, M_L, recovers towards the equilibrium state, M_0, over time t, as:

$$\mathbf{M_L = M_0(1-e^{-[t/T1]})}$$

The T1 constant is determined by the ability to transfer energy to the surrounding molecules, and this depends on the nature of the tissue. Small molecules like free water move too rapidly for efficient energy transfer, and large molecules like protein move too slowly. Mid-sized fat molecules however move at frequencies close to the Larmor frequency of protons, and absorb the energy rapidly. If a series of radiofrequency pulses is applied after a short period of time, relaxation will be incomplete for protons in water, but nearer completion for protons in fatty tissue. By adjustment of the repetition time, TR, the differences in T1-sensitive relaxation can be emphasised.

The net magnetisation is inverted by a 180° radiofrequency pulse, then a second pulse given after a short delay (known as inversion time, TI). The TI will alter the effect of the TR in relaxation. The combination of TI and TR can be adjusted to maximise the sensitivity of proton T1 relaxation to the different molecular milieux of different brain tissues, such a s grey and white matter and cerebrospinal fluid.

The transfer of energy to neighbouring nuclei (spin-spin relaxation) results in an exponential decay of the transverse net magnetisation, M_T, determined by the T2 time constant, where:

$$\mathbf{M_T = M_0.e^{-[t/T2]}}$$

As energy is passed from one spin to another, the phase of precession of neighbouring nuclei become desynchronised. If the local magnetic field is not homogenous, then the Larmor frequencies of protons in a region will vary, and they

will lose coherence rapidly. This will necessarily reduce net transverse magnetisation, M_T. The effective T2 time constant, denoted T2*, is shorter than T2 proper for any given tissue type. The shortening of T2* is the basis of the functional magnetic resonance imaging, to be discussed in more detail in the next section.

Whole brain imaging

For structural and functional brain imaging, it is necessary to measure the changes in magnetisation relaxation from every part of the brain. This is achieved by three combined techniques.

Firstly, regions of the brain may be excited slice by slice. If a gradient is introduced along Bo, then each slice of the brain will have a distinct Larmor frequency. If the excitatory radiofrequency pulse has a narrow spectrum of frequencies, only a correspondingly narrow slice of brain will be excited. For the imaging studies here, excited slices were separated by 3mm. The excited region was 2mm thick, with a 1mm inter-slice gap. This gap allows for the fact that the profile of excitation is not perfectly rectangular.

Secondly, if a weak magnetic gradient B_1 is applied across the B_o, then either side of the brain will have a slight difference in Larmor frequency. The signal from across the brain will be contained in a narrow bandwidth ω_1 ($\omega_1=\gamma B_1$), around the 'carrier' frequency ω_0 ($\omega_1<<\omega_0$). By sampling the magnetic resonance signal at different frequencies within this bandwidth, the signal from different sides of the brain may be distinguished.

Thirdly, the signal contains phase information as well as frequency information. When the transverse gradient B_1 is applied, it may be varied in one

direction, and fixed in the other. A transient change in B_1 along one axis will introduce phase differences in the spin along that axis.

These three processes produce a rectangular grid of varying phase and frequency of radiofrequency signal following excitation. Fast Fourier Transform of this spectrum is used to reconstruct the signal for each part of the grid. A small volume of tissue with its unique phase and Larmor frequency after slice-specific excitation is known as a voxel. The signal intensity for all voxels is written in a standard radiographic format (ANALYZE) for subsequent viewing and analysis.

All fMRI studies reported in this thesis used 'trapezoidal' gradient echo imaging. After initial excitation, a series of echoes, each with different phase encoding, are repetitively refocused by alternating a transverse magnetic field gradient (Mansfield, 1977). The transverse gradient in one direction (B_1y) is varied in a trapezoidal form during the echo period, allowing multiple sampling at different parts of the frequency spectrum during the successive echoes.

The BOLD signal

MRI may be used to detect changes in local metabolic activity, by exploiting the intrinsic contrast effects of oxygenated blood flowing in a magnetic field (Ogawa *et al.*, 1990; Turner *et al.*, 1991). Following an increase in local aerobic metabolic activity there is increased blood flow to, and dilation of, local capillaries. This blood flow increase is greater than that required to supply the increase in oxygen consumption, by a factor of about two (Fox *et al.*, 1988). The result is a paradoxical fall in deoxyhaemoglobin concentration in the capillaries and draining venules near increased neuronal activity that lasts for several seconds. If enhanced neuronal activity continues, vascular and metabolic changes reach equilibrium in 1-3 minutes.

Unlike oxygenated haemoglobin, deoxyhaemoglobin is paramagnetic. The intra-erythrocyte concentration of such a paramagnetic compound causes local magnetic field inhomogeneity, and reduction of T2*-weighted MRI signal (Ogawa *et al.*, 1990). This is the basis of the blood oxygenation level dependent signal (BOLD) used for fMRI. It increases quadratically with field strength (Turner *et al.*, 1993).

The BOLD response to a transient change in metabolic activity typically takes 1-2 seconds to begin, reaches a peak at 5-6 seconds, and returns to baseline by 12-15 seconds with a small undershoot that may last up to 30 seconds (Blamire *et al.*, 1992; Kwong *et al.*, 1992; Menon *et al.*, 1992). However, This may vary slightly from person to person, and from one brain region to another. Nevertheless, a canonical haemodynamic response functions, defined by the combination of gamma functions, provides an good model for the BOLD response in healthy brain tissues (Frackowiak *et al.*, 1997). This canonical response was used to model the BOLD responses in each of the fMRI studies here.

After increased metabolic activity, the increased oxygen uptake may precede the increase in blood flow, resulting in a transient fall in local haemoglobin oxygenation. This is too small and brief (~100 ms) to be reliably measured by fMRI at 2-Tesla (Menon *et al.*, 1995).

Contributors to BOLD

At a synaptic level, both excitation and inhibition are associated with increased metabolic demands (Kadekaro *et al.*, 1985; Kadekaro *et al.*, 1987; Nudo and Masterton, 1986). However, it is necessary to distinguish the demands of a *single* synapse from the metabolic activity of a large *population* of neurons in a voxel. The BOLD response in a voxel will be based on the metabolic demands of the population

of many millions of neurons. Therefore, the regional BOLD fMRI signal will reflect excitation or inhibition of a large neuronal population: excitation or inhibition refers to this population (a systems level of brain function) rather than the synapses (a synaptic level of brain function). The activity of inhibitory interneurons will have its own positive metabolic demands, but they will have inhibited target neuron activity, possibly reducing the subsequent synaptic activity within the population. The result is a reduction in metabolic demands of the local neuronal population.

Since the early demonstrations of BOLD fMRI, the association between neuronal activity and BOLD response has been poorly understood, despite its importance. Recently, it has been shown that in visual cortex at least there is a good correlation between single cell spiking activity and BOLD contrast (Heeger *et al.*, 2000; Rees *et al.*, 2000), although the details of the link remain uncertain. Combined BOLD fMRI and cortical electrode recording is now possible. It has confirmed that local field potentials correlate highly with BOLD activity, more than multi-unit spike rates (Logothetis *et al.*, 2001). This suggests that the BOLD response reflects the cortical afferents and signalling within a local neuronal population.

Neuronal encoding of information is not confined to firing rate. Synchronisation among neurons may play an important role in perceptual or motor related neuronal activity. Although the independent effect of synchronisation on the BOLD response is not clear, synchronisation and mean firing rate are linked within neuronal populations (Chawla *et al.*, 1999).

Stability of BOLD

The BOLD signal may be affected by many physical and physiological parameters. Although changes in BOLD signal are correlated with neuronal activity in

an individual over a short period of time, the actual baseline and gain in signal strength may vary over time. Physical factors in this variation include subject and scanner temperature, and magnetic field homogeneity. Physiological factors include carbon dioxide and oxygen concentrations, and the neuromodulatory environment determined in part by arousal, stress or drugs including nicotine and caffeine. Fortunately, the drift in the BOLD signal and sensitivity is gradual, and the possible artefactual changes may be distinguished from experimental effects by careful experimental design and analysis.

Echo planar fMRI samples multiple echoes during the relaxation after a single excitation pulse. However, for tissues with a short T2*, later echoes will be extremely weak. The sampling of echoes requires extreme homogeneity and stability of the Bo magnetic field, in the presence of rapidly changing transverse gradients. Differences between actual and expected field strengths and direction will result in variation in the local Larmor frequency, and therefore error in the attribution of signal to a given coordinate. This may result in **'distortion'** of the reconstructed brain image. Steep local gradients will also stop there being a single Larmor frequency for a voxel, and therefore the signal is lost rapidly, before or during acquisition. This may result in **'dropout'** of signal from certain brain regions. Homogeneity is especially difficult to maintain near the frontal sinuses or petrous temporal bones in humans. The inferior temporal lobe and anterior orbito-frontal cortex are most susceptible to the artefacts of distortion and dropout.

Head motion remains a significant problem for fMRI. The most obvious problem is the change in voxel coordinates of any given brain region. However, more serious problems also exist. For example, during slice by slice excitation of the brain,

movement across slices may result in double excitation of a brain slice. Movement in the other direction may mean that a brain slice is bypassed by its intended excitation pulse. Movement within a slice may cause accumulation in the phase shift, and therefore the reconstruction of that slice will be inaccurate. Movement will also interact with the mechanism of distortion and dropout above.

Some movement cannot be avoided during scanning, such as the pulsatility of major vessels, or whole head movement when subjects swallow or breathe. However, additional movements can be minimised. Before scanning, subjects were briefed about the importance of head fixation, and time was taken to ensure that the subjects were comfortable, including their direction of gaze to stimuli. In addition, the head was held by firm foam pads.

Special care was taken with the patients with Parkinson's disease. Patients were not recruited if their symptoms were dominated by tremor, prominent dyskinesia, or had experienced difficulty with their previous clinical MRI examination. Anxiety is a common symptom of Parkinson's disease, especially in the 'off' state, and this may be exacerbated in the claustrophobic MRI environment. In addition to the patients described in chapter 8, scanning was attempted in four patients who were unable to tolerate the protocol, due to a combination of anxiety, leg cramps and dyskinesia. They were excluded from the study before further analysis.

Data pre-processing

The fMRI images are pre-processed before analysis to allow fair comparison of images, with optimal signal to noise ratio. The details of pre-processing differs slightly between experiments, but the following general scheme was implemented using SPM99 software (http:\\fil.ion.ucl.ac.uk\spm), illustrated in figure 2.3.

Spatial Realignment

The images were realigned to the mean image by rigid body transformations (Friston *et al.*, 1995b). In three dimensions, a rigid body transformation can be defined by 6 parameters: three translations and three rotations about orthogonal axes. The parameters of these six affine transformation were estimated to minimise the sum-of-squared differences between each successive scan and the first. These transformations are applied to each image, and the data are re-sampled to the same rectilinear coordinates by sinc interpolation between neighbouring voxels' data. The mean image is also calculated. The deviations from the first image (in each direction of displacement and angle of rotation) are recorded for subsequent data analysis.

Slice timing

The acquisition of a volume takes several seconds. The acquisition time, TA, is very close to the repetition time, TR. Slices are imaged sequentially from the top of the head. The BOLD response to a stimulus will be imaged earlier in its evolution in a high slice of the brain, compared with a lower slice. However, the subsequent analysis of imaging data assumes that a volume was imaged at a single point in time. This discrepancy can be overcome by sinc interpolation of the data to a common time point, to correct for the phase advance in BOLD response during the acquisition time. The interpolation in unnecessary at very short TRs (<1s), and the interpolation inaccurate at long TRs (>6s). However, the TR for the fMRI studies reported here was approximately three seconds, and slice timing correction was implemented.

Coregistration

Two images may be coregistered, so that they can be viewed in the same coordinate space. For coregistration within the same modality, SPM minimises the sum of squares of the difference between target and object image. To coregister across modality (e.g. PET to T1-MRI in chapter 9), each image is coregistered to a modality specific template by rigid-body transformation. Then, the images are partitioned into grey matter, white matter and CSF. These partitions are then coregistered simultaneously.

Normalisation

Realignment produces a mean functional image for each subject. This mean image was used to estimate the warping parameters that transform each subject's brain to a template that conforms to an international standard in terms of size and shape. This enables the analysis of multiple subjects together, and the comparison of results between studies. The standard conforms to a normal anatomical space (Talairach and Tournoux, 1988).

Normalisation has several distinct stages. (1) The images are re-oriented to place the anterior commissure (AC) close to the zero position (in template space), and correcting any gross pitch, roll and yaw. This step is not essential, but normalisation error is less if the starting position and template are close. Gross deviations at the start can reduce the quality of final normalisation. (2) SPM99 is used to determine a 12-parameter affine transformation to approximate the template (a spatial transformation matrix similar to that used during realignment but also including zooms and shears).

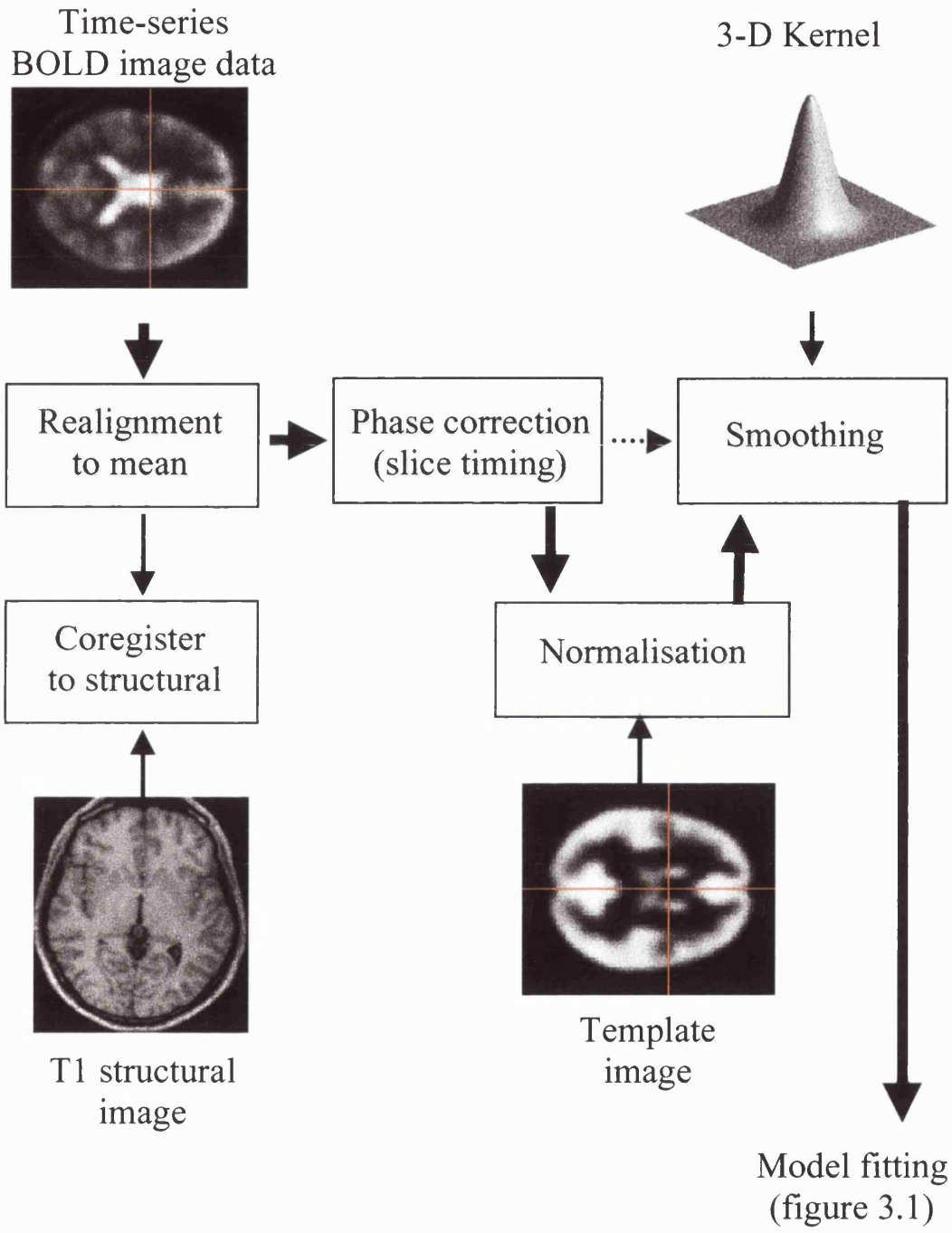


Figure 2.3 Schematic representation of data pre-processing. Coregistration and normalisation do not affect the subsequent statistical analysis, but are necessary to locate activations on a subjects own high resolution brain image, and to report activations in standard anatomic space. Both steps were performed for all data.

(3) Parameters are the estimated for a set of low-spatial-frequency basis functions (a discrete cosine set) in each dimension, to optimise a smoothly non-linear normalisation to the template.

A Bayesian framework is used to estimate the parameters, to find the deformation that is most likely given the subjects brain MRI and the template. The deformation is updated iteratively to minimise the sum of squared differences between the template and the deformed image and reflects the probability of actually getting that image if the transformation was correct. Prior information about the likelihood of a given transformation is incorporated by weighting the least squares (Ashburner *et al.*, 1997). In older brains, including patients, the best-fit normalisation may include deformation fields of low spatial smoothness i.e. high local distortion. For the subjects described in chapter 8, heavy regularisation was imposed on the normalisation parameters, to increase the smoothness of deformation fields.

Although the procedure can be extended to normalise across different imaging modalities, all fMRI data was normalised to a template derived from echo-planar images (EPI). This template was created by the developers of SPM, using EPI images from the same scanner used in my studies. These EPI images have been normalised to the mean of 151 normal brains (supplied by Alan Evans, MNI, Canada from the ICBM NIH P-20 project).

Smoothing

Before statistical analysis, the functional data was smoothed with 3-D Gaussian kernels (point-spread functions). Smoothing the data has many advantages. (1) it renders the data more parametric in their distribution and ensures the validity of parametric statistical tests, (2) Gaussian Field Theory (see chapter 3) assumes that the

data represents a lattice approximation of a continuously variable Gaussian field. In practice, the residual smoothness must be 2-3 times the voxel dimensions. (3) Smoothing enhances the signal to noise ratio, because the noise has generally a much higher spatial frequency than the evoked haemodynamic responses to regional neuronal activity. The matched filter theorem states that the optimum smoothing kernel corresponds to the size of the effect anticipated. (4) To compare or average multiple subjects, slight variations in the location of specialised regions can be accommodated better in smoothed data.

The extent of smoothing is described by the full width half maximum (FWHM) of the Gaussian kernel. Smoothing is a linear convolution, such that the final smoothing (equivalent FWHM) of repeated smoothing is the root sum of squares of the component smoothing kernels.

In view of the inherent and applied smoothing of my BOLD fMRI data, peaks of 'activation' had to be at elast 4mm apart to be considered as distinct from a neighbouring peak. If two peaks lay closer together, the higher peak was considered.

Summary

PET and fMRI can both be used to measure cerebral neuronal activity, on the assumption of a link between neuronal activity, local blood flow, and T2* fMRI signal. The PET and BOLD signals reflects afferent and intrinsic neuronal activity in a local population, rather than efferent spike activity. Standardised procedures are available to pre-process the data, to enable fair comparison of activation in different conditions and different subjects. These procedures include realignment, correction of phase advance, normalisation and smoothing.

Chapter 3

Analysis of functional imaging data

Introduction

Throughout neuroimaging studies there are two complementary approaches to understanding the organisation of the brain. **Firstly**, that there is regional specialisation by which different regions serve different functions. **Secondly**, that there are connections between specialised regions that enable functional integration. Cognitive or motor tasks utilise a network of regions distributed across the brain and are dependent on the integrity of these interconnections. Characterisation of these complementary processes requires a combination of imaging and analytical techniques.

In these experiments, Statistical Parametric Mapping (SPM) was used to define regional specialisation based on voxel-wise applications of a general linear model. Structural Equation Modelling (SEM) was used to characterise effective connectivity among regions, based on analysis of the variance-covariance structure of the time-course of BOLD data from selected regions.

A general schema for statistical parametric mapping is shown in figure 3.1. **First**, the pre-processed data are fitted to a general linear model. **Second**, the parameter estimates and residual error from the general linear model are used to create statistical images. **Third**, probabilistic inferences are made about the differences

between conditions, after correction for multiple comparisons, using Gaussian Field Theory.

A general scheme for structural equation modelling is shown in figure 3.2a-c. A model encompassing potential regional interconnections is specified. The data are fitted to this model, and the strengths of connections that best fit the variance-covariance of the observed data are estimated. The significance of connections may be tested by comparing the fits of models that incorporate different constraints.

The general linear model

Parameter estimation

A general linear model describes the activity of a given voxel in terms of a weighted linear combination of explanatory variables (such as sensory, motor or cognitive events over time), plus some error. Given a series of images, it is possible to calculate the values of these weights, for each explanatory variable for each voxel, with minimal error. Common parametric statistical tests, including multiple regression analysis, ANOVA, correlation analysis and t-tests are all based on general linear models.

For any voxel, a General Linear Model explains the variation in data values in different scans in terms of weighted explanatory variables, and residual error. The model may be written in matrix form as:

$\mathbf{Y}=\mathbf{X}\beta+\boldsymbol{\varepsilon}$,

where **Y** is a matrix containing the data value for each of **J** scans. **X** is a matrix of rank **p** that describes the presence or absence of each explanatory variable over all **J** scans. **X** is often known as the **design matrix**. β is the vector of weights for each

explanatory variable, and $\boldsymbol{\varepsilon}$ is the residual error. There are optimal values for **B**, called **b**, that minimise the sum of squares of the residual error. These best linear unbiased estimates of the weighting factors for each variable are known as the **parameter estimates**. If **X** is of full rank,

$$\mathbf{b}=(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{Y}$$

If X has linearly dependant columns, it is rank deficient, and there are many valid least-squares solutions to the general linear model. This is often the case with functional imaging studies, and an optimal solution can only exist within certain constraints.

However, if X is re-parameterised such that all explanatory variables sum to zero, the effects of a variable are estimated after the overall mean has been subtracted. When **X** is constrained to sum-to-zero, this is equivalent to using the pseudoinverse of $\mathbf{X}^T\mathbf{X}$. SPM uses the Matlab (Moore-Penrose) implementation of the pseudoinverse. Therefore, even for rank deficient design matrices, a unique least squares solution is calculated by:

$$\mathbf{b}=\mathbf{pinv}(\mathbf{X}^T\mathbf{X})\mathbf{X}^T\mathbf{Y}=\mathbf{pinv}(\mathbf{X})\mathbf{Y}$$

Residual (error) variance

The residual variance σ^2 is estimated by the residual mean square, calculated as the residual sum of squares $\boldsymbol{\varepsilon}^T\boldsymbol{\varepsilon}$, divided by the degrees of freedom, **J-p.** If the errors are independent, equally and normally distributed across explanatory variables then the estimated residual variance, $\mathrm{Est}\sigma^2$, is given by

$$\mathrm{Est}\sigma^2 = \mathbf{e}^T\mathbf{e}/\mathbf{J}\text{-}\mathbf{p} \sim \sigma^2$$

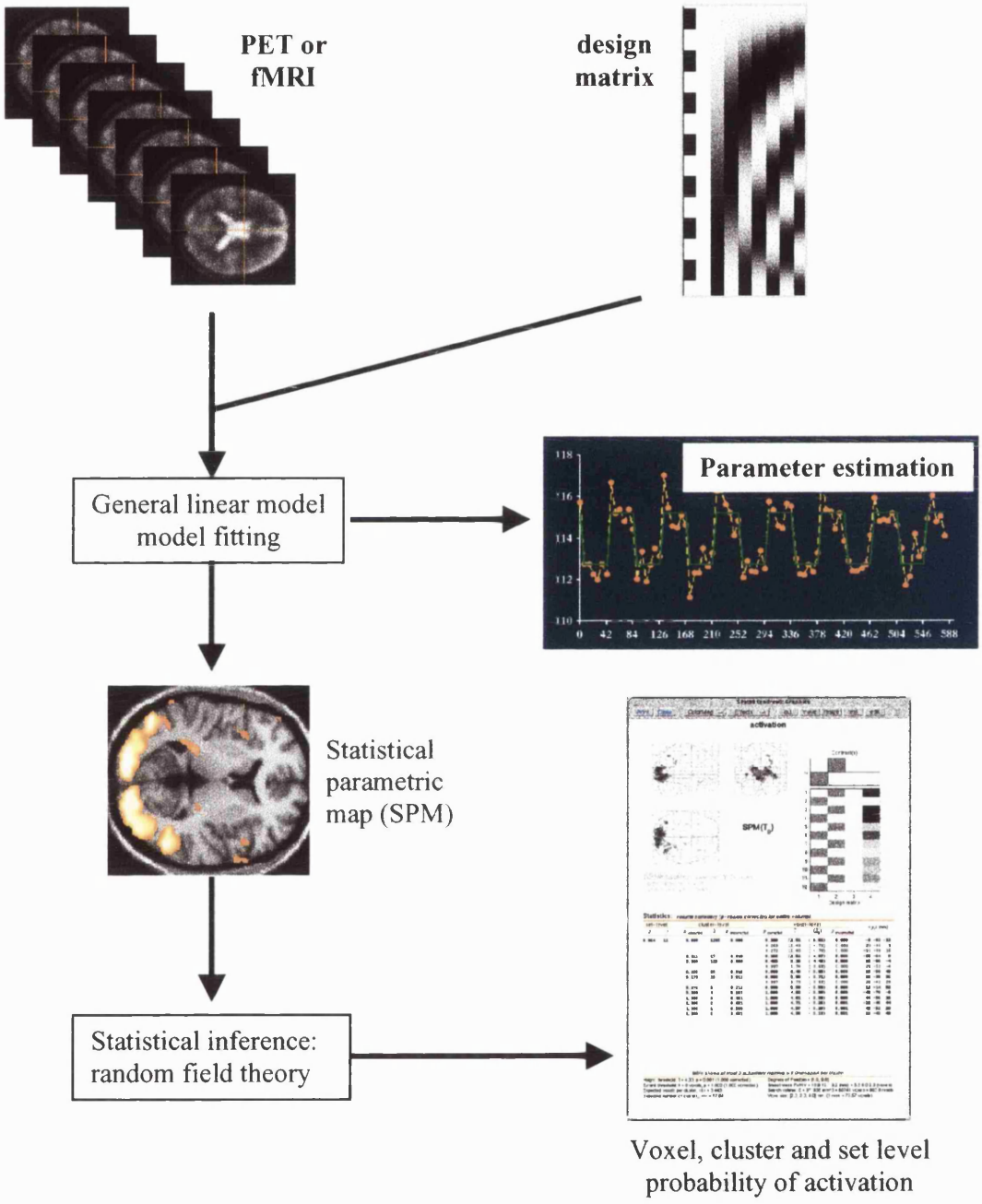


Figure 3.1 Schematic representation of statistical parametric mapping and inference

This error variance estimate is voxel specific, based on all scans, and was used in all analyses in this thesis. An alternative used elsewhere is to estimate the error variance across all voxels for any give scan/time-point (Worsley and Friston, 1995).

Design Matrices

For accurate and meaningful parameter estimation, and subsequent statistics, it is essential to design the experiment carefully, and to specify properly the explanatory variables in the design matrix. As a general rule, the design matrix should contain all the information about an experiment that may explain variation in the voxels' BOLD signal. However, for a unique solution to exist, there must be fewer explanatory variables than scans. Even within this limit, some variables may have minimal explanatory power, yet take up degrees of freedom. The inclusion of these variables would reduce the inferential power of the study. For the experiments described here, a pragmatic approach was taken. Design matrices included manipulative variables based on an analysis of the behavioural tasks in terms of major sensory, motor and cognitive components. They also included observed variables that were expected to confound experimental effects (e.g. movement parameters, chapters 4-8) or were a specific effect of interest (e.g. speed of planning, chapter 9).

Each column represents an explanatory variable, from one of several categories:

1. Blocks, or epochs, representing sustained performance of a task. In PET studies, a single scan represents cumulative activity over a prolonged period of time (90s). In fMRI, the mean activity during continuous activity over many seconds (up to the whole scanning session) may be modelled as

a box-car function. To model the gradual rise and fall of the BOLD signal at the start and end of the epoch, the box-car is usually convolved by a canonical haemodynamic response function.

For long epochs, the expected BOLD response reaches a steady state, or plateau. However, for short epochs there may not be time for this steady state to be reached. The BOLD responses to epochs of 3 and 6 seconds will differ in height as well as length. The working memory studies described in chapters 4 and 5 use this type of variable length epoch. Instead of a standard box-car (convolved by a canonical haemodynamic response function), the epochs were constructed as a string of delta functions, every sixteenth of the MRI repeat time (TR). Sixteenths of the TR are used by SPM as the minimum time bins for modelling expected BOLD responses to experimental effects.

2. Events, representing transient effects such as instructions, stimulus presentation or motor responses. The expected BOLD response was modelled as a delta function convolved by a canonical haemodynamic response function. This canonical haemodynamic response function is defined by the sum of two gamma functions, with onset, width and peak parameters determined empirically (Friston *et al.*, 1998)

3. Subject or session indices, if data from more than one subject or session are analysed.

4. Nuisance variables, such as movement parameters, that are not of primary interest but which can be taken into account to better determine the effects

of other variables. Movement parameters were used in all fMRI studies. The rigid body realignment of images assumes that movement occurs between scans, not within the course of acquiring a particular volume. Movement during volume acquisition will leave changes in BOLD signal in a realigned voxel that are not explained by experimental conditions. However, this error may be correlated with the movement during the acquisition. In the working memory experiments (chapters 4 and 5), the three translational and three rotational realignment parameters were included in the design matrix. They represent the deviations around the mean positions. Much of the realignment parameter variance is removed by the high pass filter during parameter estimation. The higher frequency variance may be considered as transient deviation form the mean position. In later experiments (chapters 6,7 and 8), the first temporal derivatives of the movement parameters were included. These represent the scan to scan change in position.

5. A parametric modulator for each scan, for example the accuracy score or thinking time for several trials during a PET image acquisition (chapter 10).

6. The data time-series from a specified voxel (a physiological measure) may be included to determine regions with which its activity correlates. If the time-series for a voxel is distinguished for different experimental conditions (psychological factors), it is possible to determine the psychophysiological interactions of cortico-cortical connectivity (Friston *et al.*, 1997a).

Event-related fMRI designs

It is possible to use a general linear model to analyse the fMRI responses to multiple transient events (Buckner, 1998; Rosen *et al.*, 1998). There are many advantages to event-related fMRI (er-fMRI) (Josephs and Henson, 1999), and all the fMRI studies used at least in part event-related designs.

For these experiments, the principal advantage of er-fMRI was to characterise the complexity of sensory, cognitive and motor events within a single trial. It was possible to distinguish the neuronal responses to one component of a trial, even though that component could never be performed in isolation.

It was especially important to distinguish the neuronal responses to sustained activity such as working memory from the transient activity related to response selection. The gradual rise and fall of the BOLD response means that events that occur within several seconds will cause very similar changes in BOLD. If the temporal relationship between these events is fixed, then there is a high correlation between the BOLD responses: the relationship of the two events types to the response cannot be distinguished.

Zarahn et al (1997) suggested that transient events separated by >4s could be distinguished, without significant effects of one event on the next despite the gradual rise and fall in BOLD responses (Zarahn, 2000; Zarahn *et al.*, 1997a). That is to say, the parameter estimate for one event type within a general linear model will not be confounded by another event type, even if they are time locked, provided that they are at least 4 seconds apart. Several studies of working memory have successfully used delay periods of ~8s, modelling memory activity as a mid-delay (+4s) transient (Postle *et al.*, 1999a; Postle and D'Esposito, 1999; Postle *et al.*, 2000c). However,

cognitive processes such as maintenance in working memory are not discrete transient events, but are sustained over a period of time. If memory is considered to be a sustained process, then short (<8s) and fixed delay lengths can introduce high correlations between the anticipated BOLD responses, and affect the parameter estimation. Longer or variable delays may reduce the correlation between these successive components of a trial, and reduce the dependence on assumptions of a canonical haemodynamic response function in BOLD fMRI (Aguirre *et al.*, 1998; Friston *et al.*, 1998; Toni *et al.*, 1999).

Another advantage of er-fMRI is that a more comprehensive model can be built, with a more realistic design matrix, such that residuals are dominated by true noise (independent and normally distributed errors) rather than additional systematic error from unspecified task components (structured residuals).

Event related studies differ in their efficiency, or their power to detect voxel-wise differences in condition related activity (Josephs and Henson, 1999). The long trial lengths and low frequency of events of interest in these studies tended to reduce the design efficiency. However, priority was given to the cognitive psychology of trials, rather than computational efficiency. That is to say, if a long memory and long rest period was needed (chapters 4 and 5), or multiple epoch types necessary (chapters 7 and 8), then other ways were used to improve the power of a study, e.g. prolonged scanning sessions.

Band-pass filter

During parameter estimation, the data were filtered by high and low pass filters. The high pass filter removes very low frequency effects such as the slow drift in BOLD signal over minutes. The filter cut off is calculated on a study specific basis,

to try to remove low frequency noise but not variation in signal due to the experimental periodicity. Typically this cut-off is 120 – 300 seconds.

Temporal smoothing can be used to improve signal to noise (Friston *et al.*, 1995c). The BOLD response has a characteristic frequency spectrum, due to the slow rise and fall in BOLD signal change after neuronal activity. Much of the noise in fMRI data is due to thermal noise, and is at much higher frequencies. By smoothing with a filter that approximates to the frequency spectrum of evoked haemodynamic responses, the noise is attenuated with little reduction in signal.

There will be intrinsic autocorrelations between successive data points in any given voxels (Friston *et al.*, 2000), due partly due to low frequency drifts in BOLD signal, and due to low frequency aliasing of high frequency events such as the cardiac cycle. Previously we assumed that $\varepsilon=N(0,\sigma^2)$, but the intrinsic autocorrelation structure, $\mathbf{V_i}$, is such that $\varepsilon=N(0,\sigma^2 V_i)$. These autocorrelations result in fewer degrees of freedom, because the data are not independent. One solution is to smooth the data and design matrix by a filter $\mathbf{k}$, swamping the unknown autocorrelations with a known correlation structure. This also renders the residuals' distribution more Gaussian. The general linear model becomes

$$\mathbf{KY = kX\beta + k\varepsilon}$$

with $\mathbf{k\varepsilon = N(0,\sigma^2 V)}$

and $\mathbf{V = kV_i k' =\sim kk'}$

The solution to this revised general linear model will be unbiased by the temporal smoothing, and enable more robust statistics (Friston *et al.*, 1995c; Worsley and Friston, 1995). The parameter estimates will be given by

$$\mathbf{b=(X^{*T}X^{*})^{-1}X^{*T}Y^{*}}$$

For a set of contrasts **c**, the variance of the parameter estimates is given by

$$\mathbf{Var}[\mathbf{c}'\hat{\beta}] = \sigma^2\, \mathbf{c}'(\mathbf{X}^{*\prime}\mathbf{X}^{*})^{-1}\, \mathbf{X}^{*\prime}\, \mathbf{V}\, \mathbf{X}^{*}\, (\mathbf{X}^{*\prime}\mathbf{X}^{*})^{-1}\, \mathbf{c}$$

$$\propto \mathbf{c'pinv}(\mathbf{X}^{*})\mathbf{V}\mathbf{pinv}(\mathbf{X}^{*})\mathbf{c}$$

There are two interesting consequences of this relationship (Friston *et al.*, 2000). **Firstly**, the bias (difference between actual and estimated contrast-variance estimate) is reduced as **k** introduces more correlations than $\mathbf{V}_i$, and V I, the identity matrix. **Secondly**, the efficiency of a contrast estimation **cb** (inversely proportional to its variance), can be estimated as a function of the design matrix **X** and filter **k.** This approach has been used to estimate the relative efficiency of different event-related designs (Josephs and Henson, 1999).

The approach taken by SPM99, and used to analyze these data, was to minimize bias in variance estimation, at the expense of some sensitivity (Friston *et al.*, 2000). Alternative approaches include pre-whitening the data and implementing autoregression algorithms (Zarahn *et al.*, 1997b).

Statistical inference

Statistical parametric maps

The most common statistics derived from the general linear model are the parametric t- and F- statistics. For t-tests, the magnitude of the parameter estimates must be considered against variability in activity due to chance alone, i.e. the error variance. To contrast the effects of two experimental conditions one can weight the parameter estimates, by a vector of 'contrast weights' **c**. Typically, **c** would contain +1 and –1 for the two variables of interest to compare, and 0 for all others. Under the

null hypothesis that the two variables or experimental conditions are not associated with differential brain activity,

$T = \mathbf{c'b} / \sqrt{(\text{Est}\sigma^2\, \mathbf{c'}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{c})}$,

where T approximates the Student's t distribution with $\mathbf{J-p}$ degrees of freedom. This is calculable for every voxel in the brain producing a statistical parametric map, known as the SPM{t}. The use of a balanced contrast vector $\mathbf{c}$ that sums to zero means that the product vector $\mathbf{c'b}$ can be estimated uniquely even for over-determined models $\mathbf{X}$. In SPM, the error term is for each voxel the residual error variance at that voxel across the whole set of $\mathbf{J}$ scans, $\text{Est}\sigma^2$.

The F-statistic is the ratio of variance explained by inclusion of a variable (or weighted combination of variables) in the model, divided by the error variance of the whole model. It may be used to compare models in a hierarchy, or to test a set of multiple linear hypotheses in a model. The design matrix $\mathbf{X}$ can be partitioned into $\mathbf{X}_1$ and $\mathbf{X}_2$, with corresponding parameters $\mathbf{B}_1$ and $\mathbf{B}_2$. Under the null hypothesis, the variables described by $\mathbf{X}_1$ do not account for additional variance i.e. $\mathbf{H_0: B_1=0}$. In this case the full model is equivalent to the reduced model:

$\mathbf{Y} = [\mathbf{X}_1:\mathbf{X}_2][\mathbf{B}_1;\mathbf{B}_2] + \mathbf{e} = \mathbf{X}_2\mathbf{B}_2 + \mathbf{e}$,

under null hypothesis that $\mathbf{H_0:B_1=0}$.

If $\mathbf{S_w}$ is the residual sum of squares for the whole model, $\mathbf{S_r}$ is the sum of squares for the reduced model, and $\mathbf{p_w}$ is the rank of whole design matrix $[\mathbf{X}_1:\mathbf{X}_2]$ and $\mathbf{p_r}$ is the rank of the reduced matrix $\mathbf{X}_2$ then:

$F = (\mathbf{S_r} - \mathbf{S_w} / (\mathbf{p_w} - \mathbf{p_r})) / (\mathbf{S_w} / (\mathbf{J-p_w}))$

where F approximates the F distribution with $\mathbf{p_w - p_r}$, $\mathbf{J-p}$ degrees of freedom. This principle can be extended from simple inclusion or exclusion of variables to multiple linear hypothesis defined by a contrast matrix **c**, such that $\mathbf{H_0: c'B=0}$.

Types of inference

There are different types of inference that can be drawn from the statistical parametric maps. There may be c or more clusters with k or more voxels above a threshold t in an SPM of known smoothness. SPM derives p values pertaining to

1 an *omnibus test,* of whether the overall number of clusters of suprathreshold voxels is significant. The omnibus test does not indicate which areas are significantly activated.

2 *set-level inference*: The set-level test determines the probability of the observed number of suprathreshold clusters that each exceed a specified size

3 *cluster-level inference*: The cluster level test determines the probability of spatial extent for each suprathreshold cluster.

4 *voxel-level inference*: The most regionally specific test is to ask whether the t- or F- value at a voxel exceeds a threshold.

Multiple comparisons

To draw voxel-wise statistical inferences, it is necessary to assign a probability value to the statistic (t- of F-) at each voxel. However, there may be hundreds or thousands of voxels even within a limited region of interest. Bonferroni correction for multiple comparisons is not appropriate however, because the voxel data are not independent.

One solution is to consider the voxels to be a lattice representation of a continuously varying field across the brain. The theory of Gaussian random fields may then be used to make clear predictions about the expected features of the SPM{t} or SPM{F}. Under the null hypothesis, that the distribution of statistics is due to random noise alone, there will still be peaks and troughs. However, very high values of the statistic, or broad clusters of moderately high values, are unlikely.

The Euler characteristic may be used to estimate precisely how high or how broad these areas must be to correspond to a given probability threshold under the null hypothesis (Friston *et al.*, 1996). The Euler characteristic of a binarised map (above or below threshold *t*) is a geometric measure that is effectively the number of clusters minus the number of holes between them. At high thresholds, the expected Euler characteristic simply counts the number of regions above *t*. The expected Euler characteristic for a given threshold gives the probability of the maximum exceeding that threshold, indicating the test level that would just reject the null hypothesis at that voxel. This produces an adjusted p-value at that voxel – the probability that the maxima in a random field are greater than the voxel value.

The expected Euler characteristic is dependent on the smoothness of the data. The smoothness of the statistical images is actually calculated from the component fields. These are the residual fields (what is left over after the modelled response at each voxel is subtracted from the data) after they have been normalised by the variance at each individual voxel. Although the smoothness is parameterised by a variance-covariance matrix of the spatial partial derivatives, it is presented as the FWHM of an assumed point spread function (PSF e.g. Gaussian kernel).

Resels (resolution elements) may be used to parameterise the number of independent tests. The total number of resels is equal to the volume of the search region divided by the product of the FWHMs of the smoothing kernel in each dimension. As the smoothness increases, the number of resels decreases yielding fewer independent tests. However, a resel has no boundaries. The application of Gaussian Random Field theory and the Euler characteristic to estimate the probability of an effect is not equivalent to Bonferroni correction for the number of resels in an SPM.

Regions of interest analysis

The volume of brain tested under the null hypothesis may be constrained by prior knowledge, such as the expected site of activation from previous similar studies, or the results of lesion studies. The application of Gaussian Field Theory holds for small volumes, and the proper correction for multiple comparisons may be made for hypothesised small regions of interest in SPM99.

The reduced search volume must be determined without bias. For these studies, small volumes were defined as spherical volumes around the maxima obtained in previous studies (e.g. in chapter 9 the small volumes were located after maxima were identified in chapter 8). Alternatively, they were drawn onto the Montreal Neurological Institute template space using MRIcro software (http://www.mrc-cbu.cam. ac.uk/imaging/~ chris.rorden), according to specified gyral anatomy (e.g. middle frontal gyrus in chapter 8). Bonferroni correction is not appropriate for correction of multiple comparisons, even within a volume the size of one resolution element (which may contain many partially non-independent voxels).

Interpretation of variance

When studying a group of subjects in several conditions, there are many possible reasons for different values in a given part of the brain in different images. For fMRI for instance, it may be that the experimental condition is associated with different activity at that part of the brain. This is called 'condition variance', and is of primary interest for the studies here.

However, it may be that the subjects have different values because of structural brain differences (despite normalisation); because they perform the task by a different strategy unknown to the experimenter; or because they have inherently different neuro-vascular coupling. These factors contribute to 'subject variance'. Even if these factors are controlled, the BOLD signal may vary. The BOLD signal and its sensitivity to neuronal activity, change gradually over time during scanning, and may change markedly between scanning sessions. This leads to 'session variance'. For these experiments, each subject is scanned only once, and therefore the session variance and subject variance are indistinguishable.

Awareness of session variance is particularly important in fMRI. It is generally large in comparison with condition variance. Session by condition interactions may significantly explain changes in regional brain activation. Condition related activations for a given subject cannot be generalised from a single session to infer 'typical' activation patterns from this subject. Therefore, differences in regional brain activations before and after learning, or before and after therapy, cannot be unambiguously attributed to that learning or therapy alone.

Fixed and random effects analyses

For many studies, one would like to be able to extend the inference from the particular subjects to the general population. Usually a group of subjects in an experiment may be considered to have been sampled randomly from the general population to which they belong, e.g. all men of that age, or all patients with a particular disease. The choice of subject is therefore a random variable, in contrast to the experimental conditions which are 'fixed' by the experimenter. Random and fixed variables must be treated differently in the analysis of variance of repeated measures such as brain images.

For the most common statistical tests in brain imaging, one calculates the ratio of the contrast **c'b** (t-test) or the variance attributable to a set of contrasts (F-test) to a denominator variance term. If all variables are fixed (a fixed effects analysis), then the denominator term is the error variance within subjects (mainly noise from scan to scan). However, with a random variable like the selection of subjects, the appropriate denominator term must accommodate the variance between subjects (random) as well as within subjects (fixed). Otherwise, the inference is restricted to the particular subjects studied.

Models with both fixed and random effects are generally difficult to analyse. However, the simple balanced designs of most imaging experiments enables a two staged approach to mimic mixed effects models. The first stage is a fixed effects model within each subject, to generate a summary image from each subject, such as a map of a particular contrast **c'b**. The summary images can then be assessed across subjects in a second level fixed effects model. The summary image form each subject at the first level is based on parameter *estimates*. The different single subject summary

images will therefore incorporate within subject error in estimation. The between subjects variability at the second level analysis therefore includes both within and between subjects variance. For balanced designs, the variance due to fixed and random effects is in the right ratio to assess the overall population effect.

It is still possible to make qualitative inferences about population effects from a single step fixed effects model (Friston *et al.*, 1999a). In calculating the t- statistic, the nominator term is the average effect size for the particular subjects, and the denominator variance term is assumed to be equal across all subjects. Just one or two subjects may dominate the results. However, one can stipulate that an effect is significant in all subjects. The refutation of the null hypothesis in all of the subjects is known as conjunction analysis. It can be shown that even for a small group of six subjects, regions of activation present in every subject by conjunction analysis are likely to occur in their general population. Such results from a small group may be regarded as typical of the general population. This form of conjunction analysis was used in chapter 5.

Chapter 10 used a different form of conjunction analysis, applicable to factorial designs (Price and Friston, 1997; Price *et al.*, 1997). For this, areas were identified at which there was a main effect of one factor (e.g. planning versus rest) but not a significant interaction with other factors (e.g. execution versus imagination). A standard statistical threshold was set for the main effect ($p<0.001$ uncorrected), and a low statistical threshold was set for the exclusive interaction ($p<0.05$). In the absence of a significant interaction, the two simple main effects are both significant contributors to the main effect.

Group data and clinical studies

The problem of extending inference to the subjects' general population is highlighted in clinical studies. The expression of disease will vary at a subject level, both between patients and over time in the same patient. If patients are rare or heterogeneous, how should they best be compared with control subjects, or studied over time? A random effects analysis may not always be possible. It requires a large group of patients (typically >15) who differ from the comparison group only in terms of the disease of interest, with no additional sources of inter subject variance e.g. co-morbidity. Many studies have used fixed effects models, and had to accept that the inference only extends to the particular patients studied. It is possible to use a conjunction analysis approach to show that each and every patient in a group differs from the control subjects with regard to a particular effect. However, if the same group of control subjects is used for comparison with each patient, the assumption of independent contrasts in conjunction analysis cannot be maintained.

Ambiguity can arise when interpreting differences in regional brain activations in patient-control studies (Price and Friston, 1999). These problems arise whether the patients have focal lesions, are subject to different drug therapies or are being studied during recovery from disease. Interpretation depends on whether the performance, behaviour and cognitive strategy in the patient group are the same as the control group. If a patient does not perform a task, or manipulations of the task suggest a different strategy is employed, then the normal pattern of brain activity cannot be expected. Neuroimaging cannot resolve whether the performance deficit is attributable to the abnormal brain activity or *vice versa*.

Even if performance is the same, imaging differences have many possible interpretations. Activation differences may be due to changes in neuronal architecture or differences in cognitive strategy. Neuronal architectural changes include the direct disturbance of those networks of regional brain activity that normally mediate performance, and longer term plasticity or reorganisation in the adult brain. The immediate disturbance may be at the site of the lesion if known, or at a remote area (known as diaschisis) (Price *et al.*, 2001).

Network analysis

Complex cognitive functions are unlikely to be mediated by isolated modules, but rather a network of inter-dependant regions. Even if there is some degree of regional specialisation within this network, effective connections may underlie cognitive performance (Fuster, 2001; Horwitz *et al.*, 2000; Horwitz *et al.*, 1999). The analysis of the connectivity between brain regions is therefore increasingly important, and is the basis of network models of brain function.

Neural network models have many applications. Dynamic modular systems have been developed to simulate sensory, motor or cognitive processes and the effects of focal lesions (Braver *et al.*, 1999; Cohen *et al.*, 1990; Cohen and Servan-Schreiber, 1992). More complex models have used neurobiological modes of interaction between elemental neuronal units to simulate macroscopic cortical or subcortical interactions and the behavioural consequences or 'pathology' in these elements (Monchi *et al.*, 2000; Tagamets and Horwitz, 1998).

The alternative approach taken here was to analyse the observed regional brain activity in terms of interacting systems within a cortical network. This *systems-*

level approach is most commonly applied to neuroimaging data. The goal is to identify critical brain areas mediating specific cognitive or motor tasks, and the strengths of the interactions between them. The strength of interaction is usually measured as a function of the covariance of regional activity.

Functional connectivity and effective connectivity

The temporal correlations between activations in spatially remote brain regions has been termed 'functional connectivity' (Friston *et al.*, 1997a; Friston *et al.*, 1993b). This is distinguished from 'effective connectivity', the explicit influence of one region on the activity in another (Friston *et al.*, 1997a; Friston *et al.*, 1993b). Effective connectivity may be assessed by systems level modelling, such as structural equation modelling, or the inclusion of second order terms in general linear models (psychophysiological interactions (Friston *et al.*, 1997a)).

Functional connectivity may arise because of effective connectivity between regions. However, there are alternative contributors to functional connectivity. For example, if two regions A and B receive common inputs from a third area C, then there will be covariance between A and B without influence of A on B or *vice versa*. These common inputs may be either neuromodulatory (e.g. monoaminergic neuromodulation) or task specific inputs from other cortical areas. This distinction between effective synaptic coupling between neurons and correlations induced by common afferents originates in multi unit microelectrode recordings (Gerstein and Perkel, 1969).

Although effective connectivity is close to the neurophysiological concept of synaptic efficacy, there are significant differences. Effective connectivity may be indirect, through polysynaptic relays, and even through multiple areas. Moreover,

effective connectivity in neuroimaging applies only at a systems level (Horwitz *et al.*, 2000). Inhibition or excitation at this level does not indicate the excitatory or inhibitory nature of the synaptic interactions.

Structural equation modelling

Structural equation modelling (SEM) is one method to analyse systems-level interactions (Buchel and Friston, 2000; Buchel and Friston, 1997; Horwitz *et al.*, 1999; McIntosh and Gonzalez-Lima, 1994a), based on the decomposition of covariance amongst brain regions. The analytical methods of structural equation modelling have existed for several decades in social and economic sciences, but in the last five years these techniques have been applied to functional imaging (Horwitz *et al.*, 1999).

Structural equation modelling does not itself produce a model of regional interactions in the brain; rather it estimates the effects of experimental manipulation on regional interactions within a model (McIntosh and Gonzalez-Lima, 1994a). The model is used to calculate path coefficients, or connection strengths, between each region that best explain the variance-covariance structure of the empirical data. The decomposition of the variance-covariance structure means that the connection strengths take into account potential common inputs from other areas in the model.

Anatomical model specification

The analyses in chapters 8 and 9 adopted a hypothesis-led theoretical perspective to constrain the model to principal anatomic and cognitive elements. It is not realistic to test all possible models of interactions between the specified regions. Iterative search algorithms have been suggested to use empirical data to derive the

best model rather than *adequate* models (Bullmore *et al.*, 2000). However, this approach may produce locally rather than globally optimal models, or computationally unstable models. In chapters 8 and 9, the permitted connections between regions in the models were specified *a priori*, based on known anatomical interconnections between primary and non-primary cortical motor areas in primates (Barbas and Pandya, 1987; Johnson *et al.*, 1996; Muakkassa and Strick, 1979; Rizzolatti *et al.*, 1998).

These models were clearly not complete accounts of all possible regions engaged in the tasks, nor all possible direct and indirect connections between them. Such a comprehensive model may be useful in an exploratory sense but it would be much less powerful in relation to our specific hypotheses. Elaborate models, permitting cyclical connections between regions for example, can become computationally unstable (McIntosh and Gonzalez-Lima, 1994a). The simplified models were nonetheless sufficient to address key questions regarding the influence of prefrontal cortex over premotor regions under different conditions.

For each region in the model, the fMRI time series was extracted for each subject. Functionally homologous regions may vary slightly in location from subject to subject. Therefore the specific coordinates for these regions were selected for each subject separately. To avoid bias towards voxels activated by particular conditions, the coordinates were taken from the nearest maxima in the subject specific SPM{F}. Regions were then defined as 5mm radius spheres, including all voxels that exceeded $p<0.001$ (uncorrected) in the SPM{F} for all effects. The first principal component of the adjusted BOLD signal was entered into the model as used by Buchel and Friston (1997, 2000).

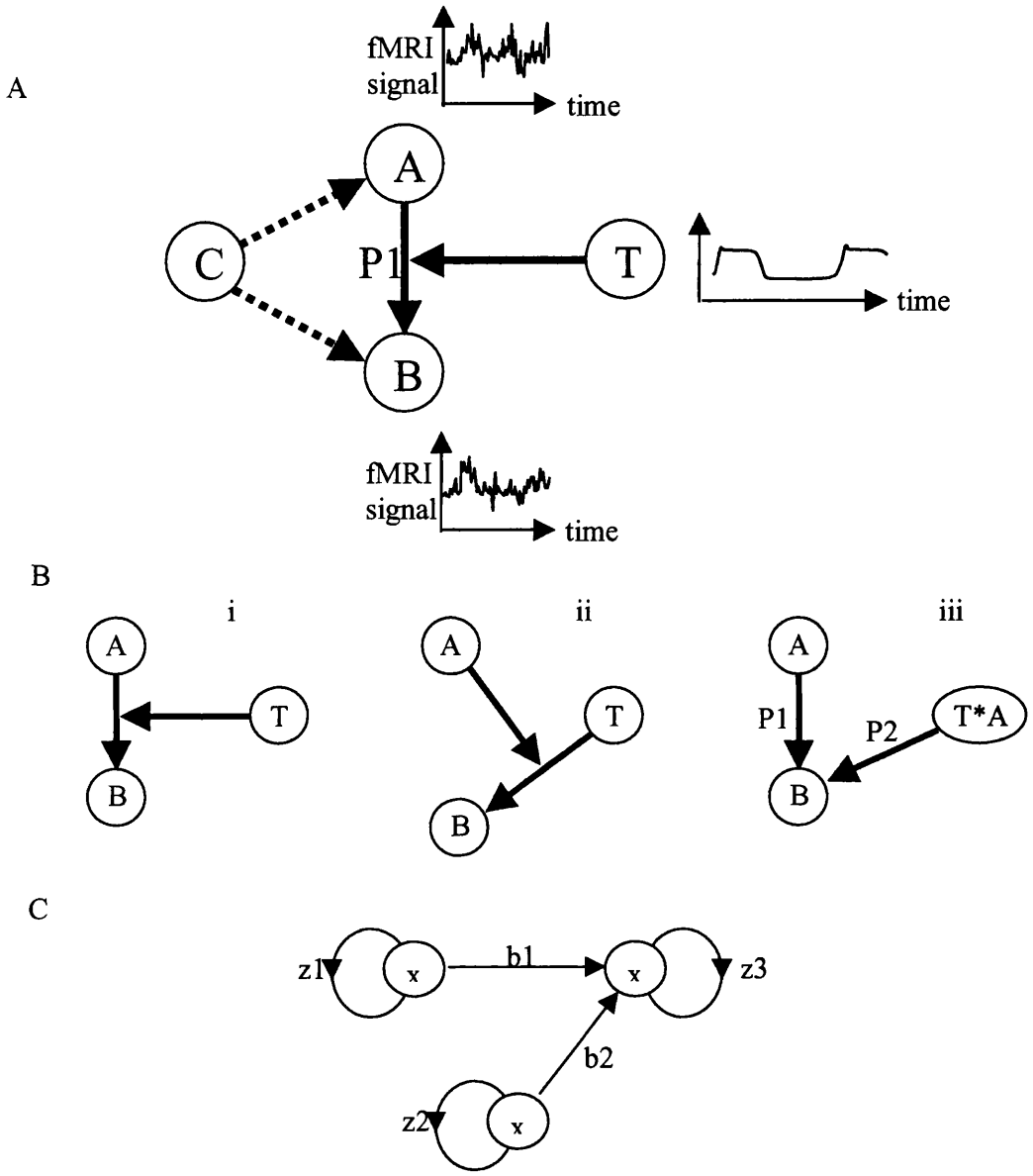


Figure 3.2. Schematic representation of structural equation modelling, SEM, of fMRI time series. (a) Using SEM one can measure the influence of one area A over another B, over and above the common influence of a specified third area C. Direct influence is indicated by the path coefficient P1. One can also assess whether changing task or context (indicated by T) alters the strength of coupling between A and B. (bi) If changing the task or context is associated with modulation of the coupling between A and B, then as illustrated in (bii) it is also interpretable that area A changes the extent to which the task causes activation in B. (biii) In SEM, such modulations are measured using the interaction term 'A*T', and modulation is indicated by the significance of the path coefficient P2, (c) In this simple model with three regions x_1, x_2, x_3, connected by two paths with path coefficients b_1 and b_2, there are residual influences z_1, z_2, z_3.

Task specific effective connectivity

Our application of structural equation modelling included data from all conditions. To assess task-related changes in coupling we included moderator variables that modelled how changing conditions altered the connectivity between two areas. These can be thought of as interactions between the psychological causes (e.g. attention) of a regional response in a target area (e.g. premotor cortex) and the physiological causes (i.e. activity in source area such as prefrontal cortex). For the analysis of fMRI data, this is preferable to comparing separate models for each condition, because the sequential scans are not independent: the gradual BOLD response to neuronal events means that the early scans of one condition may include residual effects of the previous task. The moderator variables incorporate these gradual changes and comprise the product of regional activity in the source area and the relevant psychological factor (Buchel and Friston, 1997). The psychological factor here implies a boxcar representing the alternation between two contexts (e.g. attention to action and not), following mean correction and convolution by a canonical haemodynamic response function. The principal cause of regional covariance (e.g. motor related activation relative to rest) is not explicitly modelled, but occurs within each psychological context. The moderator variables therefore may be associated with changes in regional covariance, but they are orthogonal to the principal cause of this covariance.

This differs from the alternative approach to structural equation modelling, which uses separate analyses of inter-regional covariance under different conditions (Coull *et al.*, 1999; Horwitz *et al.*, 1999; McIntosh and Gonzalez-Lima, 1994a; Nyberg *et al.*, 1996). In this form, the covariance between two regions within a

condition arises from scan-to-scan variability, which is not under direct experimental control and for which the causes are not specified by the paradigm. Furthermore, dispersion of the responses by the haemodynamic response function in fMRI cannot easily be accommodated if the fMRI data is divided between different epochs.

Implementation of SEM

The structural equation modelling was implemented using the SEM Toolbox of SPM99. A simple model is represented in figure 3.2a-c, with **p** regions $\mathbf{x_1,x_2 \ldots x_p}$ (illustrated for p=3), from which are recorded **N** observations. If **x** is the **N x p** matrix of all observations, and $\mathbf{x^T}$ its transpose, then the observed variance covariance structure is given by **S** where,

$$\mathbf{S = (1/(N-1)).x^Tx}$$

S is a symmetric matrix, with sample variances along the diagonal and inter-regional covariances off the diagonal. The variables $\mathbf{x_1,x_2 \ldots x_p}$ may be 'caused' by independent variables $\mathbf{z_1,z_2,\ldots z_p}$ outside the model. This is equivalent to unidirectional influences between the elements of **x**, specified by the matrix of path coefficients **B**, with residual influences $\mathbf{z\ (z_1,z_2,\ldots z_p)}$ on the variables in **x**. If **I** is the **N** x **N** identity matrix, then

$$\mathbf{x.I = x.B + z}$$

Therefore,

$$\mathbf{x = z.(I-B)^{-1}}$$

and, $x^Tx = (I-B)^{-1}.z^T.z.(I-B)^{-1}$

$= (I-B)^{-1}.z^T.z.(I-B)^{-1}$

$\mathbf{= (I-B)^{-1}.C.(I-B)^{-1}}$

$= \mathbf{\Sigma}$

Where $\mathbf{C} = \mathbf{z}^T.\mathbf{z}$, the diagonal matrix of residual variances, and $\mathbf{\Sigma}$ is the variance covariance matrix implied by the model. Parameters in **C** and **B** are free parameters. The free parameters are estimated by the iterative minimisation of the differences between the observed **S** and estimated $\mathbf{\Sigma}$ variance-covariance structures.

Random starting estimates are generated, from which gradient descent methods estimate the optimal parameters according to the objective maximum likelihood function (Bollen, 1989; Higham, 1993)

Significance of path coefficients

Statistical inferences about the path coefficients were based on the comparison of a free model with a constrained model for each subject. In a free model, all parameters in **C** and **B** are optimised. In a constrained model, the path coefficient in **B** for a given connection was set to zero.

In the context of multivariate normally distributed variables, the minimum of the maximum likelihood function (used to estimate the path coefficients) is distributed as chi-squared, with (q/2)(q+1)-p degrees of freedom (q, the number of observed variables and p the number of free parameters in **C** and **B**) (Bollen, 1989). The difference in goodness of fit of two models (e.g. free *versus* constrained) is given by the difference in the chi-squared values, with n degrees of freedom where n is the difference in free parameters. Under the null hypothesis, that one area has no influence over another, the free and constrained models do not differ in goodness of fit.

To make inferences about the strength of connections at a group level, the path coefficients were considered as dependant variables. They were subject to one-sample t-tests, to determine whether the coefficients were significantly greater than zero,

(given inter-subject variance). Alternatively, path coefficients were entered into two-way repeated measures analyses of variance to compare the effects of different moderator variables on different anatomical connections.

Interpretation of path coefficients

The path coefficients of the moderator variables describe the extent to which the interaction between source area activity (prefrontal or parietal cortex) and cognitive processes (attention to action or to conjunction search) influence the target (premotor areas). There are two interpretations of a significant positive value in the model. Firstly, the activity of the source area influences target area activity more under one cognitive condition than another. An alternative interpretation is that the activity of the source area changes the extent to which the cognitive condition influences target area activity. Both interpretations are valid and are identical to psychophysiological interactions as defined for neuroimaging (Friston *et al.*, 1997b).

The dimension and units of a path coefficient depend on whether it refers to an anatomical connection, or the moderating effect of task. For anatomical connections, a path coefficient of +1 indicates that a unit change (in standard deviations of the change of BOLD signal) in the source area causes a unit change in the target area. A path coefficient of 0 indicates no overall coupling between the two regions. It is in effect the regression coefficient of the two regions, scaled by the ratio of standard deviation of BOLD in each region. The path coefficient of a moderator variable indicates the difference in this inter-regional covariance under the different task conditions.

Limitations of structural equation modelling

There are of course limitations to structural equation modelling. Regional blood flow is predominantly determined by local mean synaptic activity (Jueptner and Weiller, 1995; Logothetis *et al.*, 2001; Rees *et al.*, 2000). Information conveyed in terms of neuronal synchronisation rather than rate or local field potentials may not be properly characterised (Logothetis *et al.*, 2001). In vivo recording studies indicate that mean firing rates and synchronisation may play different roles in cognitive or motor processes within a single region (Reihle 1997). Fortunately, microscopic models at least suggest that mean synaptic activity and synchronisation are closely associated in a large neuronal population (Chawla *et al.*, 1999; Chawla *et al.*, 2000).

The spatial and temporal resolution of fMRI and PET means that the activity of complex sub-populations of neurons are put together into a summary measure such as blood flow. Nevertheless, empirical systems level interactions have been reproduced when excitatory and inhibitory sub-populations are modelled separately using structural equation modelling (Krause *et al.*, 2000; Taylor *et al.*, 2000).

The current implementation of structural equation modelling also overlooks the dynamics of neuronal interactions. For example, the covariance is measured between regional activations in the same timeframe, ignoring the history of activation in a region (Friston, 1995). Non-linear models that include the temporal dynamics of neuronal coupling are now emerging (Friston, 2000a; Friston, 2000b; Friston and Buchel, 2000)). However, the maturity of structural equation modelling techniques and their established place in the neuroimaging literature gave it a significant advantage in the analysis of data in chapters 8 and 9.

Chapter 4

Selection between items in memory

Introduction

Chapter 1 has reviewed evidence that the prefrontal cortex may be involved either in the maintenance of information in working memory (Goldman-Rakic, 1987b), or in the selection of responses (Frith, 2000; Passingham, 1993). The first hypothesis accounts for the fact that in monkeys there are cells in the dorsal prefrontal cortex that continue to fire during the delay on a working memory task (Goldman-Rakic, 1998). There is also activity in this area when human subjects perform working memory tasks, though there is no agreement as to whether to emphasise its role in the maintenance of information (Goldman-Rakic, 1998), or the manipulation or monitoring of that information (Petrides, 1994). However, there is also activity in the prefrontal cortex when subjects freely select between manual or verbal responses (Deiber *et al.*, 1991; Frith, 2000; Frith *et al.*, 1991; Jahanshahi *et al.*, 1995). As reviewed in chapter 1, the activity during free selection is not attributable to the working memory load. Selection of single responses is still associated with activation of the prefrontal cortex (Desmond *et al.*, 1998), and TMS to the prefrontal cortex impairs free selection in a task without working memory load (Hadland *et al.*, 2001).

In the experiment described in this chapter, fMRI was used to try to reconcile the 'working memory' and 'response selection' hypotheses. The principal aim was to

differentiate the brain regions activated in association with different components of working memory, that is maintenance during the delay period and response selection. Activity associated with the initial perception of stimuli and the execution of the motor responses was of secondary interest.

The delayed response (DR) paradigm used by Goldman-Rakic (Goldman-Rakic, 1987b) was the basis of many monkey lesion and electrophysiological studies. We wished to maintain the simplicity of the DR paradigm. Previous functional imaging studies of working memory had often required subjects to monitor (Owen *et al.*, 1996b; Petrides *et al.*, 1993b), manipulate (D'Esposito *et al.*, 1999a; Postle *et al.*, 1999b) or rehearse information (Courtney *et al.*, 1998a), or to prepare responses during the delay period (Pochon *et al.*, 2001). These may be active processes mediated in part by PFd, explaining the observed activation of PFd in complex working memory studies.

In the present study, the design meant that the subjects simply maintained information during the delay. There was no requirement to monitor, manipulate or rehearse information during the delay. The subjects were also unable to prepare their responses, because the appropriate response was only specified at the end of the delay. The spatial stimuli were chosen so as not to be easily verbalised, and sub span memory loads were used to avoid organisational processes such as 'chunking' (Gobet *et al.*, 2001).

Previous functional imaging studies of DR tasks used fixed delay lengths. There are two problems with this. **First**, subjects may anticipate the response cue, attending to or selecting a response in preparation for the trigger. Therefore, the delay period may include response selection as well as on-line maintenance. **Second**, short

fixed delay periods introduce high correlations between the anticipated BOLD response to delay related activity and response selection activity. To overcome both of these problems, we chose *variable* delay periods as in Toni *et al.* (1999). However, longer delays were used here because in the study by Toni et al (1999) it was only possible to distinguish unambiguously delay-activity from probe-activity with delays longer than ten seconds. By varying the delay lengths, we were able to identify regional activations that persisted throughout the delay period, analogous to the sustained firing rate in neurons shown by Fuster et al (2001) for delays of 16 seconds or more.

At the end of the delay, a cue was presented that specified one of the remembered locations as the target of the response. To make the appropriate response the subject had to select that location from memory. Activity associated with response selection will be aligned to this cue, and would not be present during the delay period.

The multiple regression analysis of fMRI data within a general linear model is sufficient to statistically associate regional activation with events within working memory trials. However, we also wanted to review the data in a format that emphasised its relation to primate physiological studies of the DR task. The temporal realignment of data to cue or probe events was used successfully by Toni *et al.* (1999), to distinguish activity related to different components of a trial, supplementing the statistical parametric maps.

Methods

Subjects

Six healthy volunteers (age 24-34, 5 male) participated in the study, after written informed consent. They were recruited through the University College London Postgraduate Society. None had a history or neurological or psychiatric disease, or took regular medication.

Experimental paradigm

The experimental paradigm is illustrated in figure 4.1. It is a conditional delayed response task, in which the delay and response components depend on the initial stimuli. For a memory trial, the subjects saw three red dots presented simultaneously for 1.5 s on a screen in front of them, in random locations (solid circles). There followed a delay of 9.5 to 18.5 s (in steps of 1 s, randomly ordered) during which the subjects remembered the exact location of the dots (indicated here by dotted circles not actually presented to subjects). A line then appeared for 1.5 s across the screen, running through the location of just one of the previous red dots. This indicated which of the remembered dots now became the target for response, without specifying the location directly. The line was then replaced by a central cursor identical in appearance to the red dots. The subjects moved the cursor to the remembered target location using a joystick. After the response, the trial ended and was followed by a rest period of 8-12 seconds.

On control trials the visual and motor components of the task were similar to memory trials, but the stimuli were presented in reverse order such that there were no spatial cues to remember during the prolonged delay (nominal 'non-memory' period

in analyses). The target for the cursor response in the control trials was the location of the single red dot, with no intervening delay.

Eighty-two trials per subject were scanned (including 40-43 memory trials). The trial order was randomised for each subject. Dot locations within trials were also randomised, within certain constraints. There was a minimum dot-to-dot separation of one dot's diameter (50 pixels between the edges of nearest dots). The line was of pseudo-random orientation bisecting just one dot's location, and not passing within one dot's diameter (50 pixels) of the other dots. Behavioural measures were the distance from the final cursor position (placed by the subject) and the locations of the three dots' locations (memory trials) or the target dot (control trials). These were analysed separately for each group using Microsoft Excel.

Functional imaging

The functional images were acquired by T2*-weighted echo planar magnetic resonance imaging at 2T, TR 4500 ms, TE 40 ms, over 40 minutes continuous whole brain imaging (64x64x48 voxels, 3mm isotropic resolution). Statistical Parametric Mapping software was used for image processing and analysis (SPM99). The images were realigned to the mean image by rigid body transformation, and sinc interpolated in time to correct phase advance during volume acquisition (Aguirre *et al.*, 1998). These realigned images were transformed to normal anatomic space (Talairach and Tournoux, 1988) by non-linear transformations (Friston *et al.*, 1995b) using the Montreal Neurological Institute (MNI) template. The data were spatially smoothed with a Gaussian kernel FWHM 6mm. High resolution structural T1-weighted MPRAGE images were also acquired on all subjects to permit anatomical localisation of activation foci.

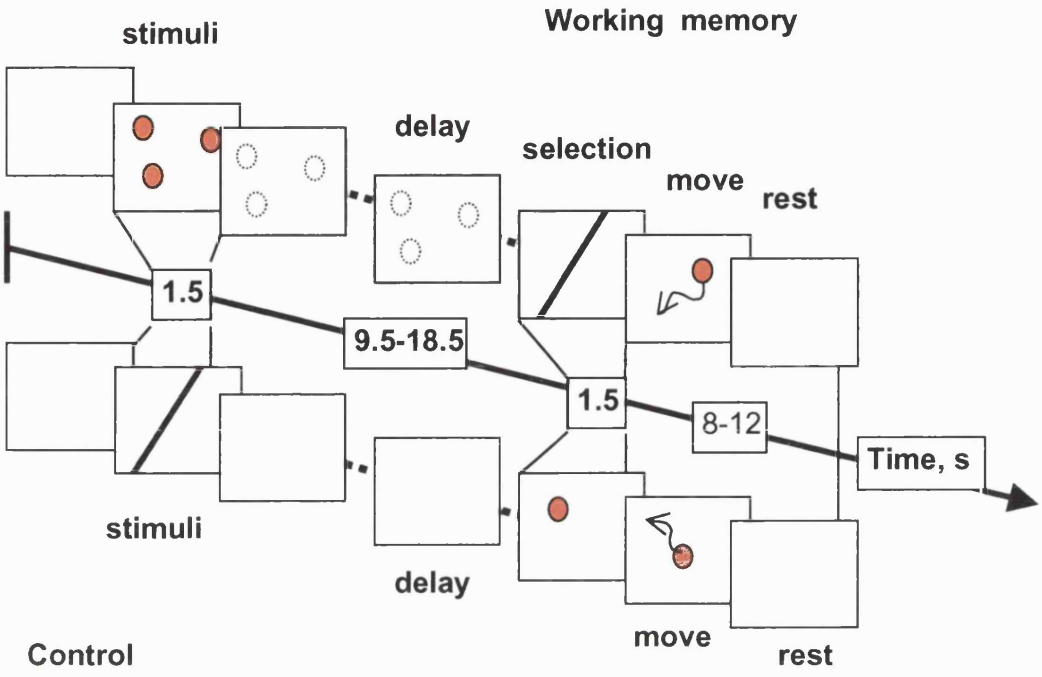


Figure 4.1. A schematic representation of the spatial working memory and control trials. For a memory trial, the subjects saw three red dots presented simultaneously for 1.5 s on a screen in front of them, in random locations (solid circles). There followed a delay of 9.5 to 18.5 s (in steps of 1 s, randomly ordered) during which the subjects remembered the exact location of the dots (indicated here by dotted circles not actually presented to subjects). A line then appeared for 1.5 s across the screen, running through the location of just one of the previous red dots. This indicated which of the remembered dots now became the target for response, without specifying the location directly. The line was then replaced by a central cursor identical in appearance to the red dots. The subjects moved the cursor to the remembered target location using a joystick. After the response, the trial ended and was followed by a rest period of 8-12 s. For control trials the visual and motor components of the task were similar to memory trials, but the stimuli were presented in reverse order such that there were no spatial cues to remember during the prolonged delay (nominal 'non-memory' period in analyses). The target for the cursor response in the control trials was the location of the single red dot, with no intervening delay.

Analysis of functional images:

A general linear model was applied to each voxel in the functional imaging data, using a fixed effects model with SPM99. The model included covariates for the presentation of visual stimuli at the start of trials, the duration of working memory and 'non-memory' periods, the selection of items from memory at the end of memory trials, and the visuomotor response in all trial types. The baseline was modelled implicitly. In addition, the movement parameters from the realignment of images were also included, as covariates of no interest, to model artefacts resulting from movement that could not be fully corrected by realignment. The covariates for stimuli, selection and response were modelled as stick functions convolved by a canonical haemodynamic response. The memory delays and non-memory periods were modelled as a box car (composed of a train of stick functions) convolved by a canonical haemodynamic response function.

Prior to parameter estimation of the general linear model, the data were band-pass filtered. The filter included a high pass filter with cut-off 400 seconds, and low pass filtering by temporal smoothing of the data based on a canonical haemodynamic response function. Subject specific grand mean scaling was applied, such that each subjects global mean signal was set to 100, and voxel specific changes in BOLD can be expressed as a percentage of this global mean signal.

For each voxel the parameter estimates and residuals were used to calculate t- and F- statistics for specific contrasts. These contrasts included the main effects of stimulus presentation, selection form memory and motor response (against implicit baseline), and the differential between memory and non-memory delay period activity. For the tables 4.1 and 4.2 and figures 4.4-4.6, voxels were identified that

exceeded t= 4.91, $p<0.05$ corrected for multiple comparisons. In addition, a conjunction analysis was used to identify voxels at which an effect was present in all subjects (Friston *et al.*, 1999a; Friston *et al.*, 1999b), with combined probability less than $p<0.05$ corrected.

The least squares best fit of the data was extracted from peak voxels in prefrontal cortex (areas 8 and 46) and parietal cortex. These were then temporally realigned to the onset of memory trials, and averaged across subjects for trials of each duration (9.5 to 18.5 s, in intervals of 1s).

Results

Behavioural results

The distribution of errors for memory and control trials is shown in figure 4.2. 84 % of responses selected from memory were within a dot's diameter of the correct target, and 95 % were within 100 pixels, the minimum separation between the original locations of the original stimuli. 100 % of control trial responses were within one dots diameter. The distribution of errors of response selection is unimodal, heavily skewed towards zero. This suggests that errors were inaccurate attempts to place the cursor on the correct dot, rather than placing the cursor close to an alternative dot's location.

Imaging results

The regions of brain activation associated with sustained maintenance of items in spatial working memory differ from those associated with transient selection of an item from within memory. Figure 4.3 shows the statistical parametric maps for maintenance (green) and response selection (red) superimposed on a representative brain from the MNI series. A full list of regions and their statistics is given in table 1.

Working memory maintenance (contrasted with equivalent 'non-memory' periods in control trials) was associated with bilateral activation in prefrontal area 8 (figures 4.3 and .4a) and intraparietal cortex (figures 4.3 and 4.4b) but not in prefrontal area 46. At a lower threshold ($t>3.10$, $p<0.001$ uncorrected for multiple comparisons), there was an activation peak more anteriorly: it lay either within the anterior part of area 8 or in the area defined by Petrides and Pandya as 9/46 (co-ordinates 32, 24, 50, $t=3.30$) but there was still no activation in area 46 proper (Petrides and Pandya, 1995; Rajkowska and Goldman-Rakic, 1995).

Figures 4.4c-d show the time course of activity during working memory trials as best fitted by the data for each length of memory delay. The time course for short delays are plotted on the near side of the graph, and longer delays are plotted further back. The heavy black line indicates the presentation of the cue line (response selection). The BOLD response to neuronal activity at these times is displaced to the right, because of the gradual rise and fall of the BOLD response.
In both area 8 and the intraparietal cortex there were sustained increases in BOLD signal throughout the course of the working memory delay, seen as a 'plateau' the length in direct proportion to the duration of the maintenance delay. This figure also shows that there was no additional activity in these areas that was associated with the selection of the response.

The selection of the target location from memory was associated with activations of the right prefrontal area 46 proper ($y=38$) (figures 4.3 and 4.5b), and a more posterior region lying either in area 8 or the region identified by Petrides and Pandya as 9/46 ($y=18$) (Petrides and Pandya, 1995). There was additional activation of the right ventral and orbital frontal cortex, and bilateral activation of the intra-

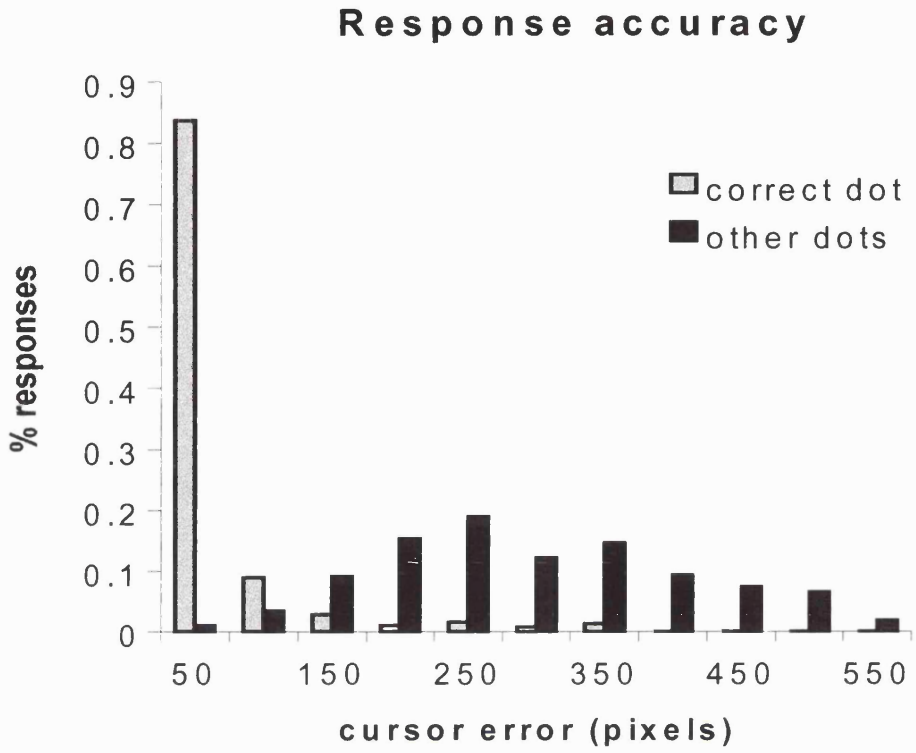


Figure 4.2 The accuracy of joystick responses is illustrated as the distance (in pixels) from the chosen cursor position to the actual position of either the correct target (the location crossed by the probe line) or the incorrect target. Dots were 50 pixels in diameter, and separated by at least 50 pixels.

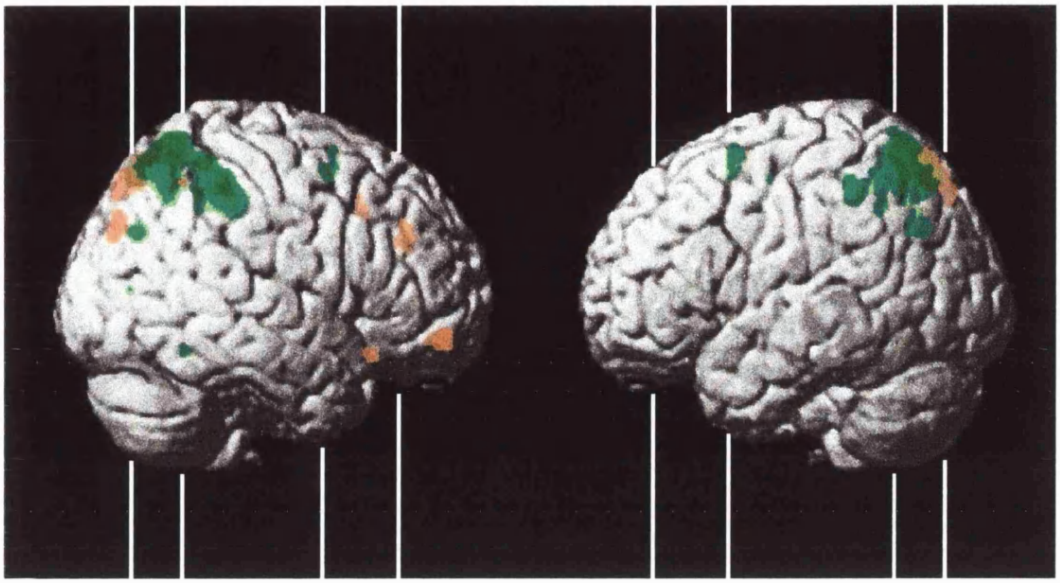


Figure 4.3. Regions of significant activation associated with response selection (red) and the memory (vs non-memory delays) (green). Statistical parametric images, SPM{t}($p<0.05$), have been overlaid on a surface rendering of a single subject representative MRI brain in normal anatomic space, projected in anterior, posterior and lateral elevations. The white lines indicate the planes of coronal sections of images in figures 4.4 and 4.5.

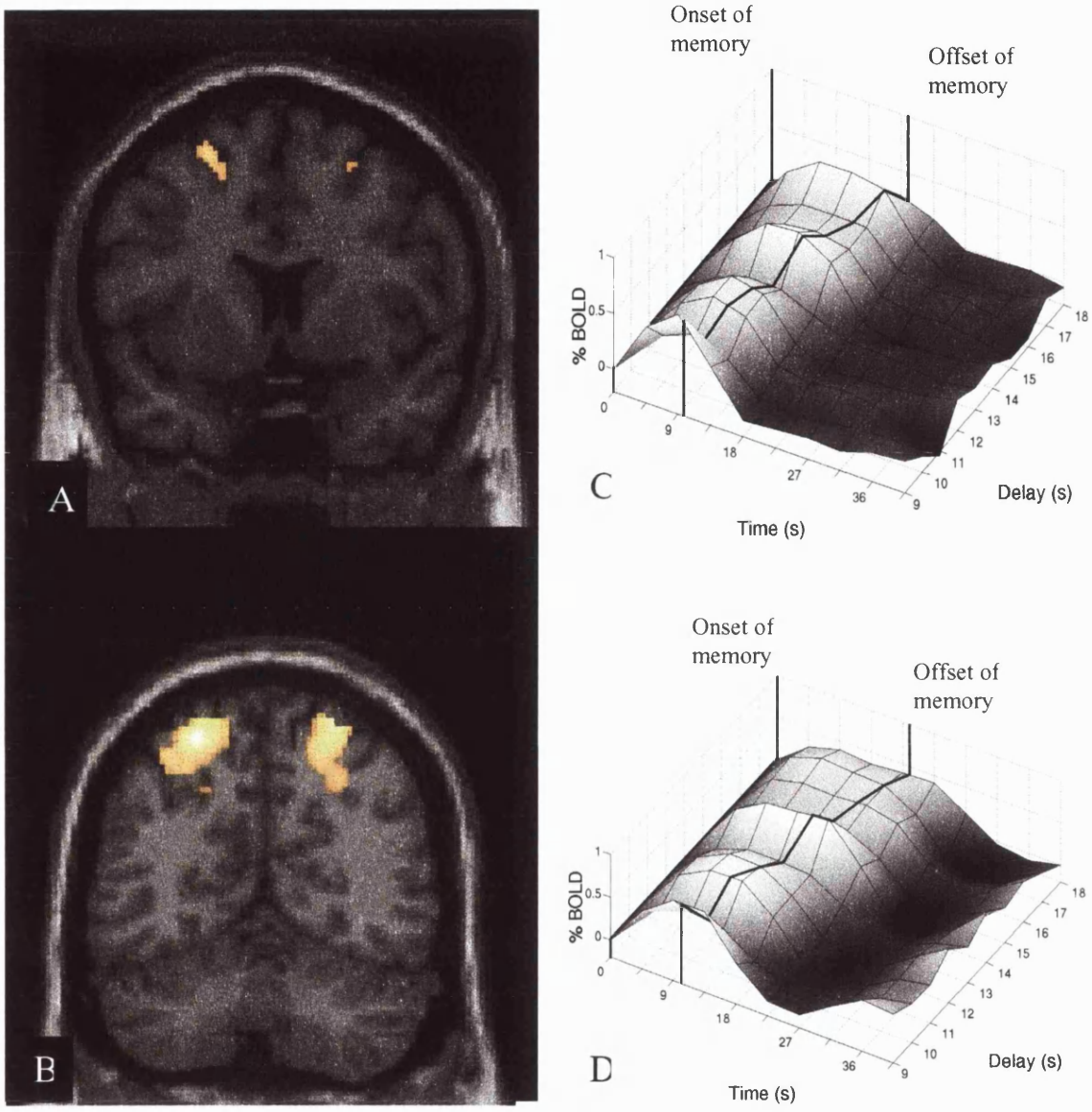


Figure 4.4. Regions of significant delay related activation. Statistical parametric images SPM{t}($p<0.05$), for the contrast 'memory delay vs non-memory delay' have been overlaid on T1 weighted coronal slice through (a) area 8, y=8mm and (b) through intraparietal cortex, y=-60 mm. The 'fitted' data from peak voxels in (a) -22, 8, 60 and (b) 26, -60, 64 have been temporally realigned to the onset of memory trials to show the BOLD activity (z-axis) over time (x-axis) for each of the different memory delay lengths (y-axis). The thick black lines indicate the onset and offset of the working memory delays, and the colour scale indicates the relative change in BOLD signal from the start of each trial. The plots demonstrate the sustained activity over the length of the working memory delay.

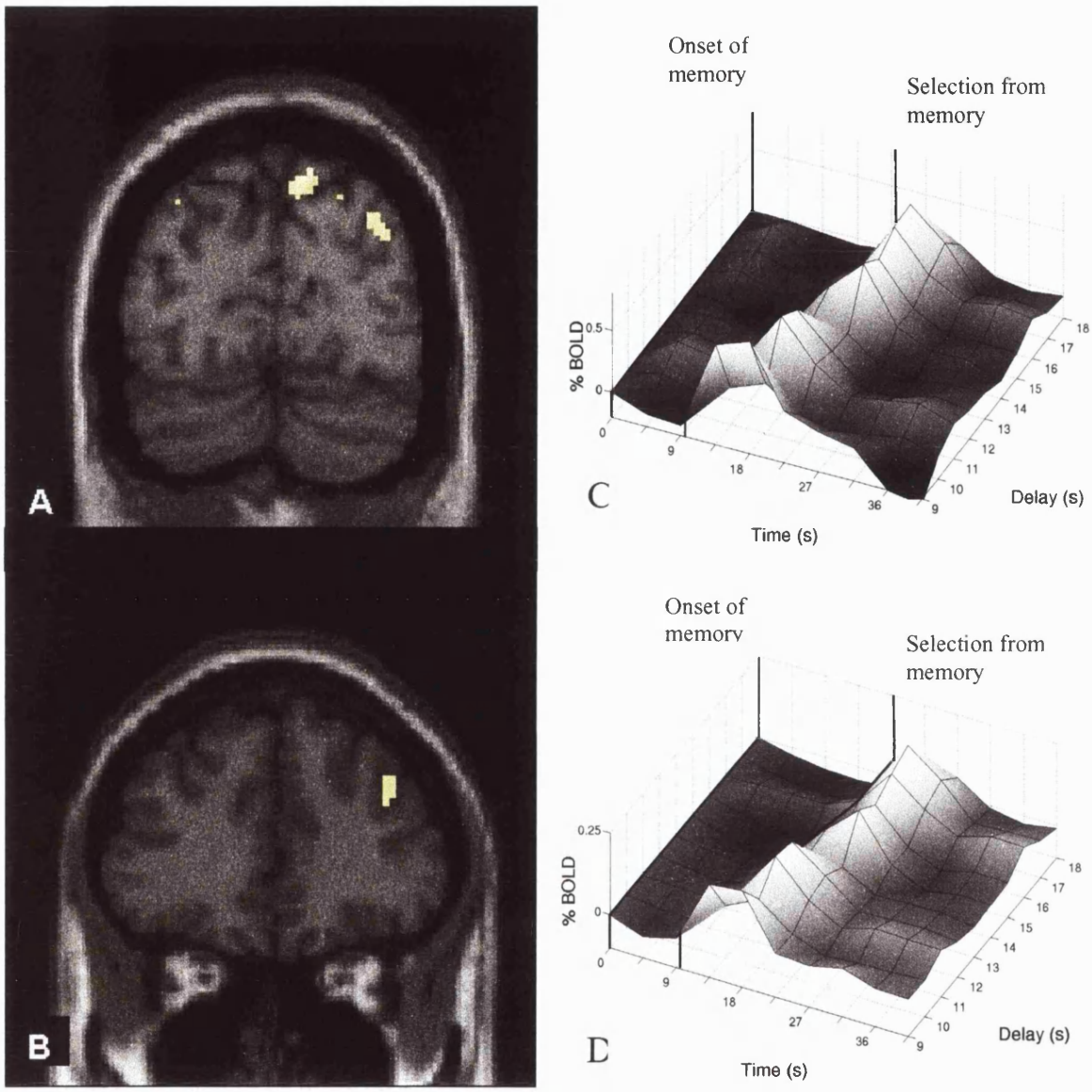


Figure 4.5. Regions of significant activation associated with response selection at the end of memory trials. Statistical parametric images SPM{t}($p<0.05$), for the main effect of selection have been overlaid on T1 weighted coronal slice through (a) parietal cortex, y=-82mm and (b) through prefrontal cortex, y=38 mm. The 'fitted' data from peak voxels in (a) 38, -82, 32 and (b) 42, 38, 28 have been temporally realigned to the onset of memory trials to show the BOLD activity (z-axis) over time (x-axis) for each of the different memory delay lengths (y-axis). The thick black lines indicate the onset and offset of the working memory delays, and the colour scale indicates the relative change in BOLD signal from the start of each trial. The plots demonstrate activation associated with response selection, and the absence of delay related activation.

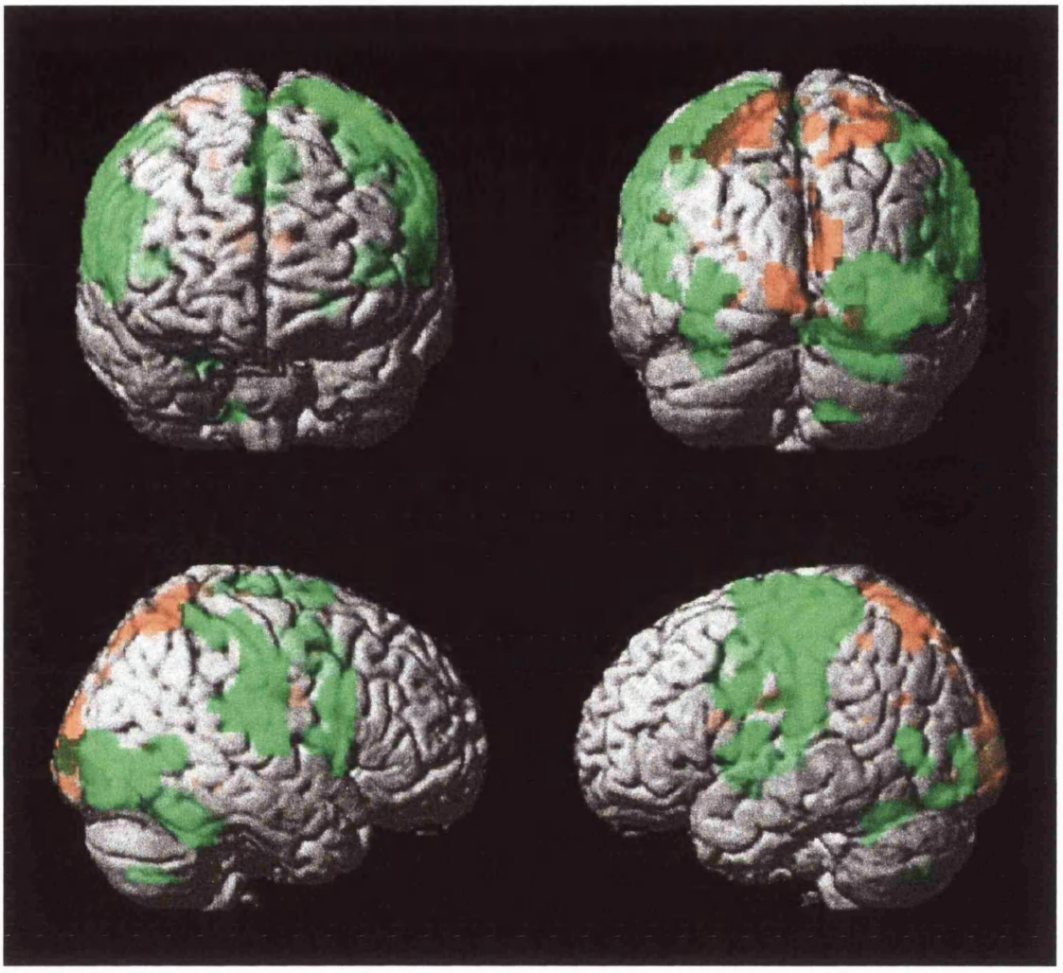


Figure 4.6. Regions of significant activation associated with stimulus presentation (red) and the use of the joystick (green). Statistical parametric images, SPM{t}($p<0.05$), have been overlaid on a surface rendering of a single subject representative MRI brain in normal anatomic space, projected in anterior, posterior and lateral elevations.

parietal cortex and the medial parietal cortex (figures 4.3 and 4.5a). The parietal activations for selection were more posterior and medial to those identified for maintenance of working memory.

Figures 4.5c-d show the time course of activity during working memory trials as best fitted by the model. In both area 46 and the medial parietal cortex there was a transient increase in BOLD signal following the selection of the target location at the end of the working memory delay. There was no sustained activity in these areas associated with the maintenance of the locations during the working memory delay.

The activations associated with presentation of visual stimuli lay in visual and parietal areas (table 2 and figure 4.6). The activations associated with use of the joystick to move the cursor included visual and motor regions, but did not include the prefrontal cortex.

Discussion

The results clearly show different fronto-parietal networks of activation associated with maintenance and the selection of items within the same working memory trial. Thus, although the attentional, mnemonic and motor response components of tasks such as the delayed response task may all be considered to constitute 'working memory' (Goldman-Rakic, 1998) they do not necessarily share the same neuroanatomical basis in humans.

Delay related activation

In our human subjects, there was activation around the superior frontal sulcus (area 8) (y = 8) but not area 46 during maintenance of spatial working memory. There have been previous reports of activation in or medial to the superior frontal sulcus

during spatial memory anterior to the frontal eye fields (Belger *et al.*, 1998; Courtney *et al.*, 1998b; Postle and D'Esposito, 1999). This posterior prefrontal activation is unlikely to represent the frontal eye-fields. Activation related to eye-movements was posterior to the delay related activation in the study by Courtney et al (1998). In our study, the activation in area 8 lies anterior to the anterior commissure (y = 8), whereas the frontal eye-fields have been located at coordinates posterior to this line (Luna *et al.*, 1998; Nobre *et al.*, 1997).

The results for frontal and parietal delay-related activations are consistent with the animal literature on spatial working memory. In monkeys, sustained neuronal activity has been reported in area 8a anterior to the arcuate sulcus (Chafee and Goldman-Rakic, 1998; Sawaguchi and Yamane, 1999b); and in the same studies activity was found in the posterior third of the sulcus principalis. This area is either 8a, or part of the area designated 9/46 by Petrides and Pandya (Petrides and Pandya, 1995). The activity of many of these neurones can be shown to be associated with the retention of the sensory cues (Funahashi *et al.*, 1993; Niki and Watanabe, 1976; Sawaguchi and Yamane, 1999b). Sustained parietal activation associated with the maintenance of spatial information has also been reported in the monkey intraparietal cortex, (Chafee and Goldman-Rakic, 1998; Quintana and Fuster, 1999).

It is, of course, possible that the negative result for maintenance in area 46 was due to insensitivity to underlying maintenance related activation. In monkeys delay related activity has been reported in area 46 in the middle third of the sulcus principalis (Funahashi *et al.*, 1989). However, in our study we specifically compared the activity during the spatial working memory interval with the equivalent period without working memory in control trials. Kojima and Goldman-Rakic made a

similar comparison in a working memory paradigm in monkeys (Kojima and Goldman-Rakic, 1984). They reported that for over 80% of cells in the sulcus principalis which had delay related activity, this activity was at least as great for trials without working memory as for trials with working memory. Furthermore in our study the subjects were not able to prepare their response; yet in the study on monkeys the activity of the remainder of cells could have represented preparatory activity.

We could test whether there was a lack of sensitivity in our methods by reducing the statistical threshold to $t = 3.10$ ($p<0.001$ *uncorrected* for multiple comparisons). This did not reveal any maintenance related activation in area 46. Further, any maintenance related activity in area 46, would be revealed in the time course of activation shown in figure 4.5d. Figures 4.4c-d and 4.5c-d show the time-course of activation derived from the condition specific covariates and their respective parameter estimates. Maintenance related activity would be seen as a rise in activity above baseline during the delay period, even if it did not reach statistical significance (figures 4.4c-d).

It is true that specific delay related activity in area 46 has been reported previously in fMRI studies. However, it is necessary to exclude from the comparison studies in which the subjects could either prepare their response or manipulate the information in memory during the delay, as on the n-back task. Courtney *et al.* (1997) instructed subjects to actively rehearse faces to themselves, and found that that in half of their subjects the activity of area 46 correlated with a period of rehearsal for 8 seconds. One difference is that in our study the subjects were not instructed to actively rehearse the items.

Postle and D'Esposito (1999) have studied consecutive object and spatial working memory and reported statistically significant delay related activity. However, the specificity of this delay-related activity is uncertain. The short memory delay used would have induced a high degree of colinearity between the covariates for stimuli, memory and probe events. If the haemodynamic response function in the general linear model is correct, then the mid delay BOLD signal is correctly attributed to delay related neuronal activity. However, variation of the haemodynamic response in the prefrontal cortex could lead to misattribution of mid delay BOLD signal to delay related neuronal activity. Although the current study also used a canonical haemodynamic response function, the long and variable delays reduced this problem.

One cannot claim that there is no delay related activity in area 46, but the current results suggest that selection *dominates* the activity of these voxels in area 46 and that in simple spatial working memory tasks the contribution of maintenance must be small, as has also been claimed by others (Owen *et al.*, 1999)

Response selection

Our design enabled us to distinguish the selection of a remembered location in memory from the maintenance of several locations in memory. In contrast to the findings for maintenance, we found transient activation in the dorsolateral prefrontal cortex area 46 when the subjects selected the appropriate location from memory. The activation at y=38 clearly lies in area 46 proper (Petrides and Pandya, 1995; Rajkowska and Goldman-Rakic, 1995), whilst a second dorsolateral prefrontal activation at y=18 is more likely to lie in the posterior frontal area 9/46 (Petrides and Pandya, 1995).

Previous imaging studies have reported activation in area 46 during working memory tasks. However, some of these tasks are complex. It is proposed that the critical feature of the tasks activating area 46 is the selection of items within memory. This distinguishes tasks that require subjects to *report the contents of memory* as presented and tasks that require subjects to *select between items in memory*. This approach can explain the activation of dorsal prefrontal area 46 in specific working memory tasks and in tasks of free selection without working memory, since both involve the selection of representations. On the self-ordered search task, the subjects must select items in turn, rejecting ones previously chosen. On tasks requiring re-ordering, the subjects must sequentially select items for report: this involves selecting out the item tagged as last, then the last but one, and so on. On the n-back task, the subjects must not only remember the temporal order of items but also select recent items in memory in preference to earlier ones. Levy and Goldman-Rakic report that lesions of area 46 impaired DR without manipulation as well as analogues of the self-ordered search tasks (Levy and Goldman-Rakic, 1999). However, even on their delayed response task, there is interference between trials (Diamond and Goldman-Rakic, 1989): the monkey must select the last location rather than the one presented on the previous trial.

It is therefore suggested that the reason for the common activation of the prefrontal area 46 in working memory tasks and free selection tasks is that both involve the selection of the target of the response. They are both examples of the general process of selecting representations to guide actions when there is no external prompt (Goldman-Rakic, 1987a; Goldman-Rakic, 1987b). In the present study an accurate response demanded selection of one particular location in memory. The

subjects needed to voluntarily focus awareness on the item in memory, a process termed 'attentional selection' by Miller (1999).

Limitations

There are several limitations to this first experiment. **First**, the current design is a conditional delayed response task. The current experiment mixes memory and non-memory trials, unlike the standard delayed response task as used in monkeys. One consequence is that there is less interference between the memory trials, due to the longer mean intervals between memory trials.

Second, we only tested memory for location. Activity of PFd has been reported during the delay interval of the n-back (Cohen *et al.*, 1997), in which subjects must remember both the order of the items and their location, not just location. Activity of the PFd may have been due to the additional memory load for temporal order, or the need for trial specific arbitrary association of the location of a stimulus with its temporal position.

Third, the task may have been too easy. It has been shown that increasing task difficulty e.g. by increasing n- during the n-back task, leads to an increase in the activity of the prefrontal cortex (Braver *et al.*, 1997; Cohen *et al.*, 1997). However, even with just three dots, the long delays used placed considerable demands on maintenance processes, and accuracy was lower than on control trials. More items can be remembered easily over shorter delays. Longer delays were necessary to reduce the correlation between maintenance and selection. The combination of long delays and high memory loads may have caused too high an error rate to enable clear interpretation of task differences.

Fourth, it could be argued that there was activation of area 46 at particular stages of the maintenance period, such as the early encoding of stimuli, but that this was not detected. Even our temporal realignment of fitted data would not have been able to reveal trends towards early or late activation. Adjusted data from prefrontal cortex would be better able to show non-significant trends towards early activation (suggestive of re-coding information before maintenance) or late activation (suggestive of response preparation or anticipation). This requires a better signal to noise ratio, more trials, or both.

Fifth, we are not able to distinguish selection from inhibition. In view of other imaging and electrophysiological evidence, the positive selection of one item from a set has been emphasised. Activation might also represent the inhibition of the other items. However, such a distinction between selection and inhibition is not necessary in biased competition models: selection and inhibition will both occur following a single top-down influence on mutually inhibitory networks.

Last, there are several possible explanations of the activation occurring at the time of response selection. It could be argued that the activation represents recall of the original stimuli, rather than selection between the remembered items. It could also be argued that the activation represents memory for the probe cue (the line), which disappears immediately before the joystick controlled cursor appears.

Summary

Event-related functional magnetic resonance imaging was used to study performance of a spatial working memory task. Maintenance of spatial items was distinguished from the selection of an item from memory to guide a response. Maintenance was associated with activation of prefrontal area 8 and intraparietal

cortex. In contrast, selection, but not maintenance, was associated with activation of prefrontal area 46 of the dorsal lateral prefrontal cortex. The results support a role of the dorsal prefrontal cortex in selection of remembered representations.

Table 4.1. Areas of significant activation associated with maintenance and response selection.

Region	laterality	Talairach coordinate			T statistic
Working memory maintenance (vs 'non-memory' interval in control trials)					
Superior frontal sulcus (area 8)	right	24,	4,	54	5.81
	left	-22,	8,	60	6.42
Intra-parietal cortex	right	26,	-60,	64	9.98
		44,	-34,	42	7.61
	left	-22,	-62,	60	10.33
Selection from memory					
Dorsal lateral PFC (46)	right	42,	38,	28	5.29
(9/46)	right	30,	18,	40	5.22
Orbitofrontal PFC	right	40,	54,	-12	6.22
Ventral PFC	right	36,	22,	-16	5.41
Medial parietal cortex	right	10,	-80,	48	5.94
	left	-14,	-76,	54	5.62
Intra-parietal cortex	right	38,	-82,	32	5.81

Table 4.2. Areas of significant activation associated with visual presentation and use of the joystick.

Region	laterality	Talairach coordinate			T statistic
Visual presentation					
Striate cortex	left	-8,	-96,	0	8.46
	right	10,	-98,	12	7.82
Parietal cortex	left	-12,	-58,	70	10.32
	right	22,	-60,	68	7.86
Cursor positioning with the joystick					
Motor cortex	left	-24,	-24,	74	21.54
SII	left	-52,	-22,	18	12.55
	right	66,	-22,	18	13.63
Prestriate cortex	left	-26,	-92,	0	10.16
Prestriate cortex	right	34,	-84,	-10	14.97
Insula	left	-38,	-2,	10	14.84
	right	42,	2,	10	10.90
Cerebellum	left	-14,	-72,	-46	7.45
	left	-30,	-54,	-22	9.73
	right	14,	-64,	-50	11.58
	right	24,	-50,	-24	17.56
Putamen	left	-26,	0,	0	8.68
	right	24,	0,	0	5.53
Thalamus	left	-12,	-18,	6	9.53
	right	10,	-16,	6	6.79
Cingulate motor area	--	0,	0,	52	14.54

Chapter 5

Selection between items in memory II

Introduction

In chapter 4, passive maintenance of spatial location in working memory was associated with activation of prefrontal area 8, and parietal cortex. In contrast, the selection between items within memory to guide a response was associated with activation of area 46. Attentional selection of items from within memory was proposed to account for the activation of area 46 in that and other functional imaging studies of working memory.

However, there were limitations to the previous study. These are addressed in a second study, presented in this chapter. **First**, the memory trials were mixed with non-memory trials. This minimised interference between memory trials. In the second study, all trials required memory for the initial stimuli. Trials only differed in terms of the events at the end of the memory delay.

Second, the first experiment only tested memory for location. In the present experiment, the subjects were required to remember the order as well as the location of the dots, as on n-back tasks (Cohen *et al.*, 1997).

Third, the task used in the first experiment may have been too easy. The addition of temporal information would be expected to make the task more difficult. The greater difficulty was shown by the greater error rate in the second study compared with the first (see behavioural results).

Fourth, we would not have been able to show transient delay related activity, for example early in the delay period. The second study more than doubles the number of trials, and it is possible to inspect the adjusted data to look for weak trends in the adjusted data.

Last, there were alternative explanations of the activation occurring at the time of response selection. It was argued that activation at response selection could have been due to memory for the probe cue (line) which disappeared immediately before the joystick controlled cursor appeared. In the present study, the cue (number or cross) remained on display during the cursor movement.

Again event-related fMRI was used to study working memory for spatial stimuli, as in the first experiment. This enables the differentiation of sustained activity related to maintenance from the transient activation when an item is selected from memory to guide a response (selection).

There were two other differences between the two studies. First, to check that negative results for maintenance activity in area 46 did not reflect a lack of sensitivity, a region of interest analysis was also performed for this area, using functionally and anatomically defined regions. Second, the selection effect was analysed in two ways. In analysis 1, selection was defined by a main effect of selection versus baseline. In analysis 2, selection was defined as a differential effect between activation at the end of selection trials and the activation at the end of control trials.

On the basis of the first experiment, it was predicted that passive maintenance of spatial and temporal information in working memory would be associated with activation of posterior prefrontal cortex and parietal cortex, but not area 46. In

contrast, the selection of an item according to its position in a series of stimuli would be associated with activation of area 46.

Methods

Subjects

Six healthy volunteers participated in the study, aged 20 –29 (three female), after giving written informed consent. They were recruited through the University College London Postgraduate Society. None had a history or neurological or psychiatric disease, or took regular medication.

Experimental paradigm

The task resembles the spatial working memory task we used previously, but with several important differences (see figure 5.1). All trials required working memory for three red dots, *and* the order in which these were presented at the start of the trial. Subjects remembered the location of the dots and also their order over long variable delays (8.5-17.5 seconds, in steps of one second). At the end of selection trials, subjects were presented with a central number (1,2 or 3), indicating whether the first, second or third dot was now the target for response. Subjects selected this dot's location from memory and used a joystick to move a cursor to its exact location. In control trials, an 'X' appeared on the screen at a random location and remained there while subjects moved the cursor to this location. All trials included similar visual stimuli, maintenance of these stimuli in working memory and use of the joystick to move the cursor. They differed in that subjects either selected one item from memory (a dot's location according to temporal order), or moved to an externally specified location. An intertrial rest period of ~12 seconds served as baseline.

One hundred trials (half selection, half control) were scanned per subject, with equal representation of all lengths of memory delay in pseudo-random order. The subjects lay supine in the scanner with the head fixed by firm foam pads. Visual stimuli were projected onto a screen mounted on the head coil, the 640 x 480 pixel display covering ~25° of central vision. The dots' diameter was 50 pixels. Stimulus presentation and response recording were controlled by Apple Macintosh 7600 computers operating Cognitive Interface software (Cogent, Wellcome Department of Cognitive Neurology, London).

The subjects' responses were recorded as distance from the final cursor position and either the 'X' target in control trials or the target dot location in selection trials. Response accuracy was analysed using Microsoft Excel.

Functional imaging data acquisition

The functional images were acquired by T2*-weighted echo planar magnetic resonance imaging at 2T, TR 4500 ms, TE 40 ms, over 45 minutes continuous whole brain imaging (64x64x48 voxels, 3mm isotropic resolution). The first five images were discarded to permit steady state magnetisation. Statistical Parametric Mapping software was used for image processing and analysis (SPM99, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/). The images were realigned to the mean image by rigid body transformation, and transformed to normal anatomic space (Talairach and Tournoux, 1988), using the Montreal Neurological Institute template, by linear and non-linear transformations (Friston *et al.*, 1995b). The data were spatially smoothed with a Gaussian kernel of full width half maximum 6mm High-resolution structural T1-weighted MPRAGE images were also acquired on all subjects to permit anatomical localisation of activation foci.

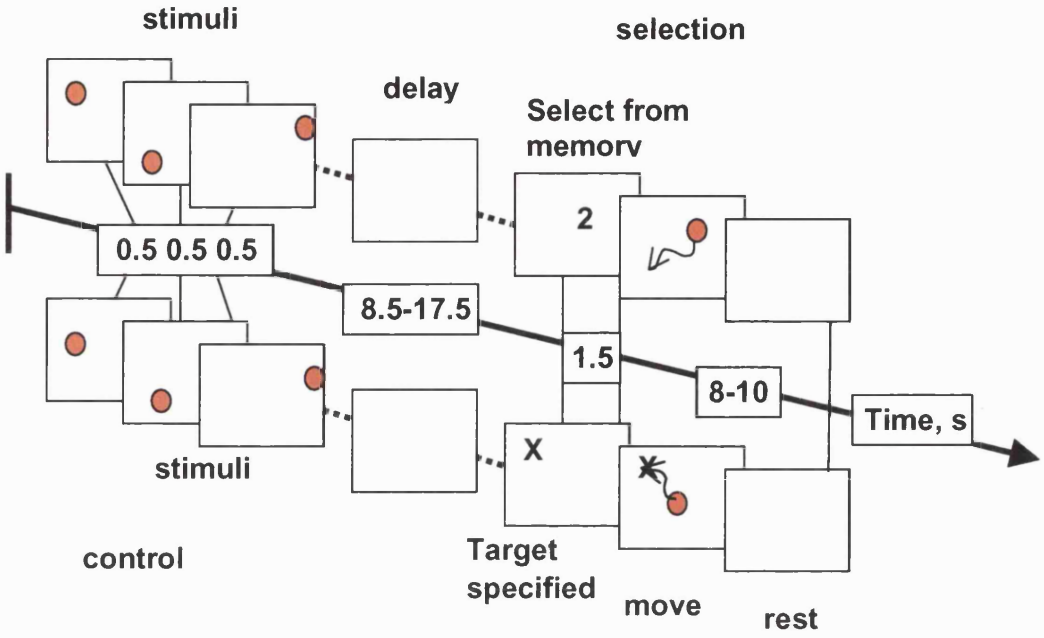


Figure 5.1. A schematic representation of the task. In all trials, the subjects saw three red dots presented sequentially for 0.5 s each on a screen in front of them, in random locations (solid circles). There followed a delay of 8.5 to 17.5 s (in steps of 1 s, randomly ordered) during which the subjects remembered the exact location of the dots and their temporal order. In selection trials, a number 1, 2,or 3 then appeared for 1.5 s centrally. This indicated whether the first, second or third dot now became the target for response, without specifying the location. The number was then replaced by a central cursor identical in appearance to the red dots. The subjects moved the cursor to the remembered target location using a joystick. After the response, the trial ended and was followed by a rest period of 8-12 s. For control trials the working memory period was identical to selection trials, but the target for the cursor response was indicated by a cross, and subjects did not select the location for response from memory

Functional imaging analysis 1

A general linear model was applied to the functional data (Friston *et al.*, 1995a; Friston *et al.*, 1996). This included covariates for stimulus presentation, the use of the joystick in all trials and the selection from memory at the end of memory trials, each modelled as discrete events convolved by a canonical haemodynamic response function. The maintenance periods were modelled by a covariate of variable length boxcars, again convolved by a canonical haemodynamic response. Six motion parameters derived from the realignment pre-processing were also included to correct for residual movement artefacts. For each subject, low frequency drifts in BOLD signal were corrected by a high pass filter with a cut-off of 300 seconds. The data were temporally smoothed with a filter derived from the canonical haemodynamic response function.

Voxelwise parameter estimates and variance were derived for each covariate across all subjects in a fixed effects model. Regions of activation were identified from specific contrasts between two covariates e.g. maintenance vs baseline, and the main effect of a given covariate e.g. selection vs (implicit) baseline. Voxels were identified for which $p<0.05$, corrected for whole brain multiple comparisons ($t>4.91$). These voxels are displayed as SPM{t}s.

We also performed a conjunction analysis across all six subjects for each contrast to the same threshold (Price and Friston, 1997; Price *et al.*, 1997). This confirmed that all subjects exhibited a particular effect in activated regions. The activations may therefore also be considered typical of the population from which our subjects were drawn (Friston *et al.*, 1999c).

In the middle frontal gyrus the threshold was lowered to $p<0.001$ (uncorrected for multiple comparisons, $t>3.10$) for the contrast of maintenance vs baseline, in case the initial negative result was due to an insufficiency of statistical power. More specific region of interest analyses were also performed. First, within a spherical region 2 cm diameter, centred on the peak voxel in area 46 in the first study (an anatomical regions of interest). Second, within the region of middle frontal gyrus activated in association with selection in the current study (a functional region of interest).

The adjusted data (adjusted for low frequency drift, and mean corrected for each subject) were temporally realigned to the onset of selection trials, and averaged across all subjects. The mean activation during and after selection trials was plotted against time for each length of delay period, for peak voxels in the prefrontal and parietal cortex. Because the trial onsets were jittered with respect to volume acquisition, the activation over time was linearly interpolated to the nearest volume. The resulting 3-D plots show the activation changes throughout maintenance and following the selection event. These plots are descriptive only: the significance of the task components' contributions to the activation of these voxels is given by the SPM{t}s, and no secondary statistics were applied.

Functional imaging analysis 2

An alternative approach would be to consider directly the difference between activation at the end of memory trials and activation at the end of control trials. For each trial type, these activations will include those arising from the visuomotor aspects of the joystick control, but the difference would be attributable to selection from memory. To determine this differential activation requires a different general

linear model. Analysis 2 therefore included a single end-of-trial covariate for all memory trials, and a single covariate for the end of control trials. The ends of trials were modelled by stick functions, again convolved by the canonical haemodynamic response function. The analysis parameters were otherwise the same as analysis1.

Results

Behavioural results

The subjects' responses were less accurate when based on remembered locations, as shown in figure 5.2. The distribution of errors on selection trials had a mean error of 59 pixels (SE 4), and a median of 42 pixels (interquartile range 26 – 66). The distribution of errors on control trials had a mean of error 20 (SE 4), and a median of 5 pixels (interquartile range 3.6 – 8.6). Using the same arbitrary cut-off definition of 100 pixels, 89 % of selection trials were 'correct'; this compares with 95 % in the first experiment. As in chapter 4, the distribution of errors was unimodal, suggesting that errors were predominantly poor localisations of the correct target, rather than accurate direction of the cursor to alternative dots' locations.

Functional imaging results: analysis1

The regions of brain activation associated with sustained maintenance of items in memory differed from those associated with transient selection of an item from within memory. Surface renderings of the SPM{t}s for maintenance and/or selection in memory are shown in figure 5.3 to illustrate the distinction between regions of activation associated with maintenance (green) and selection (red). Areas of overlap appear in yellow. Regions activated in association with maintenance and/or selection are given in table 1.

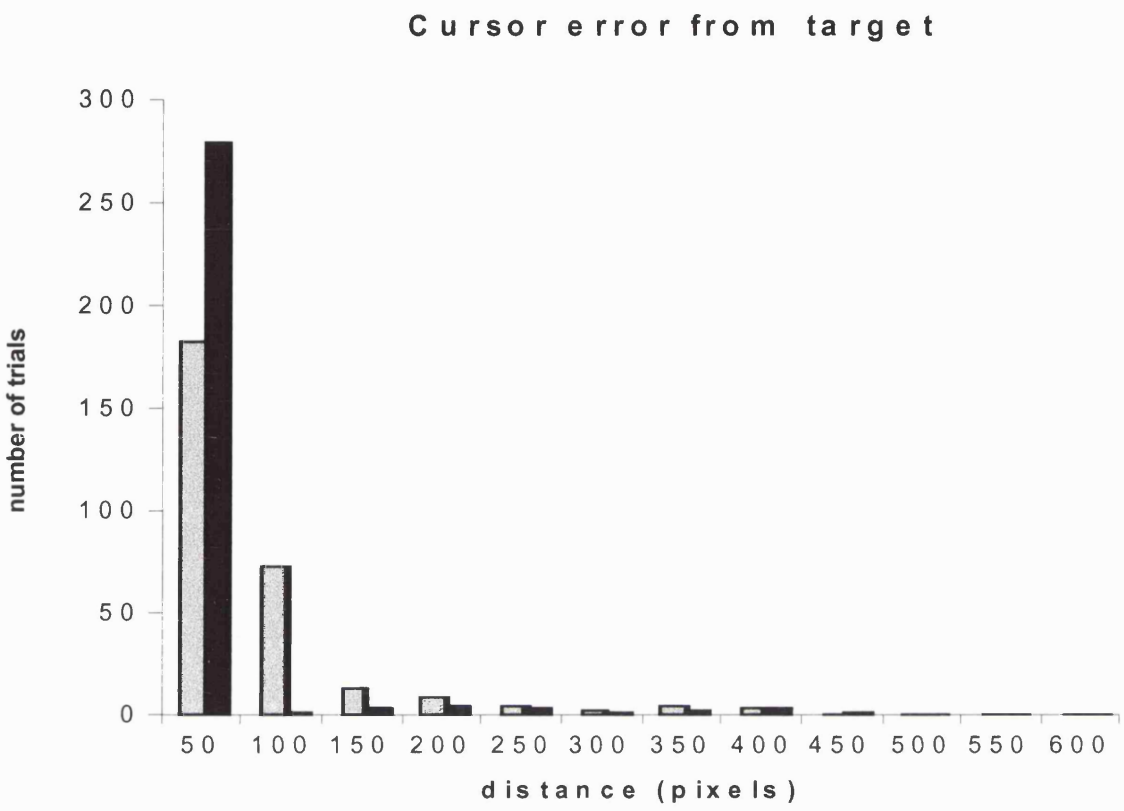


Figure 5.2. The distance between the correct target location and the position of the cursor. For selection trials (grey bars) the target was the location of that dot which was specified by the probe number at the end of the trial. For control trials (black bars) the target was the centre of the probe cross (see figure 5.1).

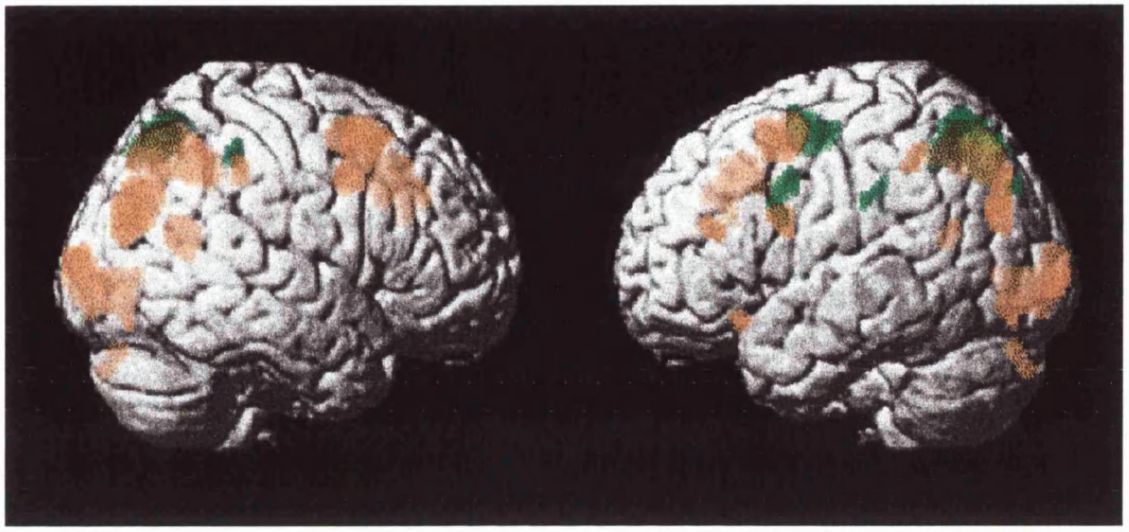


Figure 5.3. Regions of significant activation associated with response selection (red) and the memory (vs non-memory delays) (green). Statistical parametric images, SPM{t}($p<0.05$), have been overlaid on a surface rendering of a single subject representative MRI brain in normal anatomic space. The white lines indicate the planes of coronal sections of images in figures 5.4 and 5.5.

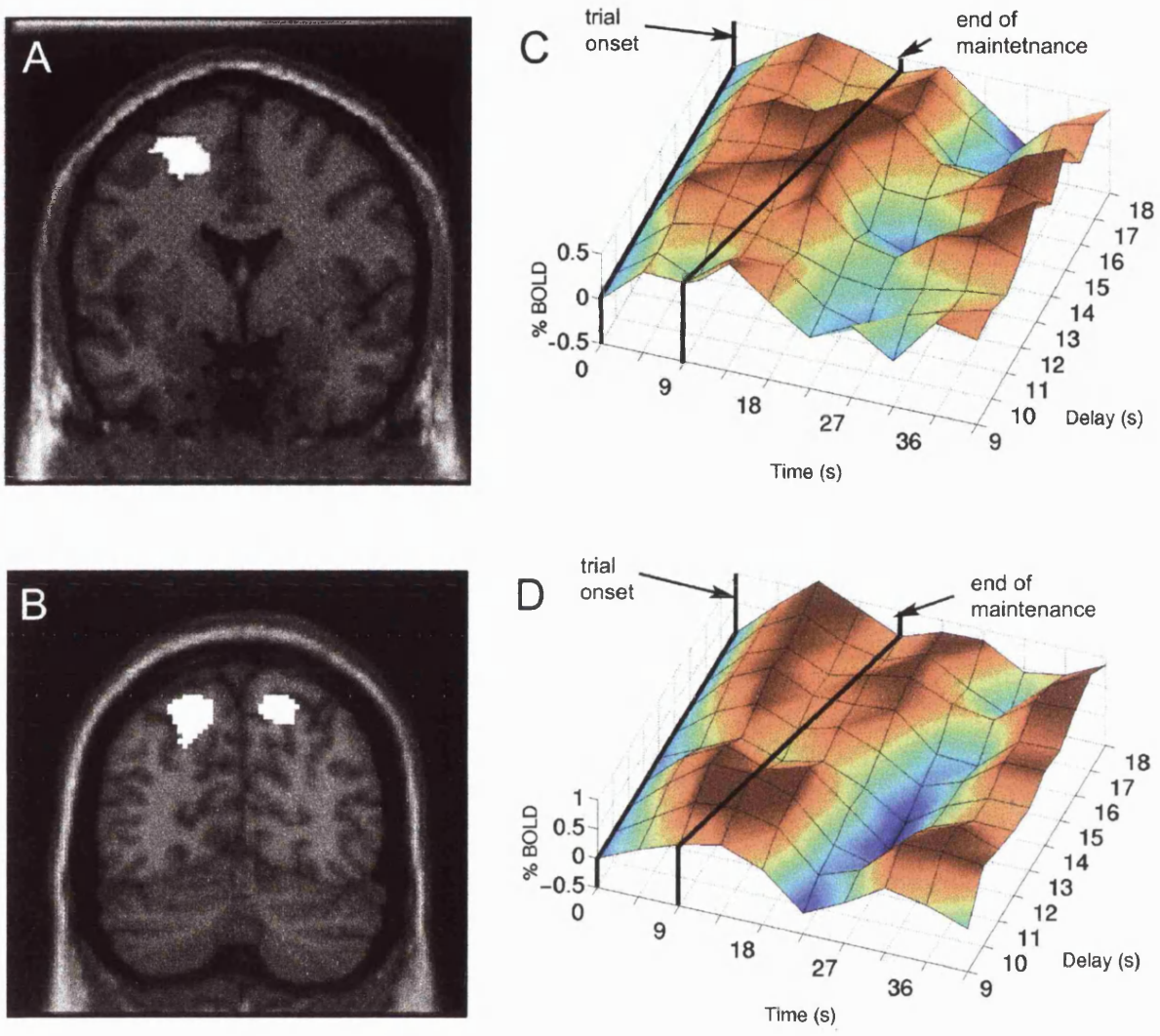


Figure 5.4. Areas of significant activation ($p<0.05$) during working memory delay versus baseline, shown on coronal slices through (A) area 8 (18,0,56) and (B) intraparietal cortex (20,-64, 56). The adjusted data from the activation peaks in (C) area 8 and (D) intraparietal cortex have been temporally realigned to the onset of working memory trials, and are shown as changes in BOLD signal (z) over time (x) for each delay length of working memory (y). The thick black lines indicate the onset of trials and offset of the working memory delays. The colour scale indicates the relative change in BOLD signal from the start of each trial. The plots demonstrate the sustained activity over the length of the working memory delay.

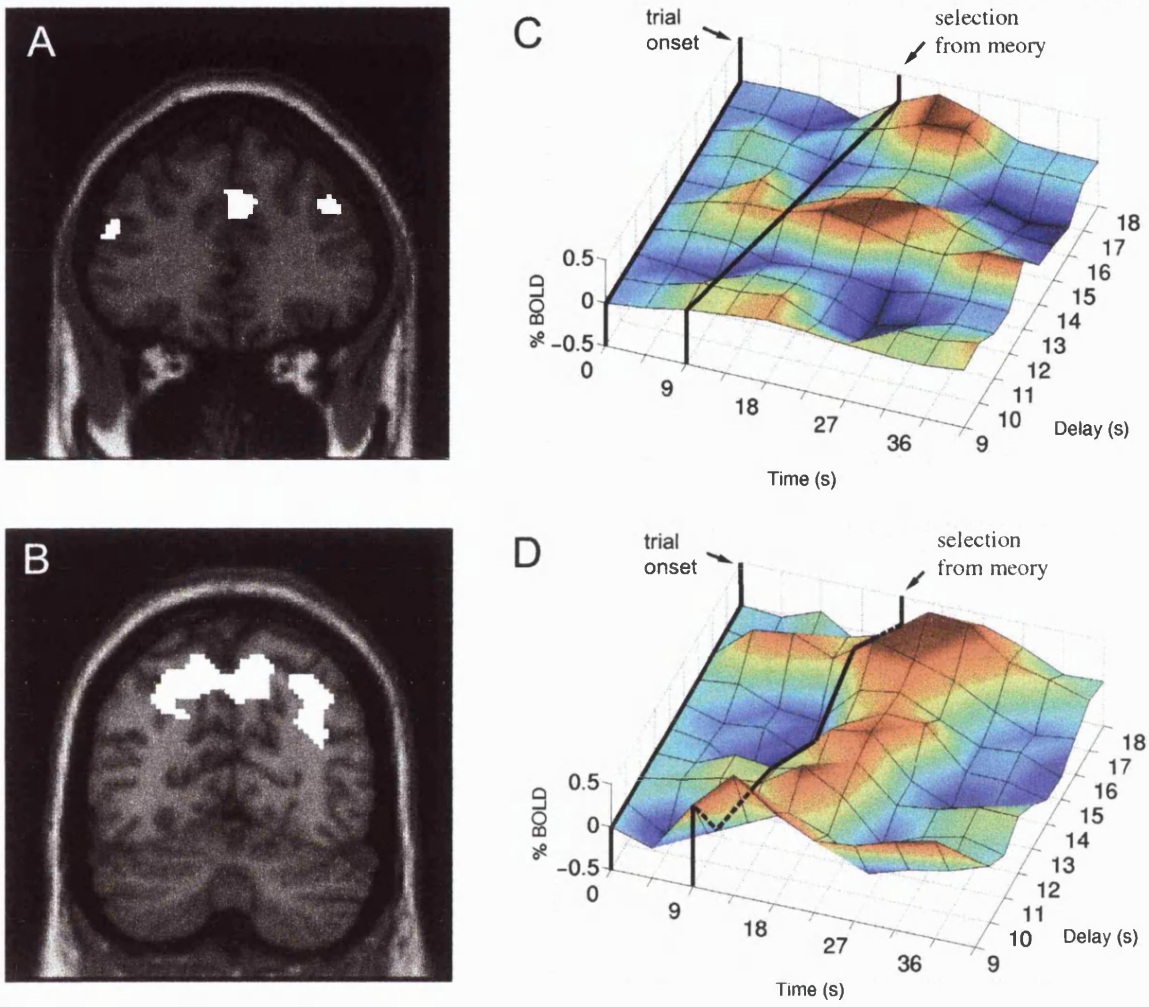


Figure 5.5. Areas of significant activation ($p<0.05$) for main effect of selection from memory, shown on coronal slices through (A) prefrontal area 46 (48, 32, 30) and (B) parietal cortex (4, -66, 44). The adjusted data from the activation peaks in (C) prefrontal area 46 and (D) medial parietal cortex have been temporally realigned to the onset of selection trials, and are shown as changes in BOLD signal (z) over time (x) for each delay length of working memory (y). The thick black lines indicate the onset of trials and the time of selection from memory and the end of the maintenance period. The colour scale indicates the relative change in BOLD signal from the start of each trial. In both areas, there is no consistent activation during the working memory interval, but a peak of activation following selection of the item at then end of the memory period.

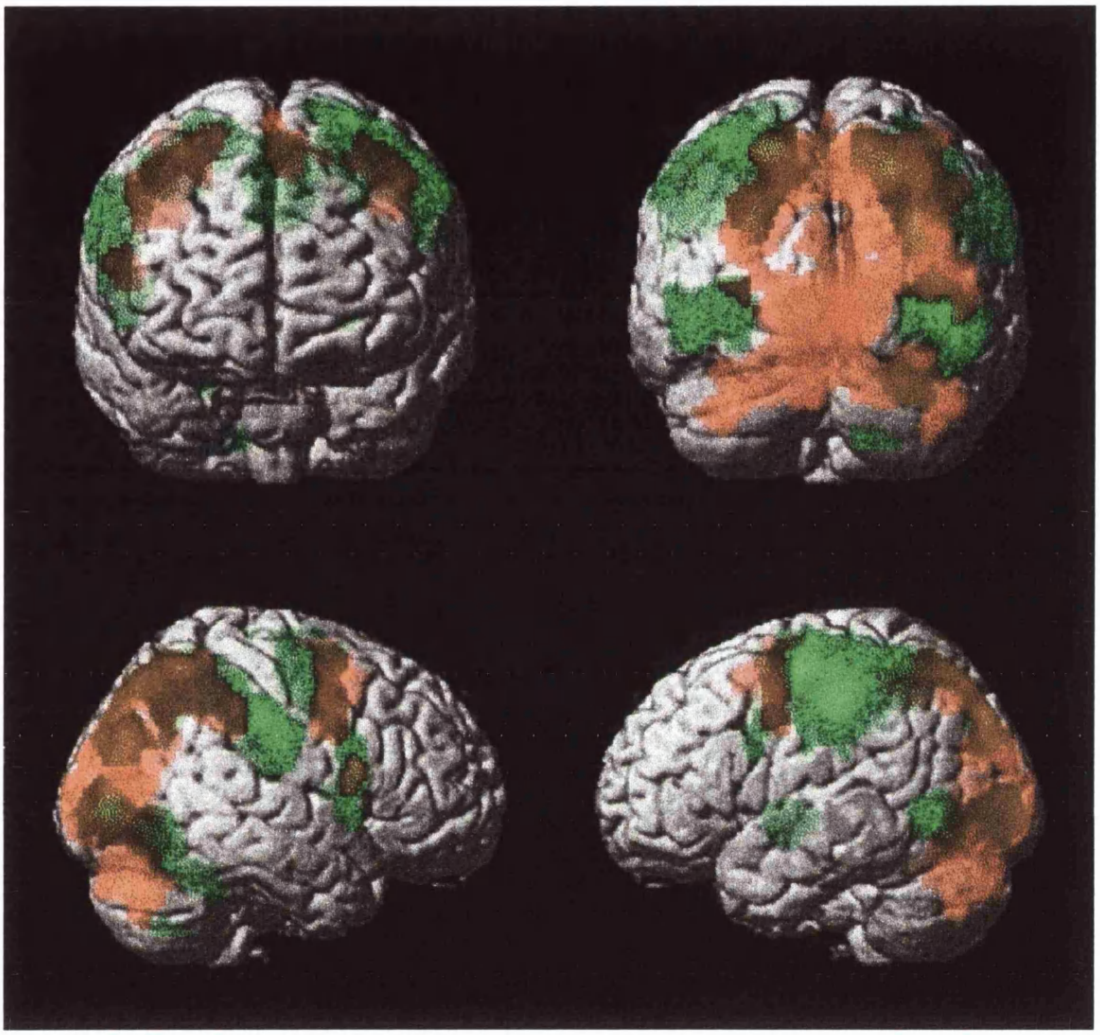


Figure 5.6. Regions of significant activation associated with stimulus presentation (red) and the use of the joystick (green). Statistical parametric images, SPM{t}($p<0.05$), have been overlaid on a surface rendering of a single subject representative MRI brain in normal anatomic space, projected in anterior, posterior and lateral elevations.

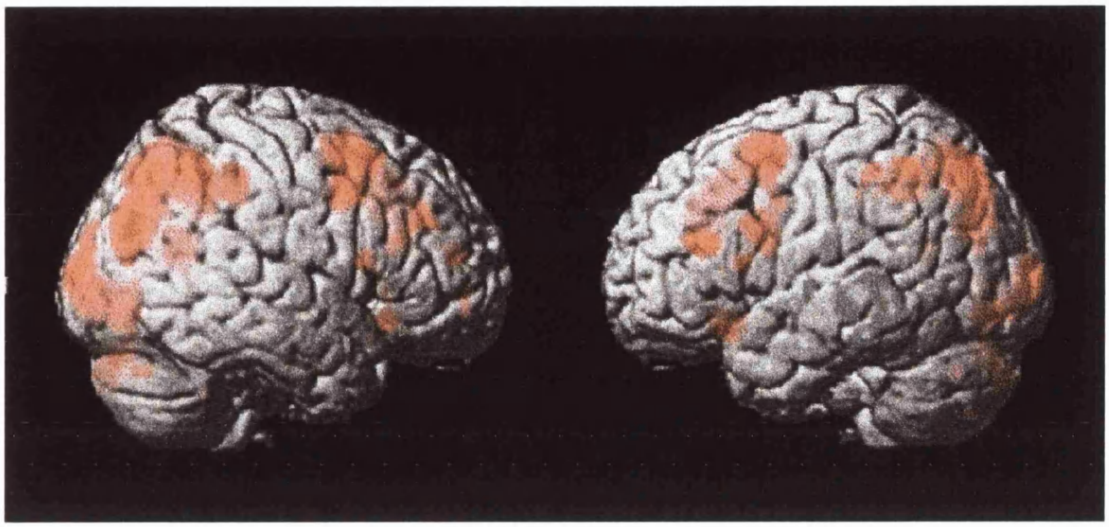


Figure 5.7. Regions of significant activation associated with response selection in analysis 2. Response selection here is defined by the difference between the transient events (stimulus presentation, selection, joystick response) at the end of selection trials and control trials. The statistical parametric map, SPM{t}($p<0.05$), has been overlaid on a surface rendering of a single subject representative MRI brain in normal anatomic space. Note the similarity to response selection in figure 5.3 (red)

The maintenance of spatio-temporal information was associated with bilateral activation of area 8 in the posterior part of superior frontal sulcus, and in the intraparietal cortex. There was also activation in the left precentral gyrus, within 5 mm of the area reported by Luna et al (1998) as the frontal eye field. Figures 5.4a-b show coronal sections through the statistical parametric map for the contrast of memory delay versus baseline. They show the location of the prefrontal and parietal activations.

The time plots of the adjusted data are given in figure 5.4c-d. The time course for short delays are plotted on the near side of the graph, and longer delays are plotted further back. The heavy black line indicates the presentation of the response cue. The data illustrate the fact that there is sustained activation in these areas throughout the maintenance period, seen as a plateau with a length that is proportional to the length of the delay period.

When contrasted with baseline, the selection of a location in memory according to the temporal position was associated with activation in middle frontal gyrus. Activation was also seen in ventral lateral prefrontal, orbitofrontal, anterior paracingulate, intraparietal and prestriate cortex. Selection related activations were bilateral, both anteriorly in area 46, and in an intermediate area defined as area 9/46 by Pandya and Petrides (1999). Figures 5.5a-b are coronal sections through the statistical parametric map for the contrast of selection versus baseline. They show the locations of activations in prefrontal and parietal cortex.

The time course of activations for the peak voxels in area 46 and medial parietal cortex are shown in figure 5.5c-d. A peak of activation can be seen shortly

after the response cue, no matter how long the delay. The peak is offset by a few seconds, because of the gradual rise in the BOLD response to neuronal activity.

This figure also shows that there was no consistent activation during the maintenance period. The data are noisy: during some delays, the BOLD signal is above baseline; in trials of other delay length, the activity at the same point is below baseline. The trials are indistinguishable to subjects during the delay period. Therefore, these differences between trials of different length can only represent fMRI noise. The SPM analyses confirm that there is no significant delay related activity. This was true even when the threshold was reduce to $p<0.001$ (uncorrected), or for $p<0.05$ (corrected) within the region of interest analyses.

Distinct patterns of significant activation on thresholded statistical parametric maps suggest, but do not prove, a functional dissociation between two regions. To further characterise the functional difference between areas 8 and 46 of the prefrontal cortex, data were extracted from the peak voxels of these areas bilaterally (see table 1), and entered into a new general linear model. The model now included region (8/46) and laterality (left/right) as factors, in addition to the experimental covariates as above, with the error term pooled across regions. The t-statistics for condition by region interactions were calculated for maintenance and selection related activations (degrees of freedom were reduced to the number of scans, to correct for potential covariance of residual error between regions). There were bilateral inter-regional differences in maintenance related activation, greater on the left side (region by laterality interaction for maintenance $t=2.77$, $p<0.01$, left simple main effect of region $t=6.67$, $p<0.0001$, right simple main effect of region, $t=4.06$, $p<0.0001$). Inter-regional differences in selection related activation were also predominantly left sided (region

by laterality interaction for selection t=3.18, p<0.001, left simple main effect of region t=2.68, p<0.01, right simple main effect of region t=1.82, ns).

Regions activated in association with visual stimulation and use of the joystick are listed in table 2. Neither stimulus presentation nor the use of a joystick to move the cursor was associated with activation of the dorsal prefrontal cortex, as shown in figure 5.6. Post hoc contrasts of selection vs presentation of the initial stimuli showed greater activation in striate cortex (coordinate 14, -92, 0, t=7.45, P<0.05 corrected for multiple comparisons) prestriate cortex (coordinate 20, -56, 18, t=9.49, P<0.05) and medial parietal cortex (coordinate -2,-58,48, t=6.85, P<0.05).

Functional imaging results: analysis 2

The regional differential activation associated with selection in analysis 2 is very similar to the main effects of selection in analysis 1. It is illustrated in figure 5.7. In analysis 2, the activations associated with selection were identified by the contrast of selection and joystick response in selection trials, and the use of the joystick in control trials. Again, significant activations were identified bilaterally in PFd (area 46, on the middle frontal gyrus), PFv (areas 45 and 47 on the inferior frontal gyrus) and the cingulate cortex.

Discussion

There was again a clear dissociation between regions activated during the maintenance of spatio-temporal information in working memory, and those areas activated when subjects select one of these locations on the basis of its temporal position. The maintenance was associated with activation of prefrontal area 8 together

with the intra-parietal cortex. In contrast, the selection between the remembered locations to guide a response was associated with activation of prefrontal area 46.

Activity related to maintenance

In the current study, maintenance was not associated with significant activation of PFd, yet delay related activity in areas 9 and 46 has been reported previously during delay periods in event-related studies of spatial (Postle and D'Esposito, 1999), visual (Courtney *et al.*, 1997)] and verbal (Courtney *et al.*, 1997; D'Esposito *et al.*, 2000b; Postle and D'Esposito, 1999; Rypma and D'Esposito, 1999; Rypma and D'Esposito, 2000) working memory. None of these studies required the subjects to manipulate the items in memory. There are several differences that may account for the activations seen in these studies but not the current or previous chapter.

There may be executive processes engaged during the delay periods in addition to maintenance. For example, Courtney et al (1997) reported delay-related activation in area 46 during working memory for faces. However, their subjects were instructed to *rehearse* the appearance of the stimuli during the delay periods, keeping the image in mind. Active rehearsal, or voluntarily focussing awareness on an imagined image, may make demands on the executive process of attentional selection. In our study no such instruction was given.

There may be different regions of the prefrontal cortex active during memory for different types of material. For example, event-related fMRI studies have confirmed that memory for verbal material can be associated with activation of the dorsal prefrontal cortex (D'Esposito *et al.*, 1999a). However, one problem with verbal material is that subjects may reorganise the material, by chunking it.

Another possibility is that maintenance for spatial items is associated with activity in areas 8 and 9/46, whereas maintenance for non-spatial material is associated with more anterior activations. This could either be due to domain specificity (Levy and Goldman-Rakic, 2000), or due to the different cognitive processes usually associated with different material types.

The current task may also have been too easy. Difficulty may increase with the number of stimuli, the quality of stimuli, and the duration of delay. Rypma and D'Esposito (1999) compared six letter maintenance over long delays with two letter maintenance. The higher load was associated with greater activation of the prefrontal cortex during encoding of stimuli, but not during the delay period (Rypma and D'Esposito, 1999). However, behavioural data in this and our previous study suggest that the subjects did find the memory conditions difficult. Accuracy was lower when spatial and temporal information was remembered (current study: 89 %) than when just spatial information was required (previous study: 95 %).

One cannot claim that there is no maintenance-related activation in area 46 at all. The current method may not have been sufficiently, despite looking at reduced thresholds or within regions of interest. Nevertheless, even if there is weak activation here during delay, the results indicate that activation in area 46 is dominated by selection rather than maintenance.

Finally, previous region of interest analyses did not always distinguish areas 46, 9/46 and 9. Important functional differences exist between these areas. In monkeys, the critical region for delayed response accuracy is the area 46 in middle third of the sulcus principalis (Butters *et al.*, 1971). Many electrophysiological studies report activity in sulcus principalis during the delay (Funahashi *et al.*, 1989; Fuster

and Alexander, 1971; Niki, 1974) but most of the recordings were taken from the posterior third of this sulcus and the convexity of area 8 (Chafee and Goldman-Rakic, 1998; Funahashi *et al.*, 1989; Sawaguchi and Yamane, 1999a). Even here, many cells fire during a delay when the cues are present throughout and there is no memory demand (Kojima and Goldman-Rakic, 1984). In two studies (Funahashi *et al.*, 1993; Sawaguchi and Yamane, 1999a) the design allowed detection of activity that was specifically related to the *maintenance* of spatial items in memory not response preparation, and again the task responsive cells lay posteriorly.

Two areas in posterior frontal cortex were activated. One lies near the superior frontal sulcus, corresponding to area 8. This is anterior to the frontal eye fields (Anderson *et al.*, 1994; Luna *et al.*, 1998; Petit *et al.*, 1997; Sweeney *et al.*, 1996) as did the region activated during working memory reported by Courtney *et al.* (1998). The second lies within 5 mm of the area identified as the ventral frontal eye field by Luna et al (1998). There is similar activation in area 8 and intraparietal cortex during covert spatial attention (Corbetta, 1998; Coull and Nobre, 1998; Gitelman *et al.*, 1999; Nobre *et al.*, 2000). The mechanism for maintenance in spatial working memory may be related to the mechanism for maintaining covert spatial attention (LaBar *et al.*, 1999).

Activity related to selection

Activity related to selection was found in the middle frontal gyrus (areas 46 and 9/46), inferior frontal gyrus and anterior paracingulate cortex. The design of our experiment does not allow one to distinguish whether selection occurs through enhancing the representation of selected items or inhibition of representations of other items. These two processes coexist in many complex cognitive tasks when there are

multiple processes, or competing responses or representations (Smith and Jonides, 1999). They may be inherently linked within local neural networks (Cohen and Servan-Schreiber, 1992; Desimone and Duncan, 1995).

The dorsolateral prefrontal cortex and anterior cingulate cortex are commonly both activated during tasks requiring executive processes dependent on selection, attention and inhibition. Hierarchical models have been proposed in which the anterior cingulate controls the allocation of attentional resources by lateral prefrontal cortex, by direct or modulatory inputs (Botvinick *et al.*, 1999; Carter *et al.*, 1999; Cohen *et al.*, 2000; Cohen and Servan-Schreiber, 1992). However, more complex reciprocal interactions between anterior cingulate and lateral prefrontal cortex are apparent from a recent study of patients with prefrontal lesions (Gehring and Knight, 2000). This study cannot directly distinguish the roles of the cingulate cortex and PFd.

In the task used in the previous experiment, the spatial relationship between cue (line) and target (dot location) may have aided the selection of that dot's exact location. In the present study, only the arbitrary ordinate cue distinguishes correct from incorrect locations. It could be argued that this produces greater conflict between the three possible responses, and may account for significant paracingulate activation in the present study but not the previous one. MacDonald et al (2000) have recently shown that at the time of response selection the activity of the anterior cingulate, but not dorsal prefrontal cortex, increased with greater response conflict.

Activation of the inferior frontal gyrus has been reported during spatial and non-spatial working memory (Cohen *et al.*, 1997; D'Esposito *et al.*, 1998; D'Esposito and Postle, 1999; D'Esposito *et al.*, 1999a; Jonides *et al.*, 1998a; Jonides *et al.*, 1993; Owen *et al.*, 1996b; Owen *et al.*, 1999; Postle *et al.*, 2000b; Smith and Jonides, 1998;

Smith *et al.*, 1998). It has also been reported in tasks requiring selection amongst alternatives (Thompson-Schill *et al.*, 1997; Thompson-Schill *et al.*, 1998). The current results suggest that selection related activity of ventral frontal cortex is not confined to the semantic attributes of information in working memory, but is a generalised process. Lesions of ventrolateral prefrontal cortex in monkeys impair selection of contextually appropriate responses (Passingham, 1993). In patients, lesions impair performance on tasks that require selection amongst many possible alternative responses (Thompson-Schill *et al.*, 1998). Two studies have failed to report activation in the ventrolateral frontal cortex during performance of the n-back task. In one, it was activated in some subjects but not others (D'Esposito *et al.*, 1998). In the other study it was equally active in a spatial span condition, but this also required serial response selection (Owen *et al.*, 1999).

In contrast with area 46, the superior frontal sulcus (area 8) did not appear to be significantly activated in association with selection. When areas 46 and 8 were directly compared, bilaterally, they differed in both maintenance-related activation and selection related activation. These differences were greater in the left hemisphere.

However, it is possible that prolonged neuronal activity during delay may reduce the neurovascular response to subsequent transient selection related neuronal activity in the same area. A negative interaction between successive events' BOLD responses has been described for repeated sensory stimuli (Friston *et al.*, 1998), and may apply to BOLD responses in the same area for different event types. If one region (e.g. area 8) was highly active during delay periods, this could exaggerate inter-regional differences in selection related activation, seen in thresholded SPMs

and the direct comparison of inter-regional activation. Inter-regional differences in maintenance related activity would be unaffected.

There was also activation related to selection in the parietal cortex and prestriate cortex. Enhanced activity has been demonstrated in these areas when specific visual features are attended rather than passively viewed (Brefczynski and DeYoe, 1999) and during mental imagery (D'Esposito *et al.*, 1997; Fletcher *et al.*, 1995). When prompted to select an item from memory, our subjects may first have imagined the stimuli as they had appeared, and from this mental image then selected the appropriate item. Neither the current nor previous study can distinguish activations in these areas that are related to the generation of visual imagery from activations due to attention to specific items within such an image.

Attentional selection

Activation of area 46 in complex working memory tasks can be attributed to attentional rather than mnemonic components of the tasks. In the n-back task for example, subjects must remember a series of spatial locations and each location must be 'tagged' or 'coded' according to its position in the sequence. In addition, there are multiple selection processes related to the updating of the list of recent items, and selecting the appropriate response to each new item. Our results suggest that it may be these selection processes, not the spatial memory nor temporal coding that accounts for the activation of area 46 reported in spatial n-back tasks.

Activation in area 46 was associated with the selection *between* remembered locations according to their temporal order. Selection involves the focussing of awareness on one particular remembered stimulus at the expense of others, and that it is this feature that is common to all tasks in which subjects must 'monitor' or

'manipulate' items in memory. Indeed, definitions of monitoring have stated that attended items are 'considered in relation to the others' (Petrides, 1996).

The voluntary focusing of attention on relevant stimuli, thoughts or actions is one possible core process underlying executive functions, and has been termed 'attentional selection' (Miller, 1999). This process characterises area 46 within prefrontal cortex, in contrast to passive maintenance of information in other prefrontal and parietal areas. It is central to tasks of monitoring, manipulation or free selection, but also occurs in other tasks that include *active* rehearsal of visual or verbal material.

Alternatively, the activation of prefrontal area 46 in the current study could be due to the retrieval of memories of *all* the original stimuli, rather than the selection *between* these remembered stimuli. Ferrera et al (1998) showed that patients with lesions of PFd succeeded in a working memory task when memory was tested by recognition. However, the patients were impaired when memory was tested by retrieval.

Retrieval of the remembered locations of the original stimuli may occur by reactivation of neuronal representations in temporal, parietal or occipital cortex. Reactivation of neuronal representations in temporal cortex has been demonstrated in the temporal lobe (Tomita *et al.*, 1999). Tomita et al (1999) have shown that this reactivation was due to top-down modulatory inputs from the ipselateral prefrontal cortex. It could be argued that modulatory influences from the prefrontal cortex may apply to retrieval of representations of all the initial stimuli (reactivation). The present study cannot distinguish activations associated with the retrieval of all the items from those associated with selection between them.

Summary

Activation in area 46 is dominated by the selection of a target of a response (location), whether based on a probe stimulus that bisected the target (chapter 4) or the temporal order of stimuli (current study). Selection between remembered items is inherent in manipulation and monitoring paradigms, also associated with activation of area 46. In contrast, 'passive' maintenance of spatial and temporal information is associated with activation of more posterior areas, including area 8 and parietal cortex.

Table 5.1. Areas of significant activation associated with maintenance and response selection.

Region	laterality	coordinate			T statistic
Working memory maintenance (vs baseline)					
Superior frontal sulcus (area 8)	right	28	8	60	5.02**
	left	-18,	0,	56	6.42
Intra-parietal cortex	right	20,	-64,	56	10.3
	left	-18,	-70,	54	16.1
Precentral gyrus (FEF)	left	-52	4	38	7.20
Selection from memory					
Middle frontal gyrus (46)	right	42	38	30	6.28
	left	-48	32	18	7.08
(area 9/46)	right	30	10	54	10.5
	left	-24	10	50	7.72
Inferior frontal gyrus	right	48	14	12	5.97**
	Left	-40	8	24	8.24
Orbitofrontal PFC	left	-32	24	-13	6.46
	Right	34	24	-12	5.15**
Paracingulate cortex	bilateral	2	24	42	9.32
Medial parietal (precuneus)	right	4	-66	44	9.01
	left	-10	-70	54	8.85
Inferior parietal cortex	right	48	-36	42	7.34
Prestriate cortex	right	16	–94	2	9.30
	left	-10	-100	0	9.03

** No voxels in this cluster survive conjunction analysis across all 6 subjects ($p<0.05$ corrected).

Table 5.2. Areas of significant activation associated with stimulus presentation and use of the joystick.

Region	laterality	coordinate			T statistic
Stimulus presentation					
Striate cortex	left/right	4	-82	0	17.2
Prestriate cortex	left	-20	-92	30	9.8
	right	36	-80	28	14.6
Medial parietal cortex	right	12	-62	58	11.7
Intraparietal cortex	right	30	-54	44	9.58
SMA	left	-4	4	58	8.44
PM/frontal eye fields	left	-42	0	48	8.83
	Right	42	2	34	9.08
Inferior frontal gyrus	right	58	12	16	7.48
Cerebellar hemispheres	left	-36	-72	-38	7.18
	Right	38	-74	-40	6.31
Cerebellum midline	--	-4	-76	-26	8.08
Use of the joystick					
Primary motor cortex	left	-36	-20	54	21.4
Premotor cortex	left	-38	-8	60	26.0
	Right	22	-6	56	8.97
Anterior cingulate	left	-4	-6	52	22.0
Post central gyrus	left	38	-38	48	17
Superior parietal cortex	left	-30	-50	58	18.1
	Left	-22	-60	58	15.8
	Right	22	-60	56	13.5
Prestriate	left	-38	-90	-6	7.80
	right	44	-86	-2	15.8
Inferior frontal gyrus	right	60	14	18	15.2
Putamen	left	-28	-6	-6	8.95
	Right	26	0	-8	7.22
Thalamus	left	-12	-22	2	6.14
Cerebellar hemisphere	Right	16	-64	-46	9.52
	Right	28	-48	-26	12.9

Chapter 6

Free selection of colour and action

Introduction

In chapters 4 and 5, it was suggested that the role of area 46 in working memory was primarily the selection of a remembered item amongst several alternatives. Elsewhere, it has been suggested that the key role of this area in working memory is monitoring or manipulation of items in working memory (D'Esposito *et al.*, 2000c; Petrides, 2000). These two hypotheses are not incompatible. Monitoring has been defined as an attentional process by Petrides (1995, 2000): attending to one stimulus in relation to others, over time. Manipulation or re-ordering of items in memory may also involve recurrent processes of selective attention to sub-sets of stimuli.

There are advantages to proposing a generalised function for the prefrontal cortex such as 'attentional selection' rather than memory specific terms such as monitoring or manipulation. **First**, it allows a parsimonious explanation of the role of prefrontal cortex in tasks that do not have a clear working memory component, but for which a response must be made in the absence of an external stimulus. For some tasks, interpretation in terms of monitoring and manipulation makes little sense. For example, tasks that require the free selection of a single response (Desmond *et al.*, 1998). **Second**, it is difficult to interpret tasks that monkeys can perform in terms of manipulation. Much of the literature characterising the role of the prefrontal cortex

has been based on monkey studies, and any hypothesis should accommodate the results and interpretation these studies. **Third**, a generic function like 'attentional selection' may also suggest a mechanism of the interaction of prefrontal cortex with other brain regions that can be tested experimentally. There is evidence of modulatory influences from prefrontal to visual association cortex, selecting neuronal activity that encodes specific objects (Tomita *et al.*, 1999).

It has been suggested that the function of prefrontal cortex can be characterised as 'attentional selection' of representations, whether of stimuli, actions or remembered items (Miller, 1999). If this is correct, then free selection of responses is attributed to the top-down bias of motor representations. The motor representations are proposed to be mediated by neurons outside the prefrontal cortex. Likely candidate regions include premotor cortex and supplementary motor areas (Rizzolatti *et al.*, 1998; Wise *et al.*, 1997).

This chapter tests two hypotheses. The first is that the prefrontal areas that are activated in association with the selection of responses should include area 46. This was the area activated in association with the selection among items in working memory (chapters 4 and 5). The second is that this area would be activated irrespective of whether the selection was between manual responses or visual items.

There is already evidence for prefrontal activation when subjects select responses other than manual movements. For example, there is prefrontal activation when subjects select between words: the greater the choice, the greater the prefrontal activation (Desmond *et al.*, 1998; Thompson-Schill *et al.*, 1997). Activation of area 46 has also been observed during random number generation (Jahanshahi *et al.*, 2000) and the randomness of subjects' responses is correlated with the activity of PFd.

There is also evidence that the prefrontal cortex is the source of top-down modulatory influences on auditory (Alho *et al.*, 1999) and visual (Brefczynski and DeYoe, 1999; Buchel and Friston, 1998) sensory cortex. Tomita et al (1999) recorded neuronal activity associated with a visual stimulus. They demonstrated that input from the prefrontal cortex was sufficient to cause stimulus specific neuronal activity in the inferotemporal cortex (Tomita *et al.*, 1999). If this is the case, then voluntary selective attention to sensory stimuli may also be associated with activation in the same regions of PFd.

To test the generalisation of attentional selection, from memory, to motor and sensory domains, fMRI was next used to measure the regional activation associated with free selection in both motor responses and sensory stimuli. The free selection of motor responses was compared with the execution of a response specified by the examiner. Finger responses on a keypad were used, using arrow cues. On externally cued trials, arrows indicated the appropriate finger. On free selection trials, the arrow pointed to a neural position.

For the sensory task, the visual stimuli included a coloured display, illustrated in figure 6.1. On externally specified trials, a colour specified the appropriate response. On free selection of colour trials, the subjects were asked to select one of the colours from a multicoloured display. On the basis of this chosen colour, they were to respond by pressing a button. The position of the button corresponded to the position of that colour on a separate part of the display. Over several trials there was no fixed relationship between the colour chosen and the finger that was to be moved.

The prediction was that selection of a colour in a multicolour display would activate the same regions of the prefrontal cortex as selection of an action from

several possible actions. These regions of the prefrontal cortex can be considered as the 'source' of the free selection. The cortical 'targets' of selection would be expected to differ: premotor cortex during the selection of action, and prestriate cortex during the selection of colour.

It is possible that the different colours were named, and the selection of colour then made from this 'mental list' of the colours. Selection from this list would still be expected to be associated with activation of the prefrontal cortex, like other tasks of word selection (Desmond *et al.*, 1998; Ojemann *et al.*, 1998; Phelps *et al.*, 1997; Warburton *et al.*, 1996). However, the target regions would be those associated with verbal representations, rather than colour sensitive prestriate cortex. Similarly, it is possible that the motor responses are selected on the basis of the spatial location of buttons, rather than the representations of action per se. In this case, the regions of selection related activity in prefrontal cortex would be similar, but the target regions would be those associated with spatial attention, in area 8 and the parietal cortex. (Awh and Jonides, 2001; Gitelman *et al.*, 1999).

Methods

Subjects

Twelve right handed volunteers participated in the study (aged 23-38 years, mean 30 years, seven men), after providing written informed consent. The subjects were recruited from a departmental register of volunteers. None had a history of neurological or psychiatric illness, and they took no regular medication.

Behavioural paradigm

The experiment used an epoch based 2x2 factorial design, plus rest periods. Each trial type was blocked for 26 seconds, with a brief written instruction cue at the start to indicate the task. Rest periods lasted 14 seconds. There were four formally similar trial types, illustrated by the schematic representations in figure 6.1. Trials were based either on finger movement selection, or colour selection. The finger movements and colours were either freely selected by the subject or specified by the trial cues.

(1) Externally specified action (EA): arrow was presented every 3 seconds (lasting 1.5s) in an instruction box in the top half of the screen, indicating one of four positions (9,11,1 and 3 o'clock) corresponding to the four fingers of the right hand. Four smaller boxes were also present below the instruction box, representing four lightly sprung buttons that could be pressed. The subjects used the specified finger to press the button.

(2) Free selection of action (FA): the arrow in the button box pointed to 12 o'clock. The subjects freely chose one of their four fingers and pressed the button. The subjects were asked to make a fresh choice on each trial, regardless of previous choices.

(3) Externally specified colour (EC): the instruction box was filled with a single colour (red, yellow, green or blue). The four response boxes were each filled with one of the colours, in a different order on each trial, and subjects pressed the button that matched the instruction colour.

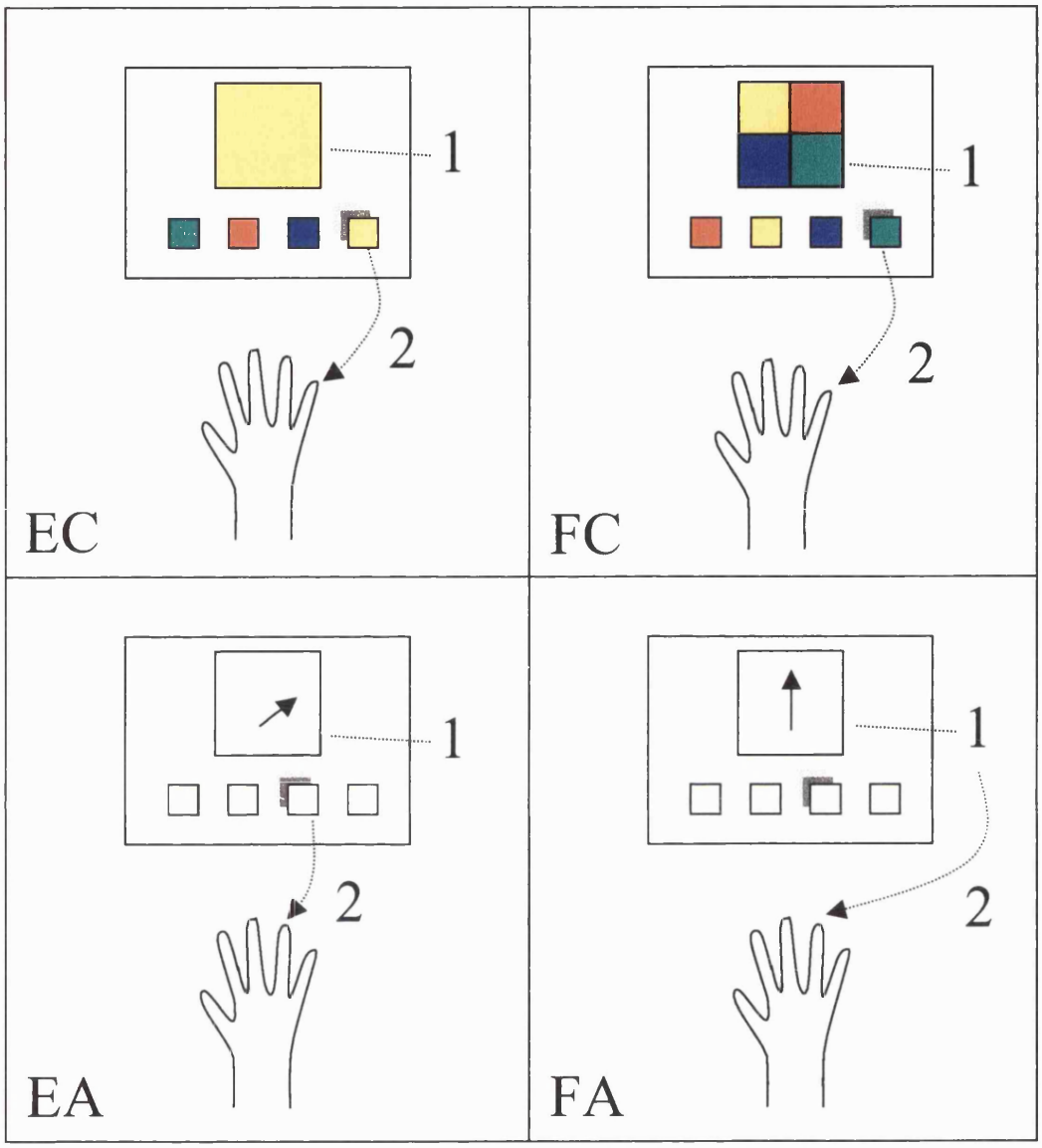


Figure 6.1. Schematic representation of the four tasks. In all conditions, a large cue box was presented above four small response boxes, each one corresponding to a finger of the right hand. In condition **EC** (externally specified colour), the cue box filled with one of four vivid colours, to indicate the necessary response (1). One of four coloured response boxes was also filled with this colour, and the subject pressed a button with the corresponding finger (2). In **FC** (freely selected colour), the cue box contained four colours, and the subject freely chose one of them (1). The subject then pressed the finger indicated by the response box of the chosen colour (2). In **EA** (externally specified action), an arrow in the cue box directly specified (1) the button press (2). In **FA** (freely selected action), the arrow pointed to a neutral location, and the subject freely chose which button to press (2). Cues and response boxes were presented for 1.5 seconds, separated by 1.5 seconds.

(4) Free selection of colour (FC): the instruction box contained all four colours, in different positions. The four response boxes were each filled with one of the colours, in a different order on each trial. The subjects were required to choose one of these four colours, then press the button represented by the response box of the chosen colour. Again the subjects were asked to make a fresh choice on each trial.

(5) rest periods were included between the trial epochs

The subjects were pre-trained on all tasks on the day of scanning. They were instructed to maintain their gaze in the top instruction box throughout the experiment, and infrared oculographic monitoring (ASL 5000 system) in four subjects confirmed that they could perform all tasks without making saccades to the responses boxes on the screen.

The mean reaction time for each subject in each of the four conditions was entered into a two-way repeated measures analysis of variance, with factors of selection (free vs externally specified) and modality (action vs colour), using SPSS8.0 for Windows.

Functional imaging

Subjects lay supine with their head fixed by firm foam pads. Task instructions, trial stimuli and the latency from stimulus to button press were controlled by Apple Macintosh 7600 computer operating Cognitive Interface software (Cogent, Wellcome Department of Cognitive Neurology, UK). The four lightly sprung buttons were mounted under the subjects' fingertips, on a moulded splint that supported a comfortable neutral hand-wrist position.

Functional imaging used T2*-weighted echo-planar MRI at 2-tesla, repeat time 3650 ms, echo time 40 ms, throughout 28 minutes continuous whole brain imaging (64x64x40 voxels, 3mm isotropic resolution). The first five images were discarded to allow steady state magnetisation. Statistical Parametric Mapping software was used for image processing and analysis (SPM99, http://www.fil.ion.ucl.ac.uk/spm). The images were realigned to the mean image by rigid body transformation, sinc interpolated in time to correct for phase shift during volume acquisition, and transformed to normal anatomic space (Talairach and Tournoux, 1988), using the Montreal Neurological Institute template, by non-linear transformations (Friston *et al.*, 1995b). For individual subject analyses, the data were spatially smoothed with a Gaussian kernel of full width half maximum 6 mm (FWHM) to allow valid statistical inference according to Gaussian random field theory (Friston *et al.*, 1995a). High-resolution T1-weighted images were acquired on all subjects.

Individual subject analysis (level 1)

A general linear model was applied voxel-wise to the functional data (Friston *et al.*, 1995a; Friston *et al.*, 1996), using box-car covariates for the epochs EA, FA, EC, FC, rest and a transient covariate for the task instructions. Individual trials were not modelled separately within each epoch. Residual motion effects were modelled by inclusion of the first temporal derivative of the realignment parameters, representing scan-to-scan movement. Effects of low frequency drifts in BOLD signal were removed by a high pass filter with a cut-off of 300 seconds, and the data were temporally smoothed using a canonical haemodynamic response function prior to parameter estimation.

Parameter estimates were derived for each covariate, and residual variance, in a subject specific fixed effects model. Contrast images of interest were calculated for each subject, including the main effect of action vs colour [(EA+FA)-(EC+FC)], colour vs action [(EC+FC)-(EA+FA)], free selection vs external specification [(FA+FC)-(EA+EC)], external specification vs free selection [(EA+EC)-(FA+FC)], the interactions between free selection and the modality [(EA+FC)-(EC+FA)] and [(EC+FA)-(EA+FC)]. The simple main effects of free selection vs external specification were calculated within each modality. The four active conditions were also each contrasted with rest: [EA-Rest], [EC-Rest], [FA-Rest], [FC-Rest].

Random effects analysis (level 2)

For each contrast, the twelve contrast images from level one were entered into a two-way one-sample t-test, to create a SPM{t}-statistic image, with 11 degrees of freedom. This two-stage random effects analysis enables the inference based on these contrasts to be extended to the general population from which the subjects were drawn (Friston *et al.*, 1999b).

To accommodate inter-subject anatomic variability, the contrast images were smoothed by a Gaussian kernel FWHM 8 mm. Sequential smoothing by multiple kernels is equivalent to a single smoothing step, when the single step uses a kernel of FWHM equal to the square root of the sum of squares of the FWHM of the multiple component kernels. In this case, the second level analysis is effectively using data smoothed by 10 mm ($10^2 = 6^2 + 8^2$).

Correction for multiple comparisons

All results are tabulated for the peak voxels in a cluster for which $p<0.05$, (corrected for multiple comparisons). Two types of correction were applied. **First**, for areas subject to *a priori* hypotheses, region-of-interest analyses were performed, correcting for multiple comparisons within the reduced search volumes ($p<0.05$). Regions of interest were defined by drawing on the mean structural images for the group, in standard anatomic space, using MRIcro software (http:\www.mrc-cbu.cam.ac.uk \imaging\chris.rorden.htm). The regions were (1) prefrontal cortex on the middle frontal gyrus and both superior and inferior frontal sulci, from y=20 to y=50, likely to include Brodmann's areas 9/46 and 46 (2) premotor cortex, on the dorsal lateral aspect of the precentral gyrus and precentral sulcus, contiguous anteriorly with the prefrontal cortex and posteriorly with (3) primary motor cortex including the anterior bank of the central sulcus, (4) intraparietal cortex and (5) the infero-lateral prestriate cortex, from y=-80 to y=-65 mm, likely to include V4. **Second**, results outside these regions are corrected for whole brain comparisons ($p<0.05$) are reported in the tables.

The figures are presented at the threshold $p = 0.001$ (uncorrected). This lower threshold was chosen to give a clearer overall impression of the pattern of regional activity, including regions outside the regions of interest. In addition, the tables present activations significant at $p<0.001$ (uncorrected) in brackets.

Results

Behavioural results

The mean (+SE) response latencies for each of the four conditions are shown in figure 6.2. There was no overall effect of modality (main effect of modality: F=0.8, df 1,11, n.s.), but there were a significantly longer intervals when responses were freely selected (main effect of free vs external: F=27, df 1,11, $p<0.001$). This effect was greater on colour based trials (interaction between free selection and modality: F= 15, df 1,11, $p<0.01$). *Post hoc* comparison of response latencies between FA and FC conditions confirmed a significant difference ($t=2.74$, $df=11$, $p<0.05$).

Imaging

The tasks shared many sensory, motor and cognitive components, and this is reflected in multiple common regional activations. Tables 6.1, 6.2, 6.3 and 6.4 list those areas in which there were significant ($p<0.05$ corrected, or in brackets $p<0.001$ uncorrected) activations in association with each task versus rest. Common areas included the cingulate, intraparietal, premotor and striate cortex, and the insula, thalamus, putamen. These areas are typical of those activated in studies of tasks requiring motor responses to visual stimuli.

There were also differences in the patterns of regional activations. The colour based tasks were associated with significant activation of ventral prestriate cortex and infero-temporal cortex. These included area V4 bilaterally. There was also greater activation of the posterior intraparietal cortex and dorsal occipital cortex. These effects were confirmed ($p<0.001$ uncorrected) by a contrast of the main effect of

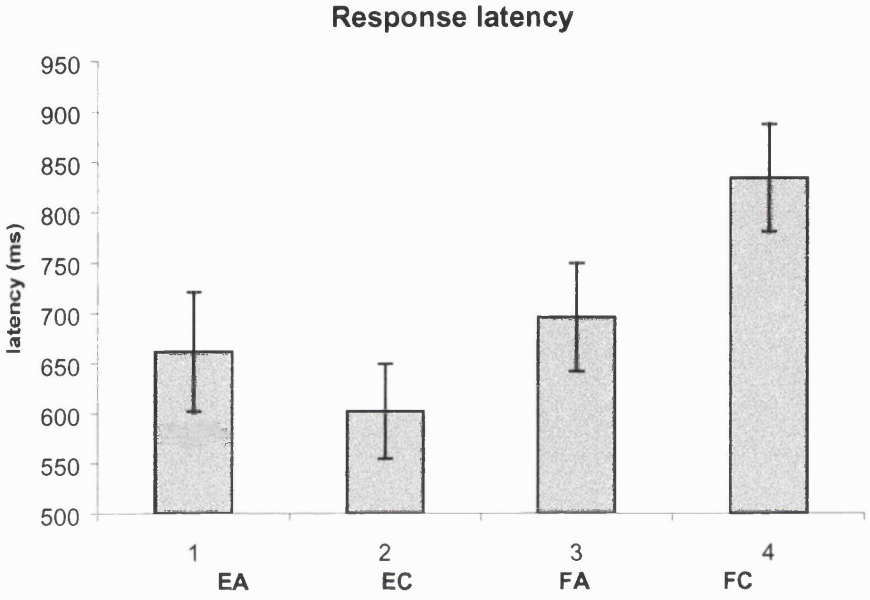


Figure 6.2. Mean (+/- SE) response latencies (ms) for each of the four principal tasks. EA = externally specified actions, EC = externally specified colour, FA = freely selected finger movement, FC = freely selected colour from the multi-coloured panel.

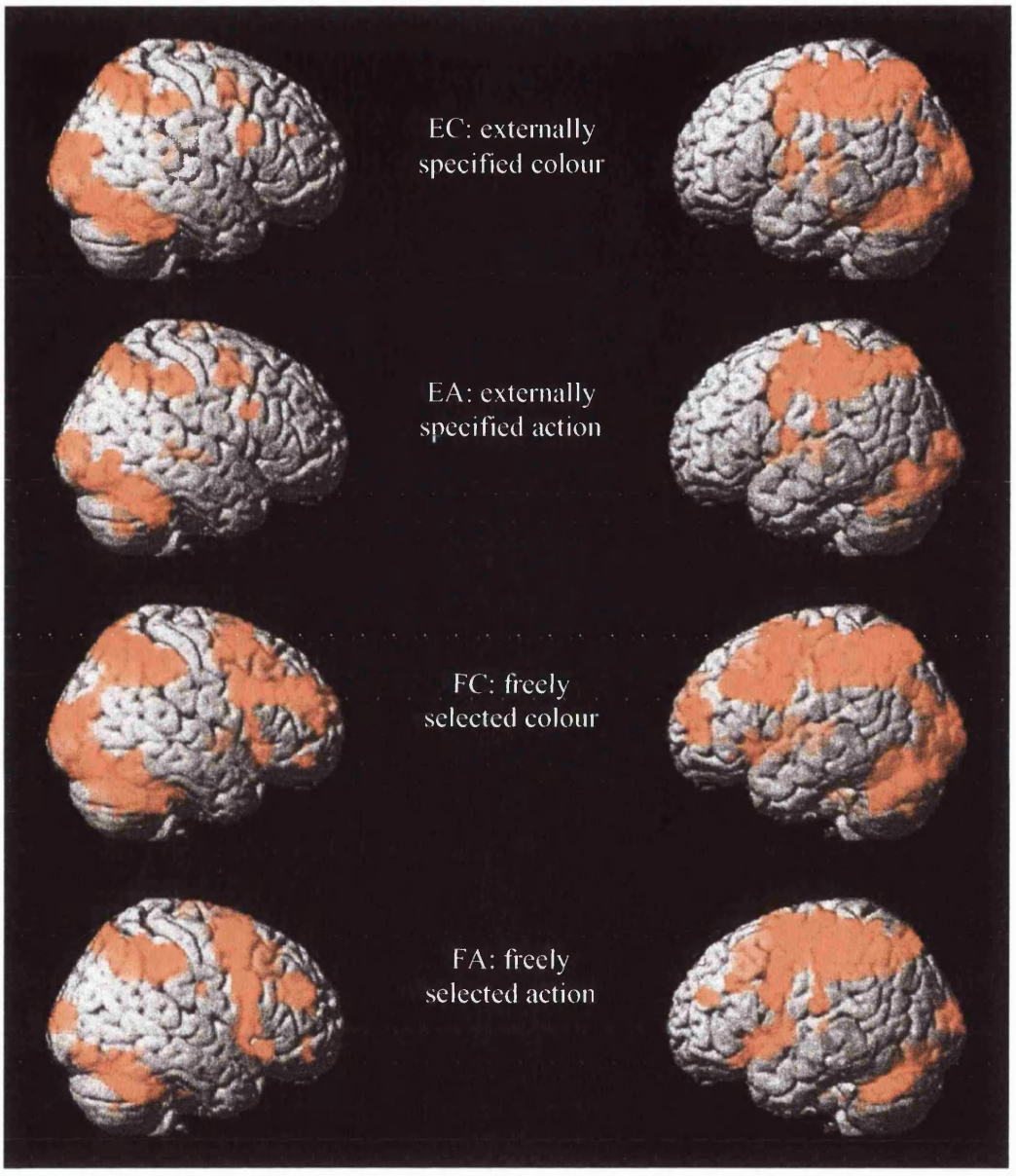


Figure 6.3. The regional activations associated with each task are displayed as surface rendered SPM{t}s, thresholded at p=0.001, projected onto a representative brain in standard anatomic space. Four pairs of renderings are presented, one for each of the main tasks versus rest. Note that in the bottom two panels (FC and FA), there was more extensive activation of dorsal and ventral prefrontal cortex. Regions that were significant at $p<0.05$ (corrected) are listed in tables 1 and 2.

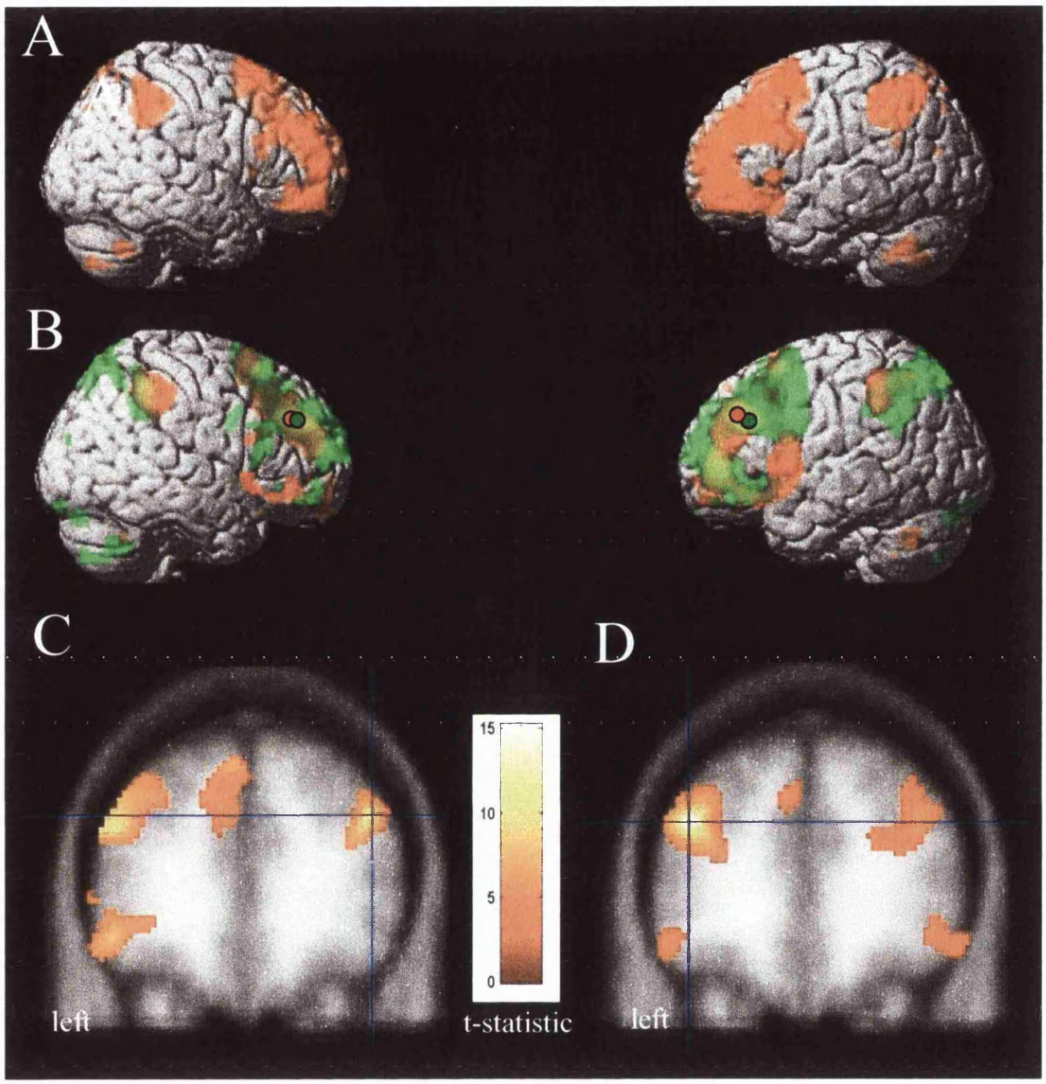


Figure 6.4. (A) The regional activations associated with free selection (versus externally specified) are displayed as a surface rendered SPM{t}, thresholded at p=0.001 (uncorrected), projected onto a representative brain in standard anatomic space. (B) The free selection effects are projected for the colour (green) and action (red) tasks onto the same representative brain. The locations of the peak voxels are indicated by the green and red dots each side (the coordinates are given in the results section). (C) Coronal section through prefrontal cortex (y=36 mm) for the simple main effect of freely selected versus externally specified colour task, and (D) coronal sections through prefrontal cortex (y=36 mm) for the simple main effect of freely selected versus externally specified action task. For both colour and action tasks, there is bilateral activation on the middle frontal gyri, and cingulate cortex, and less significant activations of the inferior frontal gyri.

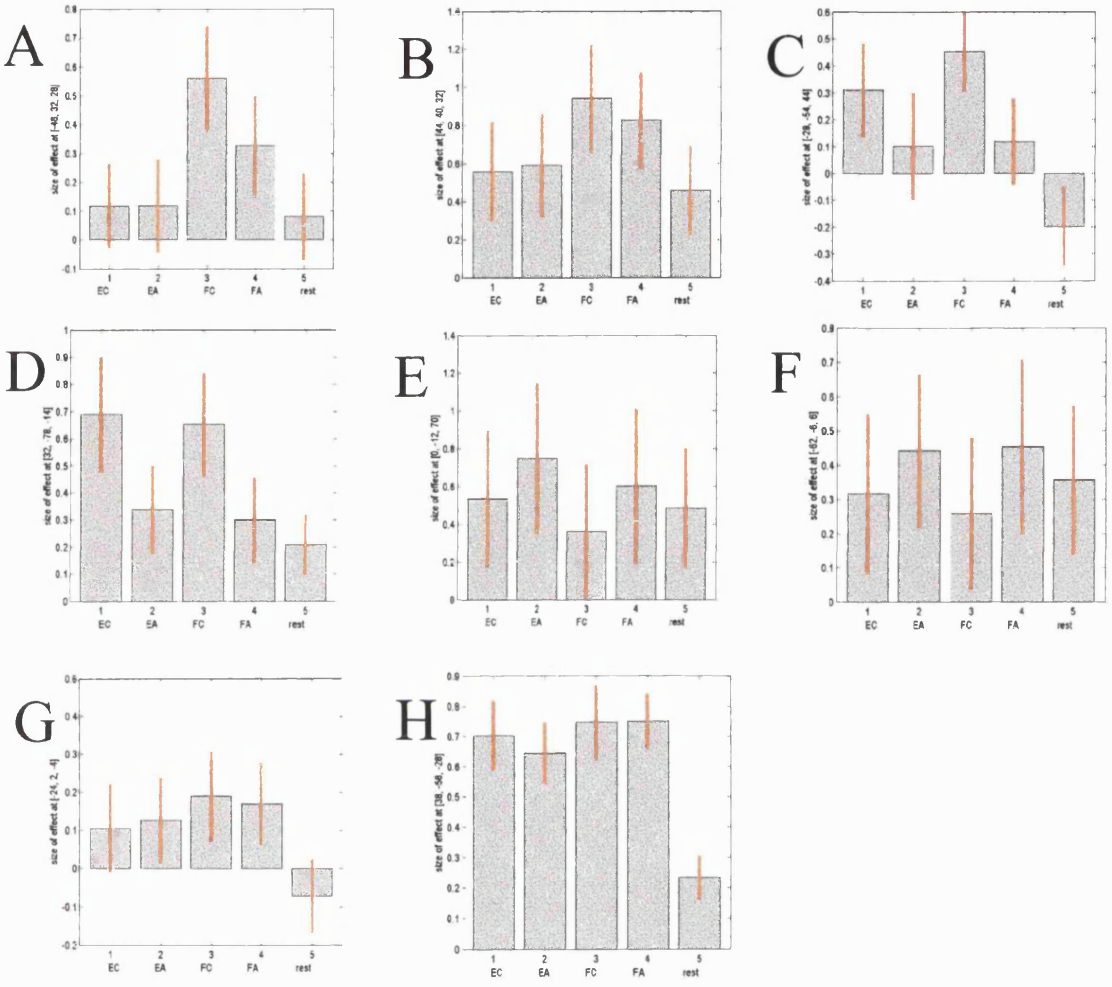


Figure 6.5. Parameter estimates and standard error (across subjects) for the four active tasks and rest. In the prefrontal cortex there is greater activity in the free selection tasks: (A) area 46 of the left prefrontal cortex (-46, 32, 28), and (B) right prefrontal cortex (44, 40, 32). In other areas there was greater activity in colour tasks, such as (C) right intra-parietal cortex (28, -54, 44) (D) area V4, in the inferior prestriate cortex (32, -78, -14), or in action tasks such as (E) the supplementary motor area, (0,12, 70) (F) SII (-62, 06, 06)(trend only). Many areas were similarly active in all tasks versus rest, for example (G) the left putamen (-24, 02, 04) and (H) right cerebellum (40, -60, -28). The scaling of 'effect size' is arbitrary, but consistent across conditions. Although one unit of 'effect size' corresponds approximately to 1.6% of global brain mean T2* MRI signal, one should consider the differences in the effect size between conditions (i.e. task versus rest) rather than the absolute values.

colour versus action based tasks ([+EC + FC –EA –FA]). Figure 6.3 shows summary images of the task related regional activations, as surface renderings of SPM(t) images for each task versus rest.

The action based tasks, but not the colour based tasks, were associated with activation of the supplementary motor area. The contrast of action versus colour ([+EA +FA –EC –FC]) confirmed greater activation in the supplementary motor area, and in area SII and the post central gyrus ($p<0.001$ uncorrected), although no differences exceeded $p<0.05$ when corrected for multiple comparisons.

There were significant differences between the free selection tasks and those in which the targets were externally specified ([+FC +FA –EC –EA]). These are listed in table 6.5. The most significant differences were on the middle frontal gyrus bilaterally.

The interaction between selection and modality was assessed by the contrasts [+EC – EA –FC +FA] and [-EC +EA +FC –FA]. There was a greater effect of free selection in colour tasks than action tasks (but only at $p<0.001$ uncorrected) in the middle frontal gyri, left medial parietal cortex, inferior parietal lobule, and the prestriate cortex. There was a greater effect of free selection of action than colour (but only at $p<0.001$ uncorrected) in the cortex adjacent to the left central sulcus and in SII. The regions are listed in table 6.6.

The peak voxels for the simple main effects of freely selected versus externally specified colour were –50, 30,28, t=13.0 (right) and 44, 38, 32, t=13.01 (right). For freely selected versus externally specified action the peaks were –40, 36, 30, t=15.2 (left) and 42, 40, 32, t=7.42 (right). That is to say, the bilateral peaks for the different modalities were separated by less than 12mm, on the middle frontal

gyrus. Figure 6.4a summarises the effects of free selection, shown as a surface rendering of the main effect of freely selected versus externally specified tasks (averaged across colour and action), and figure 6.4b shows the simple main effects of free selection for colour (green) and action (red) based tasks rendered separately. Figure 6.5 shows the SPM{t}s projected onto a coronal slice through prefrontal cortex.

Figure 6.5 shows the parameter estimates for each of the four task covariates, and rest, at the frontal, parietal and infero-temporal sites of activation. The scaling is arbitrary, but consistent across conditions: a 'size of effect' of 1 unit on the y-axis corresponds approximately to a change of BOLD signal of 1.6% of global brain mean T2* signal. These plots of parameter estimates clearly demonstrate the presence of regions specific for free selection (a, b), colour (c, d), action (e, f) or similarly active in all tasks other than rest (g, h).

Discussion

Free selection

The principal hypothesis tested was that the prefrontal cortex was the source of attentional selection of a colour from a multicolour visual stimulus and the selection of action from multiple possible finger movements. When subjects were asked to freely select an action movement (FA) or to freely select a colour (FC), there was greater activity in the prefrontal cortex than when the actions or colours were externally specified by the visual display (EA, EC). This additional activity occurred throughout a swathe of PFd and PFv, extending from the precentral sulcus to the

anterior pole. Moreover, the peaks of activation associated with free selection were the same for actions and colour.

This extensive activation of prefrontal cortex has been reported in previous studies of voluntary or 'willed action' (Deiber *et al.*, 1991; Frith *et al.*, 1991; Hyder *et al.*, 1997; Jahanshahi *et al.*, 1995; Spence *et al.*, 1998). These studies have shown that freely selected motor responses – of speech, mouth, hand or foot movement – are associated with greater activity of the middle frontal gyrus than externally specified movements of the same type. The current study suggests that the mechanisms of free selection applies not only to motor output and speech, but also to the selective attention to features in a complex visual display. This is consistent with a generic function of 'attentional selection' mediated by the prefrontal cortex (Miller, 1999).

Figure 6.4b shows regions for which there was significant activation associated with free selection. The peaks of significant activation for each modality (each exceeding $p<0.05$ corrected) were within 12 mm bilaterally on the middle frontal gyrus, suggesting a common function of this cortical region.

In figure 6.4b, there are also non-overlapping red (action) and green (colour) areas in the frontal lobes (areas 8 and 44, anterior to precentral sulcus). This might suggest that they were differentially activated by free selection of colour and free selection of action. Modality specific mnemonic activations of PFd and PFv have been reported in both monkey electrophysiological recordings and human neuroimaging studies. Cells specific for working memory are frequently identified in the bow of the arcuate sulcus (area 8) and the posterior peri-arcuate cortex (area 9) (Levy and Goldman-Rakic, 2000). Similarly, areas specific for spatial working memory have been identified in the superior frontal sulcus (Belger *et al.*, 1998;

Courtney *et al.*, 1996; Postle *et al.*, 2000a). Areas specific for verbal working memory are also frequently identified in the posterior part of the inferior frontal gyrus (areas 44) (Cohen *et al.*, 1994; Cohen *et al.*, 1997; Postle *et al.*, 1999a; Smith and Jonides, 1998; Smith *et al.*, 1996; Smith *et al.*, 1998). However, these findings are not consistent, and do not appear to extend to a domain specific effect of free selection. In the current study, the formal contrasts for interactions between free selection and modality did not reveal any significant activations in the pre-frontal cortex.

Task differences

The subjects moved a finger in all trials, to indicate either their choice of action/colour or obedience to the instructed action/colour. Differences in activation cannot be attributed to differences in the motor output, but rather to differences in the cognitive processes preceding movement, including the goal of the movement.

It is necessary to consider what was selected or specified during each type of trial. A response may be defined by its goal (the intended outcome) or the motor mechanism of its execution. In some cases, the goal and the mechanism are the same, for example when the velocity of the hand is itself the goal. In chapters 4 and 5, the selected item was the location of a remembered dot, which was to serve as the target for the joystick action. In the action tasks (EA, FA) the response is to press the particular button, with confirmatory local sensory feedback but no feedback of response accuracy. The goal of this response could be either the movement of the correct finger or the button which is pressed. However, in the current study there was a fixed relationship between the movements and the buttons pressed, confounding these two aspects of the goal.

In the EA condition, the orientation of the arrow provided the information needed for the response. A 'direct' or 'transformational' mapping between stimulus and motor response was necessary (Murray *et al.*, 2000). This arrow-to-button mapping was consistent on all EA trials, so that the target button press was directly specified by the stimulus. Once learned, this type of direct mapping is not associated with activation of PFd in monkeys or man (Murray *et al.*, 2000; Wise and Murray, 2000). No activation of PFd or PFv was observed in the EA condition (table 6.2).

When the colour was specified (EC), the colour in the cue box was not associated with any fixed target of response. However, the matching colour in one of the 'response boxes' did indicate directly the position of the button to be pressed. 'Standard mapping' of the position of the matching 'response box' to the position of the button press was possible. Standard mapping is also not usually associated with prefrontal cortex activity (Murray *et al.*, 2000; Wise and Murray, 2000), although a activation of the right middle frontal gyrus was observed at a lower threshold when EC was compared with rest ($p<0.001$ uncorrected, table 6.1). One difference between EA and EC conditions that could account for this activation of PFd is that in EC the subjects had to maintain fixation in the cue box and match the colour to one in an eccentric array of 'response boxes'. The cue colour had to be considered in relation to each of the response box colours.

In contrast to external specification of the action (EA), in the FA condition the button press was freely chosen from four alternatives. The four finger presses were equally valid moves, and this condition is similar to the free selection of movement studied by Frith et al (1991), Deiber et al (1991) and Hyder et al (1997). Bilateral activation of the middle frontal gyrus is clear, with the peak in area 46. The nature of

the target selected, or the goal of the response, is less clear. It may have been the representation of finger specific movement; or the spatial location of the chosen finger on the button box; the anticipated sensory feedback from the chosen finger; or a combination of these.

In the FC condition, when subjects freely select on of the four colours, there are several alternative explanations of the response actually made. **First**, that the subjects selected one of the colours from the cue box as instructed, and then located the corresponding colour in the response boxes, the position of which enabled direct mapping of the chosen colour to the appropriate button press. We must assume that the subjects then pressed the button corresponding to the colour they had chosen. The localisation of the appropriately coloured response box had to be made while still maintaining gaze in the cue box (as for other conditions). Infrared oculography in four subjects confirmed compliance with this instruction. **Second**, the subjects may have chosen a colour directly from amongst the response boxes, rather than the cue box, despite the instruction telling the subjects to look only in the cue box. . This is unlikely, since the subjects maintained their gaze within the cue box and the colours were the same in response and cue boxes. Nevertheless, it would still constitute free selection of colour. **Third**, the subjects chose a finger to move or a button to press, regardless of the colours. That is to say, despite the coloured cues, the subjects may have performed the FC task in the same way as FA. The behavioural data argue against this third possibility. The reaction time was significantly longer in the FA condition than others, indicated by the significant interaction between modality and selection and illustrated in figure 6.2. In FC there must have been some additional cognitive processes to account for the increased reaction time. One possibility is that

the localisation of the response box that corresponds to the chosen colour in the multicoloured cue box.

In the free selection conditions the subjects may have attended to the sensorimotor correlates of button presses, more than in EA condition, as part of the selection process. Conversely, in the FC condition, they may have attended more to the coloured visual display. Macaluso et al (2000, 2001) have used PET to study the neuronal activity associated with shifting covert attention towards different sensory modalities – touch and vision. They showed that activity in the anterior prefrontal cortex was associated with shifting covert attention, regardless of the modality (Macaluso *et al.*, 2001). In a related study they demonstrated attentional effects in the superior occipital gyrus specific to the vision conditions, and superior post-central gyrus specific to the touch conditions (Macaluso *et al.*, 2000). This supports the notion of modality independent regions of prefrontal cortex for attentional modulation, and modality specific posterior regions in receipt of these attentional modulatory influences. The current study suggests that the modality specific non-prefrontal regions also include non-primary motor cortex.

The attentional selection hypothesis predicts common areas of prefrontal cortex related to free selection of actions and colours. These areas are proposed to bias activity in modality-specific regions elsewhere. However, if there is competition between mutually inhibitory neuronal representations (Desimone and Duncan, 1995) then increased activation of the target representation may suppress activation in local competitors. This may reduce the size of the increase in the metabolic demands of the whole neuronal population. Therefore the modality specific regions influenced by

selection may not show significantly greater population activity when the sensory or motor representations are freely selected from competing representations.

Selection between colours in the multicolour stimulus may be distinguished from attention to colour per se. Attention to colour increases the responsiveness of colour sensitive cortex when compared to a condition in which colour is present but not attended to (Nobre *et al.*, 1998). In the current study, FC differs from EC in terms of the selection of one of the colours from several alternatives. It may also be associated with greater attention to colour per se. The main effect of attention to a stimulus modality can sometimes be distinguished from the effect of selective attention to one category of exemplars. This is easiest to demonstrate when there is retinotopy or somatotopy. With the retinotopic representation of the visual field in striate cortex, attention to specific locations can be distinguished from attentiveness to visual stimuli per se. The attentional modulation of cortical responsiveness is specific to the retinotopic location of the focus of attention (Brefczynski and DeYoe, 1999).

Although retinotopy may also be present in the colour sensitive regions V4 (Hadjikhani *et al.*, 1998; Tootell and Hadjikhani, 2001), it is not possible to analyse the retinotopic variation of the colour selection effect in the present study. Similarly, in premotor cortex, there is crude motor somatotopy (Luppino *et al.*, 1991), but the spatial resolution of the current study is not sufficient to distinguish the modulation of activity related to one finger movement rather than another.

The attentional selection hypothesis predicts that there are neuronal sub-populations outside the prefrontal cortex in which there would be significant selection-by-modality interactions. In the current study, the interactions between selection (free versus externally specified) and modality (colour versus action) were

significant at the reduced threshold of $p<0.001$, uncorrected. A diminution of effect size may have occurred because of the co-localisation of sub-populations representing alternative colours and actions.

Summary

The selection of a colour from a multicolour display and the selection of one of four finger movements are both associated with activation of the middle frontal gyrus, area 46 bilaterally. It is proposed that activation in these regions is the source of modulatory influences to select between neuronal representations of colour or action in non-prefrontal cortex. Modality specific effects of selection were seen in the prestriate cortex and the cortex adjacent to the central sulcus.

Table 6.1 Regions of activation for externally specified colour task versus rest. For large clusters of activated voxels extending over different cortical regions, several sub-peaks are reported, and the cluster indicated by a line to the right of the table. The table includes voxels for which $p<0.05$ corrected for multiple comparisons, and in brackets are other areas that showed activation at the reduced statistical threshold, $p<0.001$ (uncorrected). An asterisk indicates peaks that were significant only when corrected for multiple comparisons within the regions of interest.

Region	L/R	Coordinate			t-statistic
		x	y	z	
External specification of colour					
Ventral prestriate cortex*	r	40	-78	-14	9.63
	(l	-36	-70	-14	7.41)
Infero-temporal cortex	r	34	-50	-22	14.64
	(l	-26	-58	-24	7.31)
Central sulcus*	l	-38	-32	48	9.31
Premotor cortex*	l	-34	-4	50	8.14
Superior parietal cortex*	l	-26	-66	62	8.92
Insula	l	-44	-2	8	10.72
(Cingulate cortex*	l	-6	0	58	8.25)
	(l	46	0	42	7.85)
(Striate cortex	-	-6	-100	6	7.85)
(Middle frontal gyrus	r	52	40	28	7.36)
(Intraparietal cortex	r	22	-52	42	7.66)
(Precentral cortex	r	24	0	50	5.40)
(Ventral premotor	r	62	12	26	5.88)
(Putamen	l	-24	2	4	4.88)
(Thalamus	l	-24	-22	10	6.98)
(cerebellum	-	12	-68	-24	9.05)

Table 6.2 Regions of activation for externally specified action task versus rest. For large clusters of activated voxels extending over different cortical regions, several sub-peaks are reported, and the cluster indicated by a line to the right of the table. The table includes voxels for which $p<0.05$ corrected for multiple comparisons, and in brackets are other areas that showed activation at the reduced statistical threshold, $p<0.001$ (uncorrected). An asterisk indicates peaks that were significant only when corrected for multiple comparisons within the regions of interest.

Region	L/R	Coordinate			t-statistic	
		x	y	z		
External specification of action						
Premotor cortex*	l	-38	-6	50	8.93	|
Central sulcus*	l	-48	-28	48	8.47	|
(Cingulate cortex	-	-10	4	42	9.71)	
Cerebellum	r	28	-48	-26	12.22	
	(-	6	-52	-14	6.09)	
(Ventral prestriate cortex	r	42	-80	-14	5.63)	
	-	-38	-72	-10	5.75)	
(Intraparietal cortex	l	-24	-58	52	6.17)	|
(Premotor cortex	r	24	0	46	7.22)	|
(Post central cortex	r	44	-38	48	7.17)	|
(Intraparietal cortex	r	34	-54	48	5.83)	
(Supplementary motor area	l	-4	0	60	7.26)	
(Striate cortex	-	6	-92	4	5.54)	
(Insula	l	-44	-2	8	7.14)	
(Putamen	l	-22	-4	12	4.30)	
(Thalamus	l	-14	-20	4	6.05)	

Table 6.3 Regions of activation for the free selection of colour task versus rest. For large clusters of activated voxels extending over different cortical regions, several sub-peaks are reported, and the cluster indicated by a line to the right of the table. The table includes voxels for which $p<0.05$ corrected for multiple comparisons, and in brackets are other areas that showed activation at the reduced statistical threshold, $p<0.001$ (uncorrected). An asterisk indicates peaks that were significant only when corrected for multiple comparisons within the regions of interest.

Region	L/R	Coordinate			t-statistic	
		x	y	z		
Free selection of colour						
Middle frontal gyrus (areas 9/46, 46)	l	-46	30	34	12.3	
	r	44	38	32	8.75	|
	r	60	12	30	10.75	|
Superior frontal sulcus*	l	-24	4	58	8.69	|
Superior frontal gyrus	r	16	8	58	10.0	|
Cingulate cortex	-	0	26	44	11.19	|
Central sulcus	l	-38	-32	48	10.17	|
Intraparietal cortex	l	-28	-56	40	10.51	|
	r	28	-54	44	13.23	
Ventral prestriate cortex*	l	-36	-66	-12	8.79	|
	(r	38	-78	-14	7.74)	|
Cerebellum	-	4	-80	-14	14.19	
	l	-36	-56	-30	14.39	
	(r	30	-42	-40	9.01)	
(Infero-temporal cortex	r	34	-48	-22	6.88)	
(Precentral gyrus	l	-34	-14	60	6.3)	
(Supplementary motor area	-	0	0	58	9.66)	
(Inferior frontal gyrus	r	48	18	4	7.68)	
(Striate cortex	-	-2	-82	6	4.66)	
(Insula	l	-30	20	-2	6.31)	
	r	34	24	-10	8.0)	
(Putamen	l	24	2	0	6.73)	|
(Thalamus	l	-14	-20	4	6.07)	|
(Globus pallidum	r	18	-2	2	6.0)	

Table 6.4 Regions of activation for the free selection of action task versus rest. For large clusters of activated voxels extending over different cortical regions, several sub-peaks are reported, and the cluster indicated by a line to the right of the table. The table includes voxels for which $p<0.05$ corrected for multiple comparisons, and in brackets are other areas that showed activation at the reduced statistical threshold, $p<0.001$ (uncorrected). An asterisk indicates peaks that were significant only when corrected for multiple comparisons within the regions of interest.

Region	L/R	Coordinate			t-statistic
		x	y	z	
Free selection of action					
Middle frontal gyrus*	r	34	8	58	9.7
	(l	-42	32	30	6.5)
	(r	36	48	24	6.43)
Precentral gyrus*	l	-32	-2	56	8.67
(Central sulcus	l	-34	-24	54	7.8)
Intraparietal cortex*	r	36	-50	50	10.0
	(l	-28	-56	44	7.61)
Cingulate cortex	-	2	20	44	13.5
Cerebellum	r	40	-60	-28	11.5
	l	-36	-60	-34	12.8
Supplementary motor area	-	-8	2	60	14.1
Inferior frontal gyrus	r	62	12	32	10.6
	(l	-58	10	20	7.38)
(Frontal operculum	r	-40	16	0	6.54)
	(r	54	14	12	6.65)
(Striate cortex	-	8	-94	8	5.36)
(Insula	l	-46	2	0	6.32)
	r	50	8	2	4.91)
(Putamen	l	-24	2	-4	5.62)
(Thalamus	l	-28	-22	6	6.81)

Table 6.5 Regions of significant activation greater for free selection than eternally specified tasks. For large clusters of activated voxels extending over different cortical regions, several sub-peaks are reported, and the cluster indicated by a line to the right of the table. The table includes voxels for which $p<0.05$ corrected for multiple comparisons, and in brackets are other areas that showed activation at the reduced statistical threshold, $p<0.001$ (uncorrected). An asterisk indicates peaks that were significant only when corrected for multiple comparisons within the regions of interest.

Region	L/R	Coordinate			t-statistic
		x	y	z	
Middle frontal gyrus (area 46)	l	-46	32	28	13.44
	r	44	40	32	11.59
Superior frontal sulcus* (area 8)	l	-28	12	54	8.03
	(r	18	14	58	6.25)
(Inferior frontal gyrus	l	-44	34	-8	9.12)
	r	44	40	-8	5.57)
(Anterior cingulate cortex	-	2	28	42	7.45)
(Superior parietal cortex	l	-50	-44	52	6.01)
	r	54	-44	50	8.89)
(Cerebellum	r	34	-58	-40	6.47)
	l	-26	-58	-38	4.87)

Table 6.6 Regions of significant interaction between free selection (vs externally specified) and the task modality. The table includes voxels for which $p<0.001$ uncorrected for multiple comparisons. No voxels survived threshold for $p<0.05$ corrected.

Region	L/R	Coordinate			t-statistic
		x	y	z	
Free selection effect greater in action tasks than colour tasks					
central sulcus	l	–26	-32	58	4.72
SII	l	-52	-8	14	4.87
Free selection effect greater in colour tasks than action tasks					
PFd	l	-48	26	38	5.45
	r	44	12	36	4.26
anterior cingulate cortex	-	-2	46	22	8.18
left medial parietal cortex	l	8	-54	50	6.23
	r	8	-52	48	5.19
inferior parietal lobule	l	-52	-52	28	5.36
prestriate cortex (V4)	l	-40	-88	-10	5.99
	r	-22	-90	-6	4.22

Chapter 7

Attention to action

Introduction

In chapters 4 and 5, selection from memory, rather than maintenance, was associated with activation of area 46 on the middle frontal gyrus. Selection from memory was proposed to occur by 'attentional selection' of neuronal representations, similar to the attentional selection of sensory representations under prefrontal cortical influence (Barcelo *et al.*, 2000b; Desimone and Duncan, 1995; Miller *et al.*, 1996; Tomita *et al.*, 1999). The mechanisms of attentional selection of neuronal representations was proposed to be a general phenomenon applicable to sensory stimuli, thoughts, memories or actions (Miller, 2000).

This was tested in chapter 6: selection of one of four finger movements and selection of a colour from a multicolour display were both also associated with activation of area 46. Cortex adjacent to the central sulcus was more activated by free selection of actions than free selection of colour. Free selection of different finger movements was not expected to reveal spatially distinct areas of activation in non-primary motor cortex, for two reasons. **First**, the limited somatotopy in non-primary motor cortex diminished the ability to show a 'spotlight of motor attention' on different finger movements. **Second**, the mutual inhibition between alternate representations of action was expected to diminish the ability to show differential

activity between freely selected and externally specified action. However, these two problems would not diminish the main effect of attention to action on non-primary motor cortical activity (attended versus non-attended action).

Attention to action has been studied previously by Jueptner *et al.* (1997b). Subjects were trained to perform simple motor sequence task. After training, there was no pre-frontal activation associated with the task. Subjects were then asked to 'think about their next move', to specifically attend to the forthcoming action. The movements remained the same, but attention to action was associated with increased activation of the prefrontal cortex, and a trend toward greater activation of the premotor cortex and SII. There is also evidence that early performance on sequence learning is associated with attention to actions. Passingham (1993, 1996) has provided evidence that during early learning, but not later performance, the subjects attend to their actions. Early performance on sequence learning is associated with prefrontal and premotor cortical activation (Catalan *et al.*, 1999; Jahanshahi *et al.*, 1995; Jenkins *et al.*, 1994; Jenkins *et al.*, 2000; Jueptner *et al.*, 1997a; Toni *et al.*, 1998). A combined MEG and PET study suggested that prefrontal cortex is the source of the modulatory inputs to premotor cortex (Pedersen *et al.*, 1998).

The proposed modulation of target neuronal activity is specific to the object of attention, and does not simply reflect a general state of greater attentiveness. It is predicted that attention to a stimulus, thought or action will increase activity of neurons in the prefrontal cortex (the source of modulatory influences) and in the functionally relevant sensory, association or motor cortex (the target of such modulation). This task specific influence of one region over another is known as effective connectivity (Aertsen *et al.*, 1989; Friston *et al.*, 1997a; Friston *et al.*,

1993b)]. Structural equation modelling can be used to measure changes in effective connectivity (Buchel and Friston, 1997; Friston and Buchel, 2000; McIntosh and Gonzalez-Lima, 1994b)

In the present experiment, fMRI was used to investigate attentional enhancement within regions of the motor system, and enhancement of cortico-cortical connectivity amongst these regions. A motor task was used to test the hypothesis that attentional selection generalises beyond the sensory systems. Attention to action was predicted to enhance representations of action in premotor cortex, and be associated with increased effective connectivity between prefrontal and premotor cortex.

It was necessary to show that effects of attention to action were not due to increased attentiveness *per se*, but specific attention to action. Therefore a non-motor attentional task was also used to direct attention away from the motor task. It was not intended to replicate the modulation of activity in visual regions when subjects attend to visual cues (Brefczynski and DeYoe, 1999; Rees *et al.*, 1997), or the role of prefrontal cortex in that visual cortical modulation (Buchel and Friston, 1997).

The connectivity between the prefrontal cortex and premotor cortex was of primary interest. An anatomically constrained, hypothesis driven analysis of prefrontal to premotor effective connectivity was performed. Common inputs from parietal cortex to prefrontal and premotor cortex may cause covariation in activity without effective connectivity (Frackowiak *et al.*, 1997; Friston *et al.*, 1997a). Therefore, parietal cortex was also included in the model, as illustrated in figure 7.1.

The prediction was that there would be regionally specific increases in activation in prefrontal cortex and premotor cortex when attending to action (shown by SPM). In addition, it was predicted that there would be a specific increase in

effective connectivity between prefrontal and premotor cortex during attention to action (shown by SEM). The coupling between prefrontal and premotor cortex would not be attributable to common inputs from parietal cortex, nor to a non-specific effect of attentiveness per se. Effective connectivity was predicted to increase when attending to action but not when attending to a non-motor attentional task.

Methods

Subjects

Fifteen right-handed volunteers participated in the study, aged 24-34 years (mean 29), with written informed consent. The subjects were recruited from a departmental register of volunteers. They had no history of psychiatric or neurological disease, and they were taking no regular medication.

Behavioural paradigm

Motor and cognitive tasks were based on those studied by Jueptner et al (1997) and Coull et al (1998). Five principal tasks were performed, each lasting 30 seconds, with eyes open and auditory (beep) and visual (small central '+') pacing cues given throughout the experiment every three seconds. Brief written cues told the subject which task they were about to perform. The five tasks were:

(1) MOVE task: paced sequential right finger movements (1,2,3,4,1,2,3,4....).

(2) SEARCH task: in this visual conjunction search task, a sequence of different coloured different letters were presented centrally, and the subjects were required to detect a red letter 'r' as the target (Coull *et al.*, 1998). No immediate response was made to the target presentation.

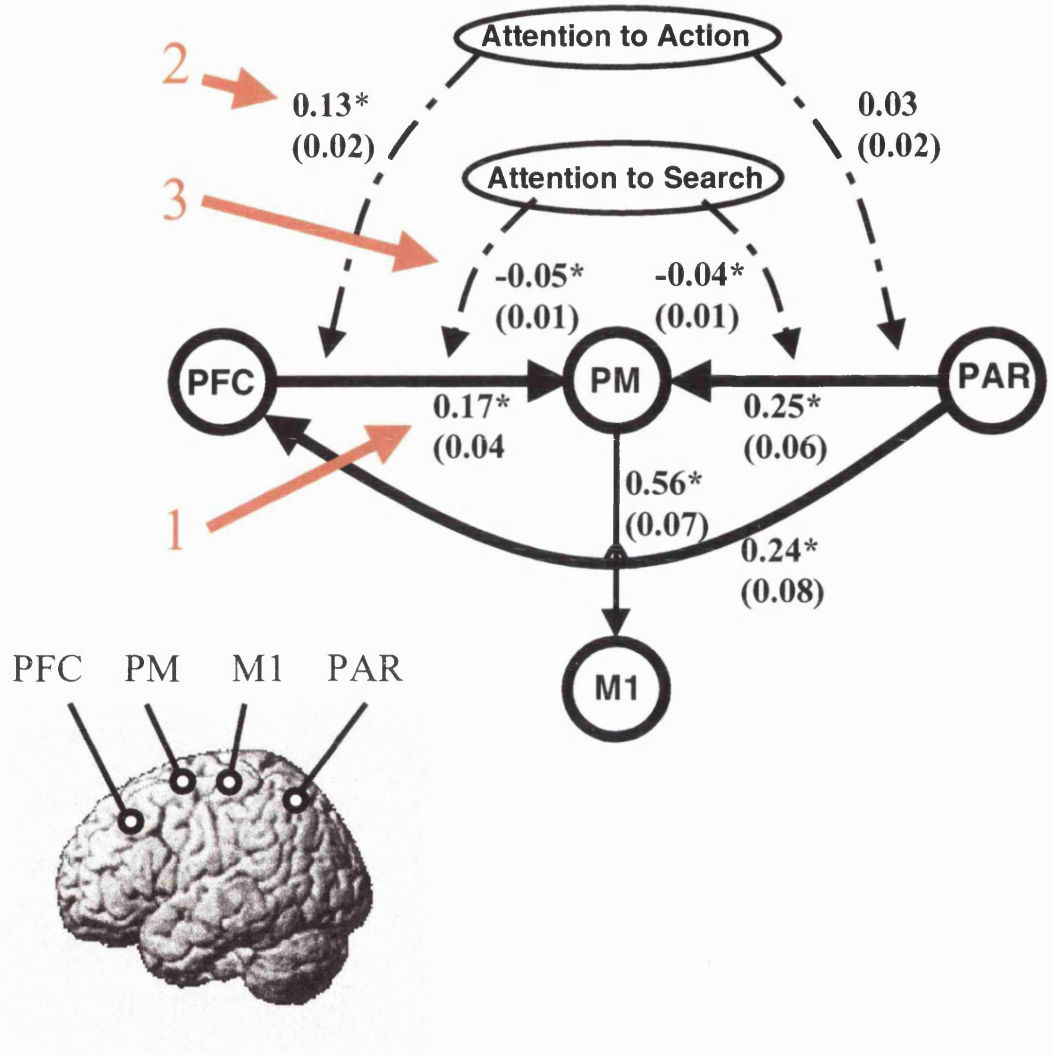


Figure 7.1. In the anatomical mode prefrontal (PFC), premotor (PM), primary motor (M1) and parietal (PAR) cortex were interconnected according to known primate anatomy (solid arrows). The inset figure shows the locations of the four anatomic regions on the cortex of the left hemisphere. In addition to anatomic connections, the modulatory influences of attention are indicated by dashed arrows. The numbers indicate the group mean path coefficients (+SE) for 13 subjects for the anatomic and modulatory connections. An asterisk indicates $p<0.05$, for 1-sample t-test (Bonferroni corrected). The three red arrows are discussed in the text.

(3) DUAL task: the subjects performed the visual conjunction search whilst performing the simple finger sequence.

(4) ATTEND task: subjects performed the motor sequence task (as in MOVE), but they were instructed to attend to the forthcoming action ("think about the next move").

(5) REST: subjects rested with eyes open, following each other task.

For statistical parametric mapping, the MOVE, SEARCH, DUAL and REST tasks constitute a 2 x 2 factorial design, with movement and visual conjunction search as independent factors. For structural equation modelling, each motor condition (MOVE, ATTEND, DUAL) was coupled with a subsequent non-motor condition (REST or SEARCH). In addition to the principal tasks, following the SEARCH and DUAL tasks there was a short response period lasting approximately five seconds, in which subjects indicated by button press whether the target had appeared in the previous epoch.

Pre-training occurred on the same day as scanning. Despite the simplicity of the MOVE condition, training was given to make the tasks performance automatic and to minimise the attentional demands. Subjects practised the MOVE condition continuously for ten minutes in a quiet room. They were then instructed in the other four conditions, and given practice for a further ten minutes. All subjects clearly understood and reported a subjective difference between the ordinary MOVE task and the ATTEND task. A further five minutes practice of the MOVE task was given in the scanner prior to imaging.

The time of each button press was recorded and the mean and variance of the time between consecutive button presses was calculated. The standard deviation of response times per subject per condition was entered into a one-way repeated-measures analysis of variance (ANOVA, SPSS 8.0 for Windows NT, using the Greenhouse-Geisser correction for non-sphericity).

Functional imaging

Subjects lay supine with their head fixed by firm foam pads. Instructions were projected onto a screen mounted on the head coil and auditory pacing cues were delivered through padded headphones, controlled by Apple Macintosh 7600 computer operating Cognitive Interface software (Cogent, Wellcome Department of Cognitive Neurology, UK). Four lightly sprung buttons were mounted under the subjects' fingertips, on a moulded splint that supported a comfortable neutral hand-wrist position.

Functional imaging used T2*-weighted echo-planar MRI at 2-tesla, repeat time 3650 ms, echo time 40 ms, throughout 28 minutes continuous whole brain imaging (64x64x40 voxels, 3mm isotropic resolution). The first five images were discarded to allow steady state magnetisation. Statistical Parametric Mapping software was used for image processing and analysis (SPM99, http://www.fil.ion.ucl.ac.uk/spm). The images were realigned to the mean image by rigid body transformation, sinc interpolated in time to correct for phase shift during volume acquisition, and transformed to normal anatomic space (Talairach and Tournoux, 1988), using the Montreal Neurological Institute template, by non-linear transformations (Friston *et al.*, 1995b). For individual subject analyses, the data were spatially smoothed with a Gaussian kernel of full width half maximum 6 mm

(FWHM). High-resolution T1-weighted images were acquired to permit anatomical localisation of activation foci.

Individual subject analysis (level 1)

A general linear model was applied voxel-wise to the functional data (Friston *et al.*, 1995a; Friston *et al.*, 1996), using covariates for the epochs MOVE, SEARCH, DUAL, ATTEND, REST and the response period, and a transient covariate for the instruction cues. Residual motion effects were modelled by inclusion of the first temporal derivative of the realignment parameters, representing scan-to-scan movement. Effects of low frequency drifts in BOLD signal were removed by a high pass filter with a cut-off of 300 seconds, and the data were temporally smoothed using a canonical haemodynamic response function prior to parameter estimation.

Parameter estimates for each covariate, and residual variance, were derived in a subject specific fixed effects model. Contrast images of interest were calculated for each subject, including the simple main effect of each task against rest, pairwise contrast between MOVE, ATTEND and DUAL conditions, and interaction effects between the simple motor task and the conjunction search. A statistical parametric map of the F-statistic for all conditions in the model was generated, SPM{F}, from which voxels were later selected for structural equation modelling.

Random effects analysis (level 2)

To accommodate inter-subject anatomic variability in group analyses, a secondary spatial smoothing kernel of FWHM 8 mm was applied to the contrast images from level 1, equivalent to an overall smoothing of the functional images by a kernel of FWHM 10 mm. For each contrast, the fifteen contrast images from level one

were entered into a two-way one-sample t-test, to create a SPM{t}-statistic image, with 14 degrees of freedom. This two-stage random effects analysis enables the inference based on these contrasts to be extended to the general population from which the subjects were drawn (Friston *et al.*, 1999b).

Two types of correction were applied. **First**, for areas subject to *a priori* hypotheses, region-of-interest analyses were performed, correcting for multiple comparisons within the reduced search volumes ($p<0.05$). The regions of interest were defined by drawing on the mean structural images for the group, in standard anatomic space, using MRIcro software (http:\www.mrc-cbu.cam.ac.uk \imaging\chris.rorden.htm). They included (a) prefrontal cortex area 46, middle frontal gyrus, $30<y<50$; (b) premotor cortex, dorsolateral part of precentral gyrus and precentral sulcus; (c) primary motor cortex, anterior bank of central sulcus extending to the surface convexity; (d) intraparietal cortex, extending to the surface convexity. **Second**, voxels outside the regions of interest are included in the tables and figures if $p<0.05$ corrected for whole brain multiple comparisons.

Individual structural equation modelling (level 1)

Analyses of effective connectivity were performed using the method described for fMRI time series by Buchel and Friston (Buchel and Friston, 2000; Buchel and Friston, 1997). Structural equation modelling of fMRI time series does not itself result in the model of regional interactions in the brain; rather it estimates the effects of experimental manipulation on connectivity among variables within a specified model. A hypothesis led theoretical perspective was adopted to constrain the model to principal anatomic and cognitive elements. The model is illustrated in figure 7.1, and included the prefrontal, premotor and primary motor cortex of the dominant

hemisphere, and the parietal cortex. It was based on known anatomical interconnections between primary and non-primary cortical motor areas in primates, indicated by solid arrows (Barbas and Pandya, 1987; Cavada and Goldman-Rakic, 1989; Johnson *et al.*, 1996; Muakkassa and Strick, 1979; Rizzolatti *et al.*, 1998).

The specific coordinates for these four regions, for each subject, were taken from the nearest maxima in the first level SPM{F}. Two subjects showed no task related activation of left prefrontal cortex ($y>15$), and were excluded from the structural equation modelling. Regions were defined as 5mm radius spheres, including all voxels that exceeded $p<0.001$ (uncorrected) in the SPM{F} for all effects. The first principal component of the adjusted BOLD signal was entered into the model as used by Buchel and Friston (1997, 2000).

Our application of structural equation modelling included data from all conditions. To allow for task-related changes in coupling we included moderator variables that modelled how changing conditions altered the connectivity between two areas. These can be thought of as interactions between the psychological causes (e.g. attention) of a regional response in a target area (e.g. premotor cortex) and the physiological causes (i.e. activity in source area such as prefrontal cortex). For the analysis of fMRI data, the inclusion of moderator variables is preferable to comparing separate models for each condition, because the sequential scans are not independent: the gradual BOLD response to neuronal events means that the early scans of one condition may include residual effects of the previous task. The moderator variables incorporate these gradual changes and comprise the product of regional activity in the source area and the relevant psychological factor (following convolution by a

canonical haemodynamic response function) (Buchel and Friston, 1997). In our model these variables were principally motor-related responses, moderated by attention.

In constructing the moderator variables, the time course for the conjunction search (SEARCH) was orthogonalised with respect to attention to action (ATTEND), such that the search task was treated as 'not-attending-to-action'. The task covariates were convolved by a canonical haemodynamic response function and multiplied by the activity in the prefrontal and parietal cortex to form the interaction or moderator variables.

The structural model was implemented with the SEM Toolbox of SPM99 using an iterative maximum likelihood algorithm (Higham, 1993) to estimate covariances that best predict the observed variance-covariance structure of the empirical data. Statistical inferences about the path coefficients were based on the comparison of a free model with a model constrained to zero for a given connection. The difference in goodness of fit between free and constrained models was expressed as chi-squared (with degrees of freedom determined by the number of constraints). Under the null hypothesis, that one area has no influence over another, the free and constrained models do not differ in goodness of fit.

Results

Behavioural results

On this paced motor task, the mean interval between movements during MOVE, ATTEND and DUAL tasks did not differ (means, 3025 ms, 3026 ms, 2985 ms, $F=0.97$, adjusted df=1,14, p=ns). However, the variability of the time between

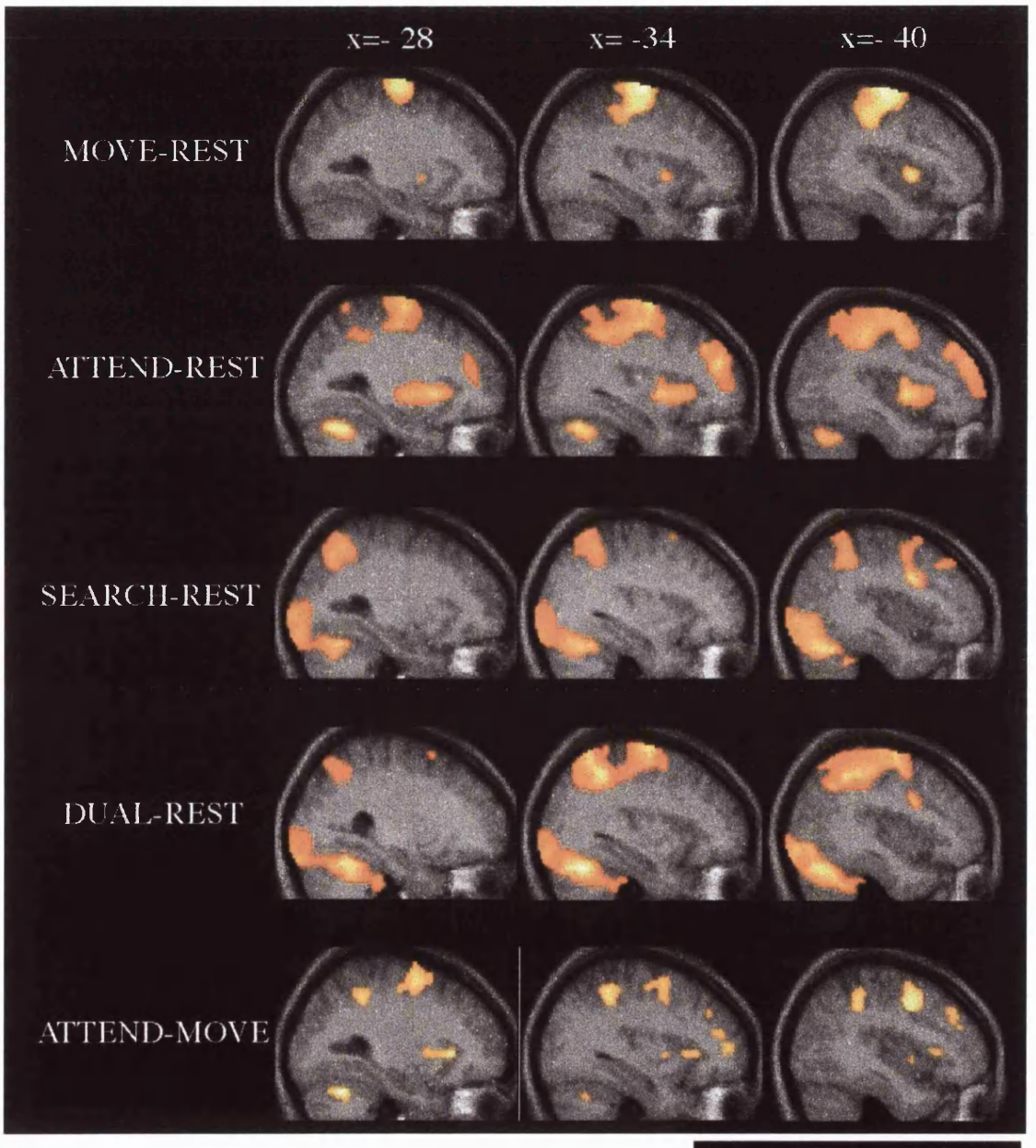
button presses did differ between conditions (group means of the subject variances were 110 ms, 150 ms, 128 ms, $F=5.01$, adjusted $df=1.3,17$, $p<0.05$). Post hoc pairwise comparisons of response time intervals confirmed that there was a significant difference between MOVE and ATTEND ($t=2.46$, $df=14$, $p<0.05$).

Imaging results

Tables 1 and 2 list those areas that were significantly activated in a random-effects group analysis ($p<0.05$ corrected for multiple comparisons) for each condition versus baseline, and in pairwise contrasts between conditions. Figure 7.2 shows left parasaggital statistical parametric maps, SPM{t}s, for the contrasts of each condition versus rest, and the difference between ATTEND and MOVE conditions. Both MOVE and ATTEND conditions showed distributed activation in the motor system compared to rest, including contralateral premotor cortex, primary motor cortex, supplementary motor area and anterior cingulate cortex, and parietal cortex. Subcortical areas included contralateral putamen, thalamus, and ipselateral cerebellum. The visual conjunction search (SEARCH) was associated with activation of bilateral prefrontal cortex, superior and intraparietal cortex, anterior cingulate cortex and prestriate areas extending along the inferior temporal lobe.

The contrast of ATTEND versus MOVE conditions identified those areas of increased activity during attention to action, event though the rate and variance of movements did not differ. These included left PFd (area 46), left premotor cortex, intraparietal and insula cortex. There was no significant difference in motor cortical activation. These activations are shown as SPM{t}s overlaid on parasaggital and coronal slices in figure 7.3. The significant activations are listed in table 2.

There was a significant interaction between performing the motor sequence (in MOVE and DUAL) and conjunction search (in SEARCH and DUAL), with less activity in the left premotor cortex during dual task performance than during separate



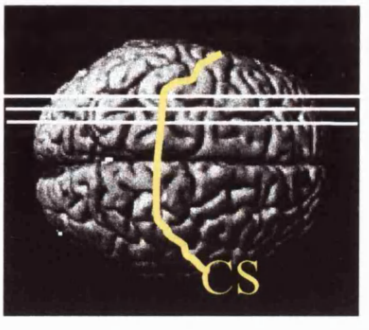


Figure 7.2. Above are the SPM{t}s ($p<0.05$ corrected) for each condition versus rest, and the contrast of ATTEND versus MOVE, overlaid on three adjacent parasaggital slices through a representative brain in standard anatomic space (right). The x-coordinate of the each plane is indicated at the top of the figure.

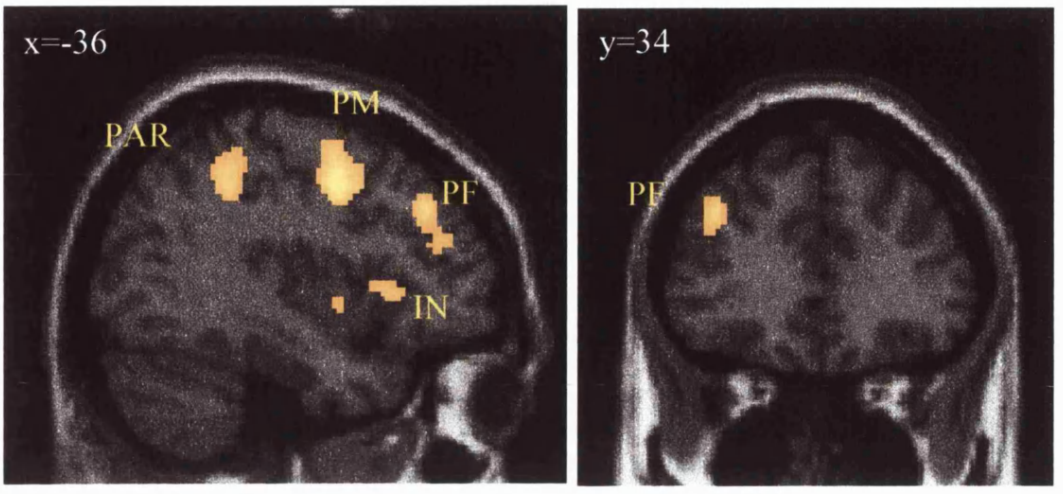


Figure 7.3. The SPM{t}s ($p<0.05$ corrected) for the contrast of ATTEND versus MOVE, overlaid on a parasaggital slice (x=-36 mm) and coronal slice (y=34 mm) through the prefrontal cortex of a representative brain in standard anatomic space. Significant activations include the left middle frontal gyrus (PF), premotor cortex (PM), intraparietal cortex adjacent to the post central sulcus (PAR) and the insula (IN).

performances of the motor sequence and visual search tasks (table 2). There were no areas in which there was a positive interaction between the two component tasks.

Effective connectivity

Path coefficients were identified for every connection in the structural model, illustrated in figure 7.1. The solid lines indicate the connections in the anatomic model, and the dashed lines indicate the modulation of these connections by the two attentional tasks. For anatomical and modulatory connections, the mean (+SE) path coefficients for the group are given in figure 7.1.

Inferences about connections were made at two levels, first within subject and then between subjects. The significance of path coefficients for the interaction terms were tested for each subject (within subject threshold $\Delta X^2=5.02$, df=1, $p<0.05$). Attention to action significantly increased the prefrontal to premotor coupling in nine out of thirteen subjects. In contrast, it increased the parietal to premotor coupling in just three subjects. Attention to the visual conjunction search significantly reduced the coupling between prefrontal and premotor cortex in one subject, and between parietal and premotor cortex in two subjects. However, eleven subjects showed a small negative effect of attention during visual conjunction search on prefrontal to premotor connectivity. This suggests a consistent effect across the group, but one that fails to reach significance in most individuals.

To test for significant group effects, the path coefficients for each connection were entered into four two-tailed one-sample t-tests (Bonferroni correction for four multiple comparisons). This will test for a significant non-positive or negative averaged path coefficient. The first red arrow in figure 7.1 highlights that there is modest motor related coupling (covariance) between prefrontal and premotor cortex.

This coupling is not attributable to common inputs from the parietal cortex. The second red arrow indicates the positive modulatory effect of attention to action on the prefrontal-premotor coupling: attention to action significantly increased the coupling between prefrontal and premotor cortex ($t=5.34$, $df=12$, $p<0.001$). Attention to action did not increase the coupling between parietal cortex and premotor cortex ($t=2.176$, $df=12$, ns). The third red arrow indicates the small but significant negative modulatory effect of attention to the search task on the prefrontal-premotor coupling: attention to the visual conjunction search significantly reduced the coupling between prefrontal and premotor cortex ($t=-4.046$, $df=12$, $p<0.05$) and between parietal and premotor cortex ($t=-3.038$, $df=12$, $p<0.05$).

To assess the differences between the effects of the two attentional tasks on the prefrontal and parietal inputs to premotor cortex, the path coefficients were entered in to a two-way repeated measures ANOVA with 'task' (attention to action and attention during conjunction search) and 'connection' (prefrontal to premotor and parietal to premotor) as factors. There was a significant interaction between these two factors ($F=8.8$, $df=1,12$, $p<0.05$). Analysis of simple main effects confirmed that attention to action modulated the connection strength between the prefrontal and premotor cortex more than it modulated the connection from parietal to premotor cortex ($F=8.125$, $df=1,12$, $p<0.05$). The modulatory effect of attention during visual conjunction search did not differ significantly between connections ($F=0.487$, $df=1,12$, ns). The two attentional tasks had opposing modulatory effects on both prefrontal and parietal connections to premotor cortex ($F=63.322$, $df=1,12$, $p<0.001$ and $F=11.831$, $df=1,12$, $p<0.01$ respectively).

Discussion

Under directed attention to action, there was increased effective connectivity (Friston *et al.*, 1993b) between the prefrontal and premotor cortical regions included in our model. Fluctuation in the common inputs from the parietal cortex to premotor and prefrontal cortex was not sufficient to account for this attentional modulation of connectivity. In addition, the contrasting effects of opposing attentional tasks suggests that changes in neuromodulatory inputs related to attentiveness *per se* also cannot explain the changes in connectivity.

The enhanced connectivity between prefrontal and premotor regions due to attention to action can be interpreted as the prefrontal cortex mediating the positive effect of attention on premotor cortical activity. The group analyses also indicate that this modulation of prefrontal to premotor cortical connectivity is itself specific to the target of attention. Whereas the dorsal prefrontal cortex mediates a positive effect of attention to action on premotor cortex, diversion of attentional resources to a simultaneous visual conjunction search diminishes the connectivity between prefrontal and premotor cortex. It was not the purpose of this study to measure the attentional modulation of the coupling between prefrontal and visual cortical areas: the visual stimuli were only presented during visual conjunction search tasks (SEARCH and DUAL), and we did not include conditions in which the subjects saw the visual stimuli without attending to them.

Our analyses were constrained to the hypothesised effects of experimentally manipulated cognitive functions within anatomically defined neuronal networks. Our modelled network of interconnections between primary and non-primary cortical motor areas, was based on known anatomical connections (Barbas and Pandya, 1987;

Cavada and Goldman-Rakic, 1989; Johnson *et al.*, 1996; Muakkassa and Strick, 1979; Rizzolatti *et al.*, 1998). This model is not a complete account of all possible regions engaged in the five tasks, all possible direct and indirect connections between them, nor the fluctuation of cognitive processes within tasks. Such a comprehensive model would be useful in an exploratory sense but much less powerful in relation to our hypothesis. This is because it would be computationally unstable (McIntosh and Gonzalez-Lima, 1994b). We therefore adopted a hypothesis led theoretical perspective to constrain the model to principal anatomic and cognitive elements. The resulting model is sufficient to address key questions regarding the influence of prefrontal cortex over premotor cortex under different conditions (Friston *et al.*, 1993a; Friston *et al.*, 1997b).

This analysis of effective connectivity is complementary to the connectionist approach applied to cognitive models, especially where these mimic neural architectures. In stimulus-response association paradigms for example, contextual information is effective through biasing the activity of response-modules following complex stimuli (Cohen and Servan-Schreiber, 1992). The selective activation of response modules according to task instructions is analogous to task-specific attentional selection of neuronal representations, whether motor (this study) or sensory (Brefczynski and DeYoe, 1999; Rees *et al.*, 1997). Simulation studies have suggested that this process is mediated by the prefrontal cortex (Cohen *et al.*, 2000; Cohen *et al.*, 1996).

Attention to action

The attentional modulation of activity representing a particular stimulus, has been demonstrated in primary visual (Brefczynski and DeYoe, 1999) and auditory

cortex (Alho *et al.*, 1999), and in the infero-temporal cortex during analysis of complex visual forms (Chelazzi *et al.*, 1998). Our results suggest that this mechanism extends beyond sensory and perceptual processes, to include premotor representations of action. In the present study attention was manipulated in two ways. The first was by instruction (ATTEND) as in studies of attention to action (Jueptner *et al.* 1997), motor imagination (Deiber *et al* 1998) and in some studies of sensory attention (e.g. Meyer *et al* 1991). The second method was the use of a distractor task (DUAL) as in the study of somatosensory attention by Meyer *et al* (1991). There is behavioural evidence that these manipulations were effective.

Compared with simple motor sequence performance (MOVE) there was a significant increase in the variability of the inter-response times in the ATTEND condition, but not DUAL condition. This suggests that there was automatic processing of the learned motor sequence task, unaffected by attentional demands. Therefore, in contrast to the 'direct' processing of action in MOVE and DUAL conditions, attended action in ATTEND condition also required 'indirect' or 'controlled' motor processes (Cohen *et al.*, 1990).

Norman and Shallice (1980) proposed that a supervisory attentional system directs the selection of action schemas. Action schemas were proposed to be selected in response to sensory-perceptual inputs (illustrated in figure 1.6), and multiple schemas were proposed to be automatically coordinated by a process of contention scheduling. However, when planning, problem solving, learning new actions or overcoming habitual responses, the supervisory attentional system may control the selection of schemas. Norman and Shallice (1980) also proposed that 'willed'

direction of action through 'conscious control' was mediated by the supervisory attentional system.

Deliberate attention to action in the ATTEND condition was not essential for the normal subjects to perform the correct movements. However, the ATTEND condition corresponds to the type of deliberate (or willed) direction of action described by Norman and Shallice (1980). The supervisory attentional system has been associated with the prefrontal cortex (Baddeley, 1986; Norman and Shallice, 1980; Shallice, 1989), and the activation of PFd in the current study supports this.

The neural substrate of schemas has attracted less attention. Likely candidate regions include the parietal and premotor cortex. These have been proposed to form a 'dorsal stream' enabling the transformation of visual stimuli into appropriate actions (Goodale and Milner, 1992). These areas are in receipt of visual information; demonstrate patterns of activity related to spatial attention and movements of the eyes and limbs; and are connected to direct motor output structures (Wise *et al.*, 1997). Activity of cells in the premotor cortex and supplementary motor area has been associated with complex purposeful actions, analogous to schemas (di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996; Tanji and Mushiake, 1996). Moreover, dorsal premotor cortex is dominated by cells that exhibit specificity for the goals of actions rather than the trajectories that can be used to reach the target (Shen and Alexander, 1997).

However, schemas were proposed following a functional analysis of attentional control of action. The neuronal activity underlying schemas may be distributed rather than localised to a single region.

The present study was not designed to distinguish between the several different cognitive processes that may occur when subjects 'attend to action' as in the earlier study by Jueptner *et al.* (1997). However, the consistency of the behavioural and neuroimaging effects across the group supports a common set of cognitive operations in response to the instruction "think about the next move". **First**, the subjects may attend to the representation of movement. Jeannerod (1997) has suggested that the 'representation' of movement involves the same mechanisms as motor preparation, but simple preparation would not be expected to increase the response time variability. **Second,** they may attend to the finger used. The activation of SII and parietal cortex in the ATTEND condition (versus REST) is consistent with attention to the finger position. **Third**, the subjects may attend to the 'goal' or target of the movement, that is the depression of the button. However, the instruction was not to attend to the sensory feedback or remote consequences of action (cf. (Blakemore *et al.*, 1998; Fink *et al.*, 1999; Jueptner *et al.*, 1996), and subjects were not required to learn a correct from an incorrect button press.

In the present study there was activity in the dorsal prefrontal cortex both in the ATTEND condition as in the study by Jueptner *et al* (1997) and in the SEARCH condition as in the study by Coull *et al* (1998). It could be argued that the prefrontal activation in these conditions reflects the operation of working memory. However, the 'on-line' maintenance of the current sequence position or the target letter represented a trivial memory load. The load is less for example than the three locations studied in chapters 4 and 5. There is evidence that activation of prefrontal area 46 is associated instead with executive processes, such a monitoring (Petrides, 2000; Petrides, 1995a), manipulating (D'Esposito *et al.*, 2000c) or selecting between

(chapters 4 and 5) items in memory. Petrides (1995) has defined 'monitoring' in terms of selective attention, that is attending to one item at the expense of others over a period of time, and this concept is related to 'attentional selection'.

In the current study, the main effect of attention to action included activation differences in premotor cortex. This contrasts with differential activations for movements of one finger versus another, as studied in chapter 6. Differential activity would be present in neuronal sub-populations, identifiable in principal by recording cellular firing patterns. But, the differential activity between neurons representing different actions might not exert an effect on a voxel's population as a whole, sufficient to be detected by fMRI. The current results therefore are consistent with the attentional selection of action representations in the premotor cortex. However, they do not distinguish between the selection of a specific sub-population of cells and a non-specific increase in activity the whole premotor population.

Inferences based on regional interactions (effective connectivity)

Structural equation modelling has many advantages in the analysis of the interactions between psychological conditions such as attention, and physiological variables such as BOLD fMRI time series (Horwitz *et al.*, 1999). Two broad approaches can be distinguished. First, the approach used in this study was to analyse all conditions in a single model. The model includes moderator variables that indicate how changing conditions alter the connectivity between two areas. These can be thought of as interactions between the psychological causes of a regional response in a target area (attention) and the physiological causes (activity in source area). This has advantages over 'stacked model' approaches (see below) when the sequential scans are not independent: the gradual BOLD response to neuronal events means that the

early scans of one condition may include residual effects of the previous task. In calculating the moderator variables, these gradual changes can be mirrored by convolution of the psychological variable by a canonical haemodynamic response function (Buchel and Friston, 1997). In addition, the inclusion of data from all scans in our single model means that the covariance between two regions is dominated by variability induced by the conditions. In our model this was principally motor-related activation, moderated by attention.

This differs from the alternative approach, which uses separate analyses of inter-regional covariance under different conditions (Coull *et al.*, 1999; Horwitz *et al.*, 1999; McIntosh, 1999; McIntosh and Gonzalez-Lima, 1991; McIntosh *et al.*, 1994; Nyberg *et al.*, 1996). In this approach, the covariance between two regions within a condition arises from scan-to-scan variability, which is not under experimental control and whose causes are not specified by the paradigm. Furthermore, dispersion of the responses by the haemodynamic response function cannot easily be accommodated.

The path coefficients from the moderator variables describe the extent to which the interaction between source area activity (prefrontal or parietal cortex) and cognitive processes (attention to action or to conjunction search) influence the target (premotor cortex). This was assessed in the context of possible direct influences from the source areas and the cognitive processes. There are two interpretations of a significant positive value. Firstly, the activity of the source area influences target area activity more under one cognitive condition than another. An alternative interpretation is that the activity of the source area changes the extent to which the cognitive condition influences target area activity. Both interpretations are valid and are identical to psychophysiological interactions as defined for neuroimaging (Friston *et*

al., 1997b). However, the anatomical and cognitive contexts may favour one interpretation over the other. It is suggested here that the pre-frontal cortex mediates the effect of attention to action on premotor cortex.

Summary

Attention to action was associated with increased activation of PFd (middle frontal gyrus, area 46), when compared with automatic performance of the same movements. Attention to action was also associated with increased effective connectivity from PFd to the premotor cortex. This coupling was not attributable to common inputs from parietal cortex. The effect was specific to attention to action, rather than a non-specific effect of attentiveness per se.

Table 7.1. Locations of peak significant cerebral activation for each task contrast, $p<0.05$ (corrected for whole brain multiple comparisons). Activations indicated by an asterisk were significant only within the hypothesised regions of interest, $p<0.05$ (corrected for multiple comparisons within the reduced volume)

Region of activation	L/R	coordinate			t-value
		x	y	z	
Simple sequence movement (MOVE) vs rest					
Premotor cortex	L	-34	-12	68	10.47
Primary motor cortex	L	-48	-22	48	8.77
Cerebellum	R	26	-58	-22	9.76
Ventrolateral thalamus	L	-16	-16	10	8.28
Attention to action (ATTEND) vs rest					
Middle frontal gyrus	L	-34	44	22	8.77
	L	-34	34	36	7.36*
Frontal polar cortex	L	-38	52	6	4.75*
Premotor cortex	L	-34	-10	68	9.89
		-42	0	46	8.01*
SMA	L	-6	-6	68	10.56
Pre-SMA	L	-6	0	54	9.92
Primary motor cortex	L	-56	-24	50	8.23
Intraparietal cortex	L	-32	-52	48	6.22*
SII	L	-62	-20	22	12.44
Insula/claustrum	L	-38	0	0	9.29
Cerebellum	R	18	–54	-22	14.35
	L	-30	-64	-26	13.67
Visual conjunction search (SEARCH) vs rest					
Middle frontal gyrus	L	-44	30	44	5.05*
Inferior frontal sulcus	L	-42	6	30	10.14
Paracingulate cortex	L	-6	10	50	8.28
Intraparietal cortex	R	32	-56	52	9.49
	L	-28	-56	52	6.42*
Inferior parietal cortex	L	-50	-52	38	9.05
Inferior temporal gyrus	R	46	-60	-22	13.66
	L	-44	-60	-24	11.66
Prestriate cortex	R	42	-84	-18	12.41
	L	-46	-76	-12	10.4
Dual task (DUAL) vs rest					
Paracingulate cortex	L	-4	6	50	14.00
Premotor cortex	L	-34	-10	68	9.99
Intraparietal cortex	L	-28	-54	44	14.09
Inferior temporal cortex	R	46	-66	-22	13.39
	L	-36	-64	-24	15.54
Prestriate cortex	R	40	-78	-20	12.02
	L	-46	-76	-12	9.14
Cerebellum	R	22	-52	-24	11.51

Table 7.2. Locations of peak significant cerebral activation for each task contrast, $p<0.05$ (corrected for whole brain multiple comparisons). Activations indicated by an asterisk were significant only within the hypothesised regions of interest, $p<0.05$ (corrected for multiple comparisons within the reduced volume)

Region of activation	L/R	coordinate			t-value
		x	y	z	
Attention to action (ATTEND) vs simple sequence movement (MOVE)					
Middle frontal gyrus	L	-36	34	34	5.65*
Frontal polar cortex	L	-34	50	6	5.37*
Premotor cortex	L	-40	0	44	7.57*
		-24	0	62	6.62*
Intraparietal cortex	L	-32	-42	50	6.26*
Cerebellum	L	-28	-60	-28	9.25
Dual task (DUAL) vs attention to action(ATTEND)					
Intraparietal cortex	R	36	-56	52	10.38
Inferior temporal gyrus	R	38	-34	-26	13.91
	R	42	-62	-20	12.24
	L	-34	-56	-20	11.15
Prestriate cortex	R	36	-84	-6	10.55
	L	-46	-74	-12	15.53
Negative interaction between movement and visual conjunction search					
Premotor cortex	L	-48	-6	54	4.96*

Chapter 8

Attention to action in Parkinson's disease

Introduction

It has long been observed that movements in patients with Parkinson's disease are more impaired when distracted from their primary motor task, whether by synkinesis (Brown and Marsden, 1991; Serrien *et al.*, 2000) or a simultaneous cognitive task (Oliveira *et al.*, 1998). Conversely, movements may be improved transiently by specific attention towards the goal of the primary motor task (Oliveira *et al.*, 1997). However, even when they attend to their actions, patients with Parkinson's disease do not exhibit entirely normal kinematics.

The phenomenon of attention to action has been studied in healthy young adults using positron emission tomography (PET) (Jueptner *et al.*, 1997b) and fMRI (chapter 7). In chapter 7, subjects were scanned during performance of a pre-learned motor sequence. When subjects were asked to 'think about the next move', there was greater activation of the dorsal prefrontal and premotor cortex compared with simple execution of the same sequence. Attention to actions may also be essential for free selection of actions including trial and early error learning (Passingham, 1993; Passingham, 1996), which also has been associated with prefrontal and premotor cortical activation (Catalan *et al.*, 1999; Jahanshahi *et al.*, 1995; Jenkins *et al.*, 1994; Jenkins *et al.*, 2000; Jueptner *et al.*, 1997a; Toni *et al.*, 1998).

In addition to the increased activation within prefrontal and premotor cortex, chapter 7 described an increase in connectivity between prefrontal and premotor cortex during attention to action. This increase in connectivity was a predicted consequence of top-down bias from prefrontal to premotor cortex, during attention to action.

If attention to action in healthy subjects is mediated by pre-frontal-premotor interactions, could this be the mechanism of attentional modulation of motor performance in patients with Parkinson's disease? A problem with such a simple assumption is that psychometry of patients has suggested impairments on tests sensitive to frontal lobe damage (Lange *et al.*, 1993; Owen *et al.*, 1997; Stam *et al.*, 1993), proportional to the reduction in frontal and striatal dopamine metabolism (Rinne *et al.*, 2000). It remains unclear whether these impairments are primarily related to mesocortical dopamine deficiency or abnormal dopamine dependant fronto-striatal interactions. Nevertheless, these interactions between prefrontal and premotor areas were the subject of the current study of Parkinson's disease.

Functional imaging of patients with Parkinson's disease during simple movements has yielded a complex pattern of results. A recurrent finding has been reduced activity of the supplementary motor area (SMA), as measured by PET (Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1992; Samuel *et al.*, 1997a; Thobois *et al.*, 2000), fMRI (Haslinger *et al.*, 2001; Sabatini *et al.*, 2000) and ERP (Jahanshahi *et al.*, 1995), especially when the movement or its timing are chosen by the subject themselves (Catalan *et al.*, 1999; Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995; Praamstra *et al.*, 1996). Further, this underactivity has been reversed by treatments including l-dopa (Haslinger *et al.*, 2001), apomorphine (Jenkins *et al.*,

1992; Rascol *et al.*, 1992), pallidotomy (Grafton *et al.*, 1995; Samuel *et al.*, 1997b) and stimulation of the subthalamic nucleus (Ceballos-Baumann *et al.*, 1999).

However, impaired activation of the SMA is not a consistent finding. Catalan *et al.* (1999) showed that increasing complexity of a learned motor sequence task lead to greater increases in activation of the SMA in patients than controls. Sabatini *et al.* (2000) reported increased activity of caudal SMA in patients during sequential finger movements, and Samuel *et al* (2001) observed no difference in SMA activation in a task that required execution and working memory for freely selected moves.

Many of the studies that had shown SMA impairment with Parkinsonism used motor tasks requiring a degree of attention to action, including free selection of movement or freely selected timing of movement. In contrast, movements that were specified by an external cue, or by their place in a fixed overlearned sequence, were associated with lesser or no deficits in SMA activity (Catalan *et al.*, 1999; Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995; Nakamura *et al.*, 2001; Praamstra *et al.*, 1996). It is therefore necessary to distinguish impairments related to movement per se, and deficits related to the selection of or attention to action.

Compensatory increases in premotor and parietal cortical activation have also been reported in some studies (Haslinger *et al.*, 2001; Sabatini *et al.*, 2000; Samuel *et al.*, 1997a). It is possible that these represent neuronal plasticity for movement in the presence of a dysfunctional SMA in Parkinson's disease. However, the different patterns of regional activation may also represent different cognitive strategies for the initiation of movement, for example by greater attention to action than is given by normal subjects.

The current study had three principal aims. **First**, to determine regional cortical activations in patients and control subjects during a motor sequence task and the additional activation attributable to attention to action. This includes a replication of the study in chapter 7, with patients and an elderly control group. In addition, we aimed to distinguish the specific effects of attention to action from attentiveness per se, and therefore we also used a non-motor visual attention task. However, we did not aim to repeat the analysis of visual attentional modulation of connectivity between visual cortical regions (e.g. Buchel and Friston, 1997). As in chapter 7, the visual search task was used to distract attention away from the motor sequence task.

The **second** aim of this study was to permit a valid comparison between patient and control groups. For this it is necessary to estimate the variability of cortical activation during a task from subject to subject within each population (Friston *et al.*, 1999a; Friston *et al.*, 1999b). Previously fMRI studies of Parkinson's disease have employed fixed effects models, that do not support such direct patient-control contrasts (except Haslinger et al, 2001). In fixed effects models, group differences may be mis-interpreted as disease related abnormalities in task effects, rather than less relevant inter-subject differences, or (in fMRI) artefacts due to sessional variance in fMRI signal and sensitivity ('session effects') (McGonigle *et al.*, 2000).

So far we have discussed the abnormalities *within* frontal regions in patients with Parkinson's disease. However, it may be more relevant to consider abnormal interactions *between* different brain regions. For example, the motor programming deficits of Parkinson's disease have been proposed to result from a functional disconnection of the SMA (Dick *et al.*, 1986). In addition, effective treatment of

Parkinson's disease by pallidotomy has been associated with changes in cortical and subcortical connectivity of the SMA (Grafton *et al.*, 1995).

The **third** aim of the present study was therefore to study the interactions *between* frontal brain regions, not just activations *within* discrete brain regions. Effective connectivity is measured by structural equation modelling of fMRI data over time (Buchel and Friston, 2000; Buchel and Friston, 1997; McIntosh and Gonzalez-Lima, 1994a), within specified constraints based largely on consideration of anatomical connectivity of the brain.

The same tasks were used in the current study that had been used in chapter 7. The analytical approach was also similar. However, our new model also included the supplementary motor area, because of the previous evidence of abnormal function in Parkinson's disease. We proposed that patients with Parkinson's disease are able to activate the SMA in association with some motor tasks, but that they are impaired at modulating this activity under different conditions, particularly those that include attention to action.

Methods

Subjects

Twelve patients with idiopathic Parkinson's disease (IPD) and twelve age matched controls participated in this study, with written informed consent in accordance with the Declaration of Helsinki. They were recruited from outpatient clinics at the University College London Hospitals NHS Trust. Inclusion criteria were a clinical diagnosis of idiopathic Parkinson's disease; without dementia; without symptomatic autonomic dysfunction; with normal ocular movements; bilateral disease of mild to moderate severity, Hoehn and Yahr grades II to III (Hoehn and Yahr,

1967); with no current depressive illness; and no history of other neurological or psychiatric disease. Unified Parkinson's Disease Rating Scale (UPDRS) interview and examination was conducted on all subjects, at recruitment and again in the 'off' state immediately prior to scanning. Anti-parkinsonian medication was stopped at least twelve (standard l-dopa preparations) or twenty-four (controlled release l-dopa and dopamine receptor agonist) hours prior to scanning, such that all subjects were in their 'off' state. Demographic details, medication and UPDRS (Fahn *et al.*, 1987) motor function scores are outlined in table 8.1. Twelve age matched controls (mean 62, +/- 6 years, seven men) were recruited from patients' spouses and a departmental register of volunteers, with no history of neurological or psychiatric disease.

Behavioural paradigm

The behavioural paradigm was identical to that outlined in chapter 7.

Behavioural data analysis

The time of each button press was recorded, from which we calculated the mean and variance of the time between consecutive button presses within each condition, and the latency between pacing cues and button presses. Subsequent behavioural data analysis used SPSS 8.0 for Windows NT.

For each motor task (MOVE, ATTEND, DUAL) the response latency and standard deviation of response intervals were separately entered into repeated-measures analyses of variance (using the Greenhouse-Geisser correction for non-sphericity), with factors of disease (patient vs control) and task (MOVE vs ATTEND vs DUAL). In addition, the response latency and interval standard deviation were

fitted to the UPDRS motor severity score, across all subjects, using linear and quadratic polynomial regression models.

Functional imaging

The acquisition of fMRI and structural MRI data on all subjects was similar to that described in chapter 7. Subjects lay supine with their head fixed by firm foam pads. Instructions were projected onto a screen mounted on the head coil and auditory pacing cues were delivered through padded headphones, controlled by Apple Macintosh 7600 computer operating Cognitive Interface software (Cogent, Wellcome Department of Cognitive Neurology, UK). Four lightly sprung buttons were mounted under the subjects' fingertips, on a moulded splint that supported a comfortable neutral hand-wrist position.

Functional imaging used T2*-weighted echo-planar MRI at 2-tesla, repeat time 3650 ms, echo time 40 ms, throughout 28 minutes continuous whole brain imaging (64x64x40 voxels, 3mm isotropic resolution). The first five images were discarded to allow steady state magnetisation. Statistical Parametric Mapping software was used for image processing and analysis (SPM99, http://www.fil.ion.ucl.ac.uk/spm). The images were realigned to the mean image by rigid body transformation, sinc interpolated in time to correct for phase shift during volume acquisition, and transformed to normal anatomic space (Talairach and Tournoux, 1988), using the Montreal Neurological Institute template, by non-linear transformations (Friston *et al.*, 1995b). In the determination of normalisation parameters, greater regularisation was used than for the younger subjects in chapter 7. This was because the age related changes in skull and sinus formations can cause greater distortion of T2* weighted images in older subjects. For individual subject

analyses, the data were spatially smoothed with a Gaussian kernel of full width half maximum 6 mm (FWHM). High-resolution T1-weighted images were acquired to permit anatomical localisation of activation foci.

Individual subject analysis (level 1)

The first level analysis of data from each subject was similar to that described in chapter 7. A general linear model was applied voxel-wise to the functional data (Friston *et al.*, 1995a; Friston *et al.*, 1996), using covariates for the epochs MOVE, SEARCH, DUAL, ATTEND, REST and the response period, and transient covariates for the instruction cues and responses. Each covariate was convolved by a canonical haemodynamic response function. The first temporal derivatives of movement parameters estimated during the realignment pre-processing were also included in the model, in case of movement related artefacts that could not be corrected by rigid body realignment.

Subject specific grand-mean scaling was used, without proportional scaling of each image. The two groups did not differ in their mean brain T2* MRI signal ($t= 0.1$, $df=22$, ns), and therefore there was no significant difference between patients and control subjects in the grand-mean scaling factor. Low frequency drifts in BOLD signal were removed by a high pass filter with a cut-off of 400 seconds.

For each voxel, parameter estimates and variance were derived for each covariate in a subject specific fixed effects model. Contrast images of interest were calculated for each subject, including the main effects of movement and conjunction search (excluding ATTEND condition), interactions between movement and conjunction search, and the pairwise contrast between MOVE and ATTEND conditions. A statistical parametric map of the F-statistic for all conditions in the

model was generated, SPM{F}, from which voxels were later selected for structural equation modelling.

Random effects analysis (level 2)

The first level analysis of data from each subject was similar to that described in chapter 7. To accommodate inter-subject variability in group analyses, a secondary spatial smoothing kernel of FWHM 10 mm was applied to the contrast images from level 1, equivalent to an overall smoothing of the functional images by a kernel of FWHM ~12 mm. For each contrast, the contrast images from level one were entered into a second level t-test, to create a SPM{t}-statistic image.

For the within-group analysis, a one-sample t-test was used (11 residual degrees of freedom), and for group by contrast interactions, a two-sample t-test was used (22 residual degrees of freedom). This two-stage analysis is equivalent to a mixed effects ANOVA and enables the inference based on specific contrasts to be extended to the general population from which the subjects were drawn (Friston *et al.*, 1999a), thereby permitting direct comparison of patients with control subjects.

For whole brain analysis, voxels were identified at which $p<0.05$ (corrected for multiple comparisons). Given our hypotheses regarding the effect of attention within the motor system, regions of interest analyses were also performed, with small volume correction for multiple comparisons (again $p<0.05$). The regions of interest were defined as spheres of 2cm diameter, centred on voxels of peak activation that had been identified on the separate group of young subjects using in chapter 7. These included the primary motor cortex, premotor cortex, SMA, prefrontal cortex, intraparietal cortex, cerebellum and putamen.

I assumed homogeneity of variance (homoscedasticitiy) in the second level analyses. The behavioural data suggest that patients are more variable than controls. Fortunately however, with similar group sizes, the analysis of variance is robust to heterogeneity of variance (Howell, 1992).

Individual structural equation modelling (level 1)

Effective connectivity analyses were performed using the method described for fMRI time series by Buchel and Friston (Buchel and Friston, 2000; Buchel and Friston, 1997) and used in chapter 7. The model is illustrated in figure 8.1, and included the prefrontal, premotor and primary motor cortex of the dominant hemisphere, and the supplementary motor area. It was based on anatomical interconnections between primary and non-primary cortical motor areas in primates, indicated by solid arrows (Barbas and Pandya, 1987; Johnson *et al.*, 1996; Lu *et al.*, 1994; Muakkassa and Strick, 1979; Rizzolatti *et al.*, 1998)

The specific coordinates for these four regions for each subject were taken from the nearest peak voxel in the first level SPM{F} map. Regions were defined as 5mm radius spheres, including all voxels that exceeded $p<0.001$ (uncorrected) in the SPM{F} for all effects. The first principal component of the adjusted BOLD signal was entered into the model as used by Buchel and Friston (1997, 2000). All subjects had significant regional activations in the SPM{F} and were included in the analysis, in contrast to chapter 7, in which 2 subjects had not.

Our application of structural equation modelling included all conditions in a single model. It included moderator variables that indicated how changing conditions altered the connectivity between two areas. The moderator variables were constructed in the same way as those in chapter 7. They can be thought of as interactions between

the psychological causes (e.g. attention) of a regional response in a target area (e.g. premotor cortex) and the physiological causes (i.e. activity in source area such as prefrontal cortex). The moderator variables were calculated as the products of the vectors of the time-course of the attentional paradigms and the activity in the source area (Buchel and Friston, 1997). The time course for the conjunction search (SEARCH) was orthogonalised with respect to attention to action (ATTEND), such that the search task was nested within the 'not-attending-to-action' time. The task covariates were convolved by a canonical haemodynamic response function and multiplied by the activity in the prefrontal and parietal cortex to form the interaction or moderator variables. Figure 8.1 illustrates that attention to action (AA) and attention to visual search task (VS) may influence the coupling between the anatomic regions of the model (dashed lines).

Group effects structural equation modelling (level 2)

A path coefficient from the subject specific structural equation model indicates the influence of one region, or one moderator variable over another. Although the significance of a path coefficient can be determined for each subject separately, the primary interest was to compare the patient and control groups in terms of the attentional effects on their inter-regional connectivity. Therefore, for each interaction term representing potential attentional modulation of cortico-cortical connectivity in the model, the moderator path coefficient was entered in to a second-level three-way analysis of variance (SPSS 8.0). The presence of disease was a between-groups factor (two levels: patient vs control). There were two repeated-measures factors: attentional moderator (two levels: attention to action and attention to search) and the connection

subject to moderation (four levels: prefrontal to premotor, prefrontal to SMA, SMA to primary motor and premotor to primary motor cortex).

Results

Behavioural data

The variability of the response interval (the standard deviation of response intervals) for each subject has been averaged for each group for each task, and is shown in figure 8.2. The response interval variability differed significantly between tasks ($F=3.8$, df 1.6,35.2, $p<0.05$), but also between groups ($F=5.9$, df 1,22, $p<0.05$). Both groups were more variable during ATTEND condition, and the patients were more variable in all conditions. The task by group interaction was not significant ($F=0.8$, df 1.6, 35.2, ns), indicating that the two groups did not differ significantly in the effect of attention to action on the response variance.

The response latencies for the two groups on the three movement tasks are shown in figure 8.2. Response latencies were longest in the MOVE condition, for both groups: analysis of variance indicated a significant main effect of task ($F=3.7$, df 1.8,36.7, $p<0.05$), but no main effect of disease ($F=0.2$, df 1,21, ns) and no disease by task interaction ($F=0.3$, df 1.8,36.7, ns).

In the patients, there was no significant linear or non-linear relationship between the UPDRS severity score and the mean response latency across subjects for the MOVE condition ($F=1$, df 21, ns, and $F=1.9$, df 20, ns respectively). The variability of response intervals (as indicated by the standard deviation of response intervals for each subject) did increase linearly with severity of motor symptoms ($F=4.3$, df 22, $p<0.05$), at approximately 3 ms per point on the UPDRS motor scale.

Statistical Parametric Mapping

Table 8.2 lists those areas for which there was a significant main effect of movement (MOVE + DUAL - REST - SEARCH) in normal subjects, patients, and the difference in this effect between groups. The pattern of activations is similar in patients and control subjects, including medial and lateral premotor regions, primary motor cortex, parietal cortex and cerebellum. Significant disease by contrast interactions are present, including relative under-activity of the putamen in patients, and over-activity of the caudal SMA.

Table 8.3 lists those areas in which there was a significant main effect of conjunction search (DUAL + SEARCH - MOVE - REST) in normal subjects, patients, and the difference in this effect between groups. Parietal and infero-temporal regions are activated in both groups, but patients failed to show the normal pattern of prefrontal activation during the visual search task. There were no significant interactions between the motor task and visual search task, in terms of activation within the specified regions of interest.

Table 8.4 lists those areas in which there was activity attributable to attention to action (ATTEND – MOVE), in both groups and the difference in this effect between groups. There was increased activation of prefrontal cortex, SMA, paracingulate cortex and cerebellum in control subjects but not patients. The patients showed significantly less activation in the SMA and parietal cortex.

Figure 8.3 shows the SPM results for normal controls, patients, and the group differences, superimposed on a T1 image of a representative brain. Results are shown for the main effects of each task, and the additional activation associated with attention to action. The formal statistical comparisons of controls vs patients, shown

in figures 8.3 bottom two rows and 8.4b, show fewer areas of significant difference than do superficial visual comparisons of the thresholded images shown in figures 8.3 (top two rows).

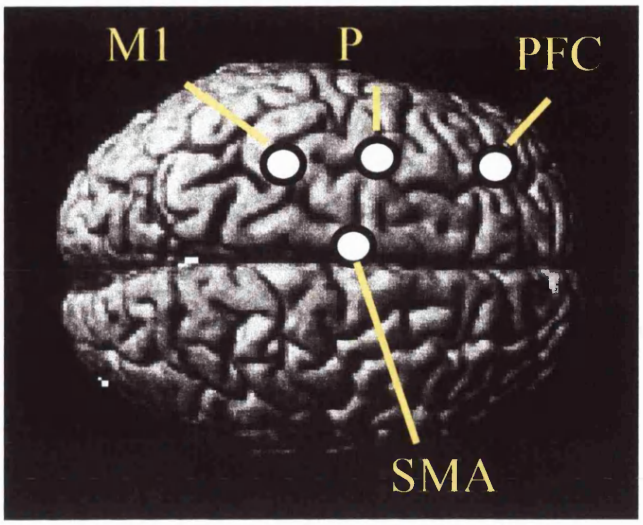
Structural equation modelling

Path coefficients for the anatomic connections and moderator variables were calculated for each subject. The modulation of each connection by each attentional task for each group is summarised by the group mean (+/- SE) path coefficient. These are displayed in figure 8.5. In normal subjects, attention to action was associated with stronger coupling between prefrontal and premotor cortex, and between prefrontal cortex and SMA. In patients, this attentional modulation of coupling did not occur, either to premotor or to SMA. Attention to the visual conjunction search was not associated with changes in inter-regional connectivity in either controls or patients.

Analysis of variance of these values indicated a significant difference between the two attention tasks ($F=10.1$, df 1,19, $p<0.01$) and an interaction between the effects of task and the patient group ($F=16.8$, df 1,19, $p<0.001$), confirming the greater modulatory effect of attention to action in the control group. There was a trend to an overall effect of connection ($F=2,2$, df 3,57, $p<0.1$), but no overall effect of patient group ($F=0.6$, df 1,19, ns).

Discussion

The techniques of SPM and SEM are complementary in understanding the neural activations associated with movement. SPM reveals activation *within* brain regions, associated with different tasks, and the interaction between disease and task related regional activation. In contrast, SEM reveals the interactions *between* brain



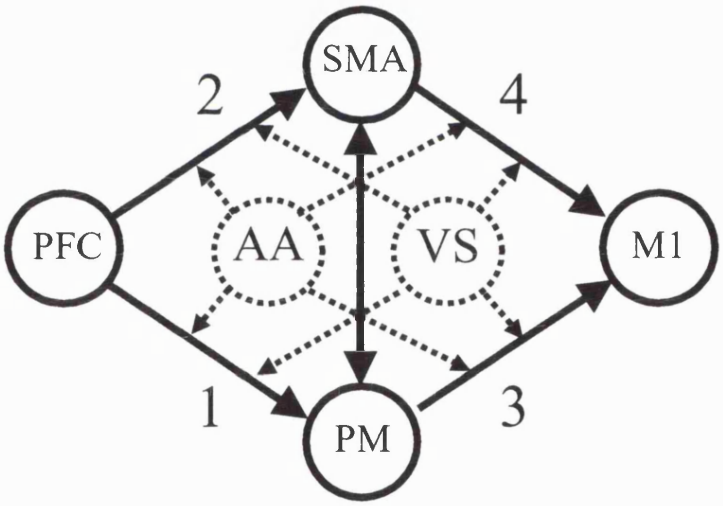


Figure 8.1. The structural equation modelling included BOLD fMRI time-series from four cortical motor regions: prefrontal cortex (PFC), premotor cortex (PM) primary motor cortex (M1) and the supplementary motor area(SMA). The connections between these regions are indicated by solid lines. Connections 1-4 may be modulated by the attentional context of motor performance. Attention to action (AA) or attention to the visual search task (AS) were included in the model as moderators of connections 1-4.

Behavioural data: PD and control

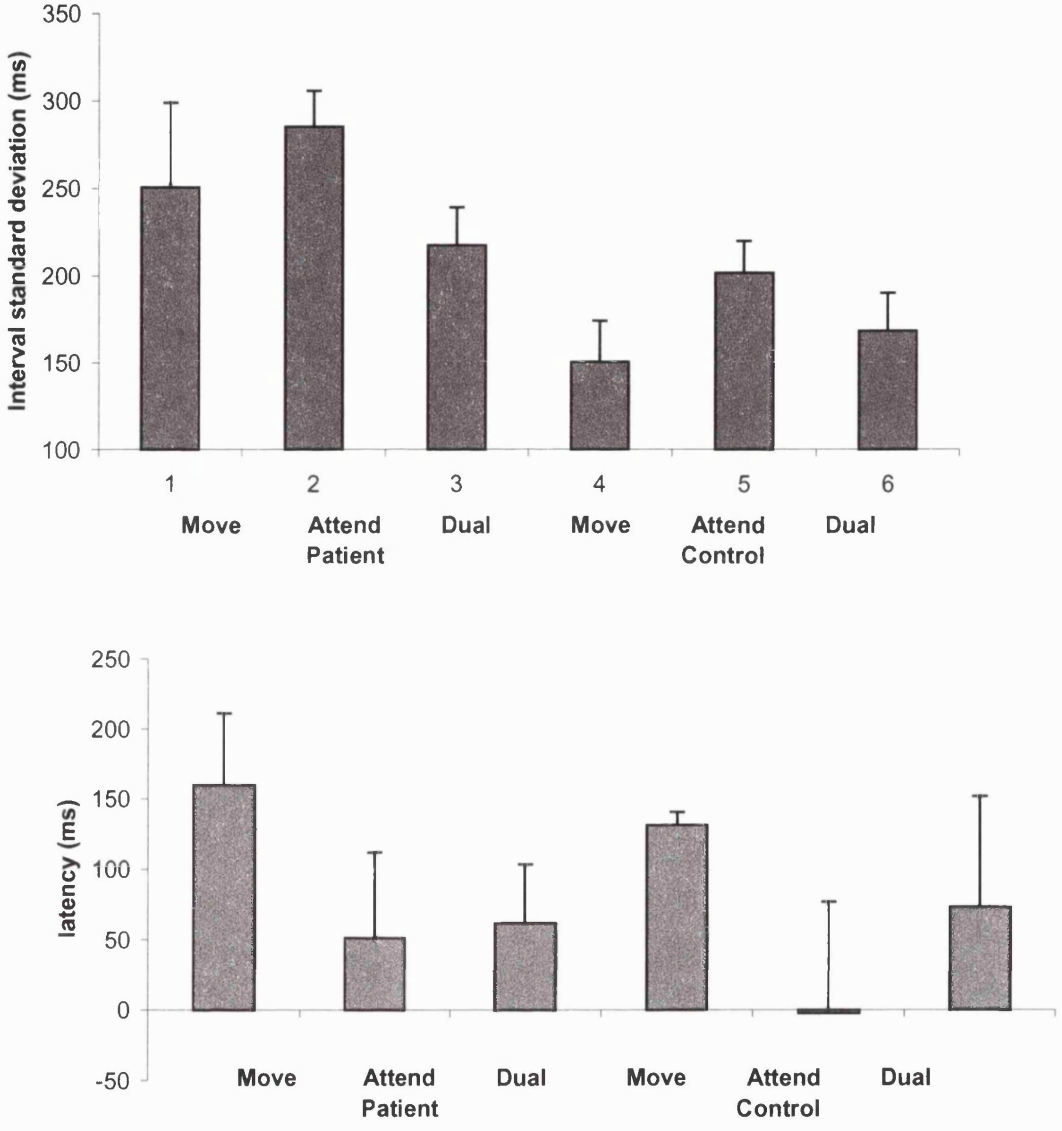


Figure 8.2. The mean (+/- SE) interval standard deviation (above) and response latency (below) for both patient and control groups, for the three tasks in which motor responses were made (MOVE, DUAL, ATTEND).

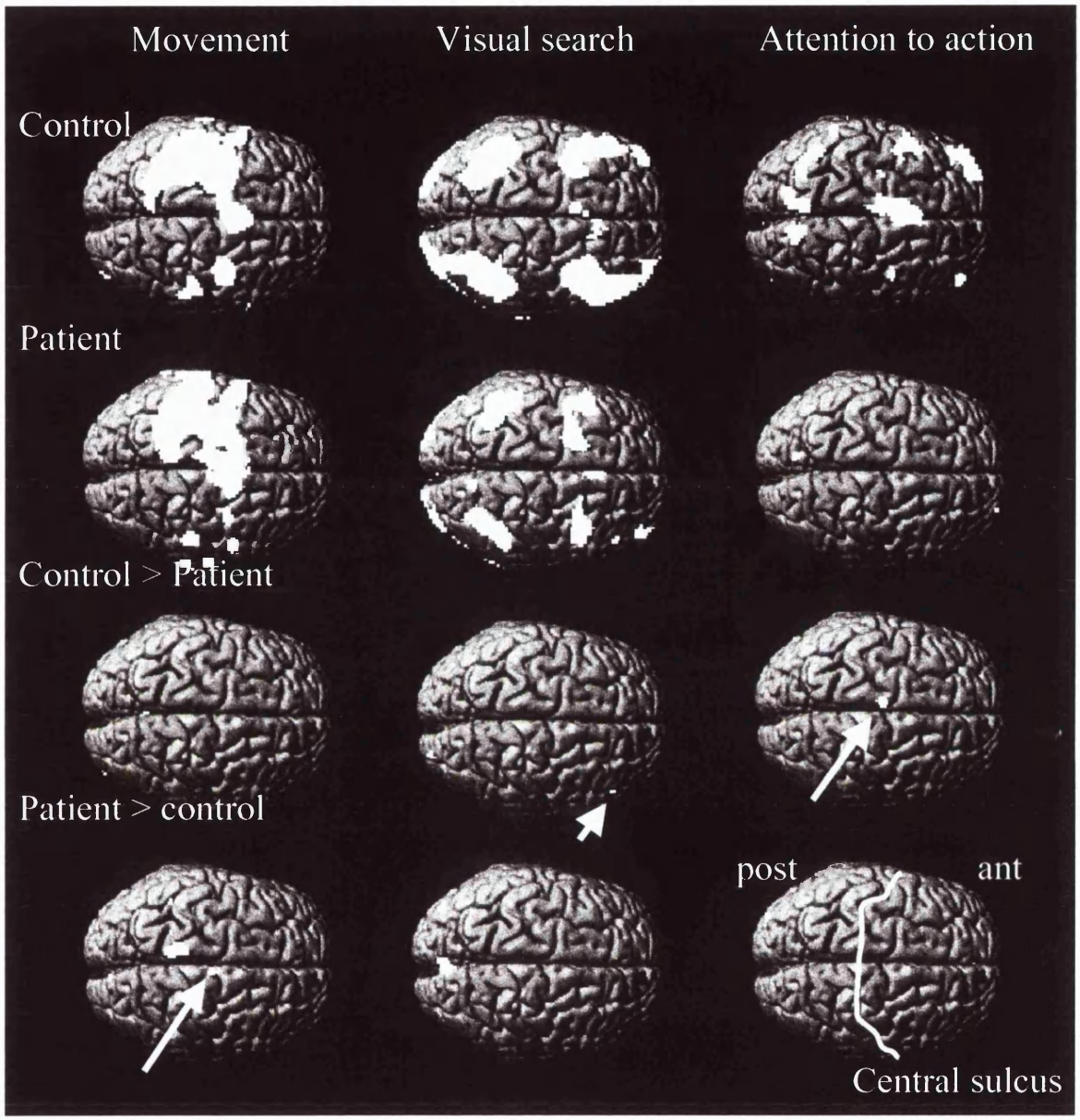


Figure 8.3. Regions of significant activation associated with movement (versus rest), visual search (versus rest) and attention to action (versus simple movement) , shown as thresholded SPM{t}s at $p<0.001$(uncorrected) superimposed on a representative brain in normal anatomic space. For each contrast of conditions, the effects are shown for normal controls subjects, patients with Parkinson's disease, and the difference between groups (contrast by disease interactions). For the corrected significance of regional effects, see table 1 and table 2, and the results section.

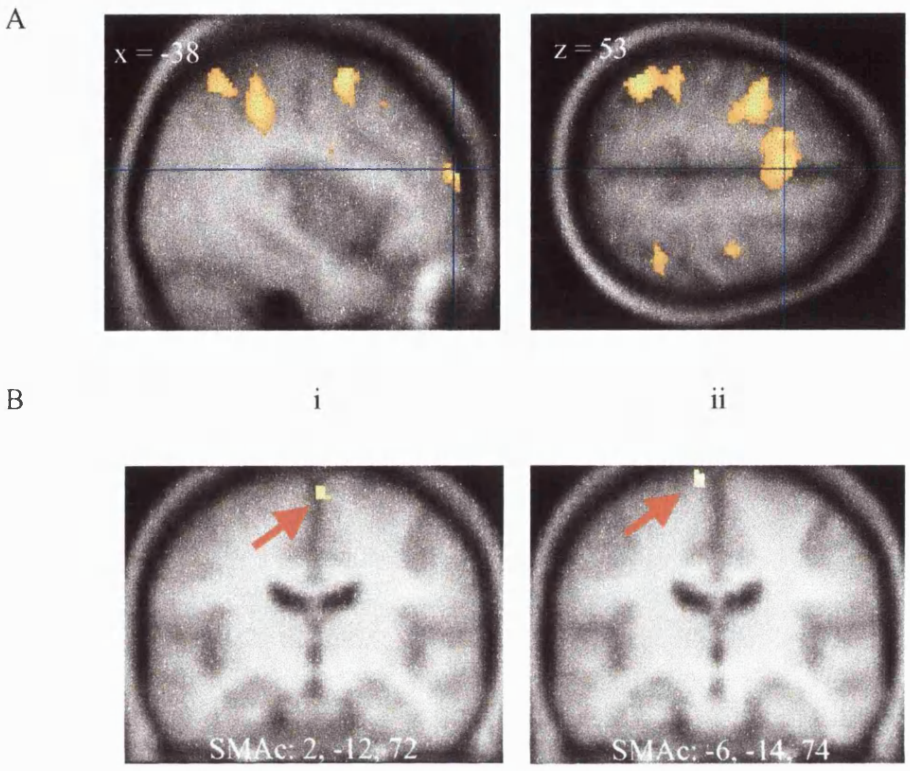


Figure 8.4 (a) Regions of significantly greater activation in normal controls for the contrast ATTEND vs MOVE, showing greater activation in prefrontal, premotor, parietal cortex and the SMA when subjects attended to their actions. These activations are significant at $p < 0.05$ within the region of interest. The SPM{t}s are thresholded at $p = 0.001$ and superimposed on parasaggital and axial slices from the mean T1 structural image of the group. Compare with figure 7.4, for the same contrast in young subjects. (b) SPM{t}s for the disease by contrast interactions indicating (i) that the caudal SMA (arrowed) is ***more*** active in patients than controls for simple movement, but (ii) the additional activation in the caudal SMA during attention to action is ***less*** in patients than healthy controls.

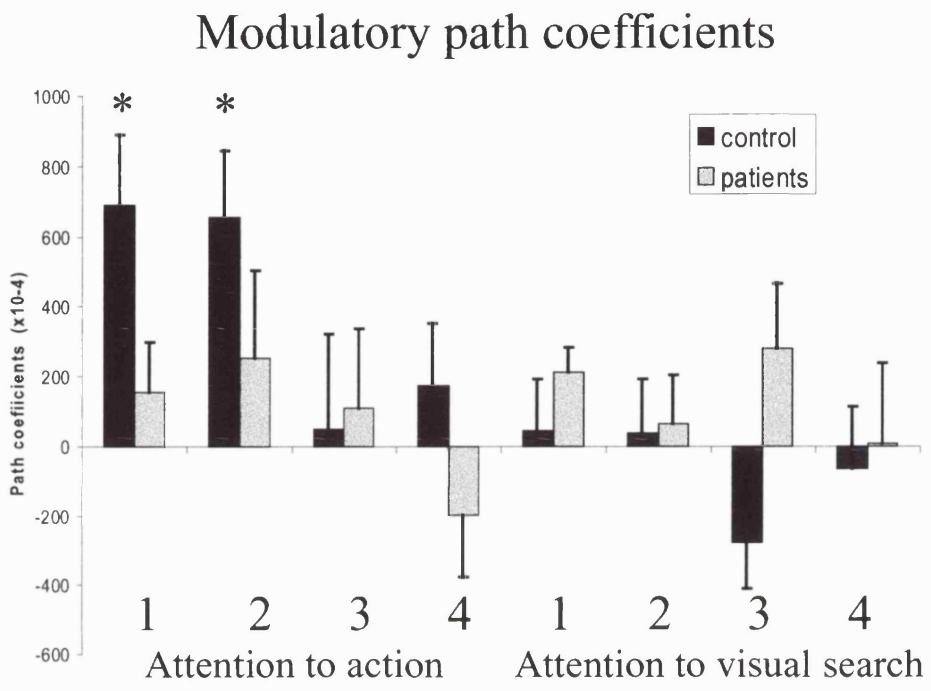


Figure 8.4 Path coefficients for the modulatory effects of attention to action and attention to the visual search task on the coupling between the four cortical motor regions, indicated by the four paths (1-4) in figure 8.1.

regions under different experimental conditions (attention to action, attention to visual search and no specified attention), and the effect of disease on these interactions. The current results show specific changes in motor related neural activity in Parkinson's disease, including abnormalities in effective connectivity and specific regional activations.

Task related activations: within and between groups

The attention tasks were designed to be as similar as possible to those used by Jueptner et al (1997) to study attention to action and Coull et al (1998) to study visuospatial attention with no motor component. Intermittently throughout the experiment, our subjects also performed a simple motor sequence task. In normal subjects, performance of the motor sequence (MOVE and DUAL) was associated with a typical network of cortical (primary motor cortex, premotor, paracingulate, parietal cortex and SMA) and subcortical (putamen, thalamus, cerebellum) regions. These regions are similar to those associated with the task in young normal subjects (chapter7). The absence of significant prefrontal activation is consistent with the motor task having become automatic, following pre-training (Toni *et al.*, 1998). The behavioural data also suggest that after pre-training, the motor task was automatic or 'directly' processed (Cohen *et al.*, 1990), in that the addition of a visual distractor task did not significantly increase the response time variance (DUAL vs MOVE) (see figure 8.2).

The patients showed a broadly similar pattern of motor related activations (see figure 8.3, top two rows), with two notable exceptions. Firstly, there was increased activation of the caudal SMA (see figure 8.3, bottom row, and table 2). Secondly, there was diminished putamen activation associated with movement (table 2),

consistent with functional imaging and metabolic studies that have shown reduced putamen metabolism in Parkinson's disease (Brooks, 1997, 1999; Eidelberg, 1998).

The dysfunction of the SMA in Parkinson's disease has been emphasised in previous neuroimaging studies. The current results indicate that on a simple over-learned motor sequence task, patients with Parkinson's disease do show activation of the SMA relative to rest, as part of a typical distributed network of non-primary motor areas. In fact, the caudal SMA activation is slightly greater than that in normal subjects. This has been reported previously by Sabatini *et al.* (2000). They speculated that it may have been due to the early stage of disease in their subjects; the complexity of their motor sequence (c.f. Catalan et al, 1999) or due to a greater functional similarity between caudal SMA and parietal-premotor cortex than rostral SMA. The current results argue against at least the first two of these explanations: the data was obtained from more severely affected patients, on a very simple sequence.

In contrast to the patterns of regional activation during the MOVE task, when patients were asked to attend to their actions, they failed to show the normal increase in SMA activation (see figure 8.3, third row, third column). This occurrence of reduced activation of the SMA in some contrasts between motor tasks but not others has been reported in PET and ERP studies of Parkinson's disease (Catalan *et al.*, 1999; Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995; Nakamura *et al.*, 2001; Praamstra *et al.*, 1996).

The reason for this variable SMA deficit is suggested by the analysis of effective connectivity. Attention to action is associated with greater coupling between prefrontal cortex and both the SMA and lateral premotor areas, in normal subjects but not patients (see figure 8.5). In other words, in Parkinson's disease the SMA was not

differentially sensitive to input from prefrontal cortex under different task demands. This represents a functional disconnection or de-afferentation of the SMA, rather than persistent under-activity.

One might have expected compensatory increases in activation of premotor and parietal cortical in patients (Haslinger *et al.*, 2001; Sabatini *et al.*, 2000; Samuel *et al.*, 1997a). However, these areas were not significantly different on direct comparison of the two groups. Nevertheless, the magnitude of premotor activation associated with movement was greater for patients than controls bilaterally (left 1.36/0.55, right 0.58/0.31, % signal change). This was not significant on the formal group comparison, because of the high inter-subject variability within each group.

Performance of the visual search task (SEARCH and DUAL) by control subjects was associated with activation of prefrontal, parietal and inferotemporal cortex bilaterally, These areas had been identified in young healthy subjects by Coull et al (1998), using the same task. Patients showed significant activation only in parietal and infero-temporal cortex. On direct comparison between groups, the only significant difference ($p<0.05$ corrected) was in parietal cortex. However, at reduced threshold ($p<0.001$ uncorrected), patients did show less activation than normal subjects in dorsal (42, 28, 30, t=4) and ventral (50, 20, 14, t=4) prefrontal cortex. There were no regions of greater activity in patients than controls. Although patient's with Parkinson's disease often perform worse on tests typically associated with frontal lobe function (Lange *et al.*, 1993; Owen *et al.*, 1997; Stam *et al.*, 1993), they do not necessarily show reduced frontal hypometabolism during these tasks (Owen *et al.*, 1998, Owen, 1997 #16). These impairments have been linked to striatal deficits

within hypothesised cortico-striatal-thalamo-cortical circuits (Alexander *et al.*, 1990) rather than primary cortical dysfunction.

The relationship between dual task performance and activation of prefrontal cortex is more complex. When two tasks are performed together, then there may be activation of prefrontal cortex even though neither task in itself is associated with prefrontal cortical activity (D'Esposito *et al.*, 1995; Smith *et al.*, 2001). When one task is normally associated with prefrontal activation, then the addition of a second task may be associated with a reduction in activation (Fletcher *et al.*, 1998). Our simple motor sequence and visual conjunction search were independent tasks, forming a 2x2 factorial design (REST, MOVE, SEARCH, and DUAL). We found no significant interaction between these tasks in either patient or control group, and no difference between groups in terms of this dual task interaction.

Attention to action

Attended action compared with simple execution was associated with greater activation within the prefrontal and paracingulate cortex, and the SMA in control subjects (see figure 8.3, third column). Jueptner et al (1997) also reported greater activation in prefrontal and cingulate cortex, with trends towards greater activation of SMA, premotor cortex and cerebellum, when subjects attended their action. Patients failed to show this pattern of enhanced activation, and direct comparison confirmed significant impairments in the attention related activation of SMA and parietal cortex (see figure 8.3, third column, third row, and table 4).

The analysis of effective connectivity is particularly useful in understanding the patient related deficits associated with attended action. For normal subjects, attention to action is associated with increased coupling between prefrontal areas and

both the medial and lateral premotor regions. It has been proposed that the prefrontal cortex exerts cognitive control by a general mechanism of attentional selection of neuronal representations (Miller, 1999). This may operate in the motor domain (chapters 6 and 7) as well as sensory (Brefczynski and DeYoe, 1999; Rees *et al.*, 1997) and mnemonic (chapters 4 and 5) domains. The predicted consequence would be increased activity in neuronal populations representing actions (e.g. in premotor regions), in response to specific activity in the prefrontal cortex, appropriate to a particular task.

An increase in local activity in premotor regions induced by activity in prefrontal cortex would be measured as an increase in effective connectivity (Friston *et al.*, 1997a). This was confirmed in control subjects by the second level analysis of the path coefficients from the structural equation modelling: attention to action increases the coupling between prefrontal and premotor regions, including the SMA.

Impaired activation associated with attention to action could account for the deficits in SMA activity reported in many earlier motor studies in PD. SMA activation is reduced in tasks that require free selection of actions, rather than execution of pre-learned sequences or set responses to external cues (Catalan *et al.*, 1999; Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995; Praamstra *et al.*, 1996). Biased competition models of attention (Desimone, 1999; Desimone and Duncan, 1995) have proposed that there are mutually inhibitory neuronal populations representing alternate actions. One representation may temporarily dominate if the balance of mutual inhibition is disturbed. This perturbation may result from 'bottom up' or 'top-down' influences, including inputs from prefrontal cortex. In the prefrontal cortex, there are neurones whose activity may encode arbitrary task specific rules or goals (Asaad *et al.*, 1998;

Asaad *et al.*, 2000)], or the context of behaviour (Cohen *et al.*, 1996). These neurons may control the selection of motor representations within the SMA or premotor cortex regions, by top-down influence appropriate to the current task (attentional selection) (Miller, 1999).

It is proposed that both the free selection of movements and attention to action are mediated by attentional selection. For the current experiment, the consequence is increased activation of premotor cortex under the influence of prefrontal cortex, specific to the attention to action condition. The increase does not occur during attention to the visual conjunction search. In contrast to studies of visual attentional selection (Brefczynski and DeYoe, 1999), we have not attempted to show the selectivity for one motor representation over another within premotor cortex, since there is limited motor somatotopy in premotor cortex.

The ATTEND condition required subjects to 'think about the next move'. Although this may at first seem open to different interpretations, the consistency of the behavioural and neuroimaging results across all subjects in both groups suggests that the instruction induced a common set of cognitive processes. Tasks requiring imagination or preparation of movement may involve attention to action, and have been associated with increased activity in a similar distributed network including prefrontal, premotor and parietal cortex and SMA (Decety *et al.*, 1994; Jeannerod, 1998; Richter *et al.*, 1997). An attentional formulation of imagination, preparation and free selection of action has several advantages. First, attentional selection of action by prefrontal modulation of premotor regions represents a parsimonious explanation of the effects of these multiple motor-related paradigms. Second, by drawing on the mechanisms of attentional selection of visual representations in occipital and

inferotemporal cortex, it presents a testable hypothesis of the mechanism of underlying neuronal interactions. Third, it acknowledges that individual neurons of the prefrontal cortex have different properties according to the specific current task (Asaad *et al.*, 2000), and that attentional selection by these neurons may be supra-modal, occurring in the sensory, mnemonic and motor domains.

Interpretation of between group comparisons

To make inferences about patient abnormalities in functional neuroimaging data there are two essential criteria. **First**, that the inferences may be extended to the general patient population, and are not restricted to the particular subjects studied on particular days. This second criteria is especially important for fMRI studies, in which there are significant differences in MRI BOLD signal and sensitivity in different subjects, and between different days even for the same subject under the same conditions (McGonigle *et al.*, 2000). The implementation of a two-stage random effects model enables the direct comparison of patients and controls at the second level.

Second, that the patients and controls are actually performing the same tasks (Price and Friston, 1999). The equality of tasks and performance between our groups is suggested by the behavioural data. Although patients' response times were overall more variable, the differences between tasks were similar in both groups. Relative to MOVE condition, both groups increased response variance during ATTEND condition, but not during DUAL condition. Similarly, there was no group difference, or group by task interaction, in response latencies.

Other sources of bias must be considered. Our within subjects analyses at the first level used grand mean scaling. This preserves the regional independence of task

related activations, in preference to proportional scaling. Systematic group differences in signal intensity could affect between group comparison for a given task effect. However, in our study, there was no significant difference of global MRI signal between our groups. It remains possible that Parkinson's disease leads to different neurovascular responses to neuronal activity. For example, there is direct dopaminergic innervation of the vascular bed in the frontal lobes (Krimer *et al.*, 1998), which may be reduced in Parkinson's disease. However, we would expect this to cause a reduction in MRI-BOLD response for all tasks, rather than a mixed picture of some regional increases in activation for some contrasts and reductions in others.

Although our model is based on primate cortico-cortical interconnections, inferences cannot be drawn about whether the connections are mono- or poly-synaptic, or whether they are excitatory or inhibitory. The interpretation remains limited to the systems level (Horwitz *et al.*, 2000). Indeed, indirect cortico-striatal-thalamo-cortical connections of the type proposed by Alexander and DeLong (1990) could contribute to the influence of prefrontal cortex on the medial and lateral premotor cortex. For example, Owen et al (1998), has shown that in Parkinsonian patients, performance of tasks sensitive to frontal lobe damage was associated with abnormal basal ganglia activation in PET, rather than intrinsic frontal cortical dysfunction. The patients impaired performance may have resulted from impaired connectivity between frontal regions, without reduced activation per se. Analogous changes in connectivity between regions rather than activation within regions has been demonstrated in normal subjects after manipulation of monoaminergic neurotransmission by clonidine (Coull *et al.*, 1999).

The current results raise a difficult question. This chapter began with the recognition that attention to action can modify the motor performance of patients with Parkinson's disease. Attention towards movement could improve performance, and distraction could impair performance. The current results suggest that the normal cortical mechanisms of attention to action are not operating in patients with Parkinson's disease. It was expected that a functional disconnection between prefrontal cortex and the SMA would be accompanied by compensatory increases in activity within, or connectivity to, the lateral premotor regions. This was not found. The current results do not suggest the alternate mechanism for the effects of attention to action in patients.

Summary

Attention to action was again associated with increased coupling between prefrontal cortex and the medial and lateral premotor regions in healthy adults. This is not the result of increased attentiveness *per se*, since another attentional task was not associated with increased coupling. This effect was not found in patients with moderate Parkinson's disease. The results suggest that the motor abnormalities in Parkinson's disease are due at least in part to a functional disconnection of the SMA and premotor cortex from prefrontal influences, measured here as a reduction in effective connectivity. The consequence is impaired activation of the SMA on tasks that require additional attentional selection of motor representations, including attention to action and free selection of movement.

Table 8.1. Demographic details of the patients, the severity of their Parkinsonism, and usual medication.

Age	Sex	UPDRS motor score (off)	Hoehn and Yahr grade	l-dopa daily (mg)	Dopamine agonists	other medication
61	f	13	2	300	x	x
61	f	36	3	400	pergolide	x
56	f	34	2	0	x	amantadine
61	m	32	2	900	ropinirole	x
63	m	35	2.5	800	bromocriptine	x
68	f	30	2	300	pergolide	x
72	f	32	2	0	x	x
50	f	39	2.5	0	cabergoline	x
63	f	42	3	200	x	x
57	m	42	2.5	400	x	x
69	m	25	3	600	x	x
62	m	44	3	300	pergolide	Amantadine benzhexol
mean: 62 SD: 6		mean: 33.7 SD: 8.54		mean: 350 SD: 295		

Table 8.2: Regions of significant activation for the main effect of motor sequence execution (MOVE and DUAL vs REST and SEACRH). The voxelwise uncorrected p-value (Pu) and corrected p-value within regions of interest (Pc-ROI) are shown, together with the mean effect size (%), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and t-values are also shown. (SMA = supplementary motor area).

Region	l/r	x	y	z	t	Pu	Pc-ROI	Size
Controls								
Premotor	l	-32	-8	60	7.54	0.0001	0.001	0.63
	r	40	-4	64	5.41	0.001	0.01	0.31
SMA	x	0	2	68	7.86	0.0001	0.001	0.89
Paracingulate	l	0	4	52	6.21	0.0001	0.001	0.92
Primary motor	l	-50	-28	48	7.88	0.0001	0.001	1.10
Parietal	l	-38	-46	52	5.41	0.001	0.01	0.53
Putamen	l	-28	2	2	5.44	0.001	0.01	0.26
Thalamus	l	-16	-18	-2	4.85	0.001	0.05	0.21
Cerebellum	l	-22	-56	-26	5.55	0.001	0.01	0.62
	r	26	-52	-24	10.6	0.001	0.001	1.36
Patients								
Premotor	l	-32	-4	66	6.95	0.0001	0.01	1.36
	r	-32	-4	60	3.94	0.01	0.05	0.58
SMA	l	-6	-12	74	7.16	0.0001	0.01	0.96
Paracingulate	l	-6	-2	52	5.28	0.001	0.01	1.02
Primary motor	l	-42	-28	64	7.46	0.0001	0.01	1.26
Parietal	l	-36	-46	32	5.54	0.0001	0.01	0.47
Thalamus	l	-4	-14	8	4.62	0.001	0.05	0.53
Cerebellum	l	-26	-64	-22	5	0.001	0.05	0.71
	r	36	-60	-26	5.47	0.0001	0.01	0.92
Controls greater than patients								
Putamen	r	28	0	-8	3.89	0.001	0.05	0.31
Patients greater than controls								
SMA	r	2	-12	72	3.57	0.001	0.05	0.78

Table 8.3: Regions of significant activation for the main effect of visual conjunction search (SEARCH and DUAL vs REST and MOVE). The voxelwise uncorrected p-value (Pu) and corrected p-value within regions of interest (Pc-ROI) are shown, together with the mean effect size (%), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and t-values are also shown. (PFd = dorsal lateral prefrontal cortex, PFv = ventral lateral prefrontal cortex, ITc = inferotemporal cortex)

region	l/r	x	y	z	t	Pu	Pc-ROI	Size
Controls								
PFd	l	-46	32	26	4.48	0.0001	0.01	0.62
	r	42	40	26	5.3	0.001	0.01	0.81
ITc	l	-44	-54	-8	12.3	0.00001	0.001	0.92
	r	48	-66	-18	22.4	0.00001	0.001	1.51
Parietal	l	-32	-62	58	7.59	0.0001	0.001	1.38
	r	38	-56	44	10.04	0.00001	0.001	1.10
Patients								
ITc	l	-48	-64	-18	6.38	0.0001	0.01	1.36
	r	44	-58	-20	6.12	0.0001	0.01	1.36
Parietal	l	-38	-58	56	6.78	0.0001	0.01	1.02
	r	38	-56	56	5.51	0.0001	0.01	1.11
Controls greater than patients								
Parietal	l	-26	-56	44	3.73	0.001	0.05	0.71
PFv	l	50	20	14	4	0.001	x	x
PFd	l	42	28	30	4	0.001	x	x

Table 8.4. Regions of significant activation for Attention to action (ATTEND) compared with simple execution of the same moves (MOVE). The voxelwise uncorrected p-value (Pu) and corrected p-value within regions of interest (Pc-ROI) are shown, together with the mean effect size (%), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and t-values are also shown. (PFd = dorsal lateral prefrontal cortex, SMA = supplementary motor area, PFd = dorsal lateral prefrontal cortex)

region	l/r	x	y	z	t	Pu	Pc-ROI	(%)
Controls								
PFd	l	-38	52	18	5.51	0.0001	0.01	0.22
SMA	l	-6	-16	74	4.17	0.001	0.05	0.27
Paracingulate	l	-6	8	54	5.85	0.001	0.01	0.20
Cerebellum	r	28	-60	-32	5.66	0.001	0.01	0.09
Controls more than patients								
SMA	l	-6	-14	74	3.76	0.001	0.05	0.18
Parietal	r	32	-50	52	4.16	0.001	0.05	0.15

Chapter 9

The Tower of London: the selection of responses

Introduction

The 'Tower of Hanoi' and related 'Tower of London' (TOL) tasks have been used to assess planning in clinical populations. However, planning involves many component processes. This chapter explores the contribution of response selection.

Planning is an example of executive processing (Rabbitt, 1997), dependent on the functions of the central executive (Baddeley, 1986) or the supervisory attentional system (Shallice, 1989). Planning describes the ability to think ahead and evaluate the consequences of possible actions, to "model a sequence of actions in preparation for carrying out a particular task" (Shallice, 1982). A clear operational definition comes from Dehaene and Changeux (1997), who define planning as "the goal-directed, trial-and-error exploration of a tree of alternative moves. When no direct move is available, a move must be generated, tried out, and accepted or rejected depending on its ability to bring the problem closer to a solution". This highlights the key processes required in planning: to be aware of the goal; to generate possible moves; to make moves mentally; to evaluate these moves with respect to the goal; to reject or select moves; and to hold these moves in memory until ready to execute the complete sequence of moves.

The planning demands and problem-solving strategies suitable for the Tower of Hanoi and Tower of London tasks differ slightly (Dehaene and Changeux, 1997; Goel and Grafman, 1995; Ward and Allport, 1997) and differences in performance of the two tasks have been reported (Humes *et al.*, 1997). The Tower of London has a clear rating scale for problem difficulty (Goel and Grafman, 1995), and has been widely used to assess planning deficits in patients with neurosurgical lesions (Johns, 1996; Owen *et al.*, 1990; Shallice, 1982), neurodegenerative diseases (Dagher *et al.*, 2001; Owen *et al.*, 1998), and psychiatric illness (Elliott *et al.*, 1997a; Elliott *et al.*, 1998; Morris *et al.*, 1995; Pantelis *et al.*, 1997).

In the TOL, subjects are presented with two sets of three balls (start and goal arrays), each on three pegs (Shallice, 1982) or in three pockets (Owen *et al.*, 1990). Subjects must plan how to move the balls on the start array, one at a time, in order to match the goal array. Constraints on valid moves are provided by the different colours of the balls and the different heights of the pegs (or depths of the pockets). Legal moves consist of moving the top ball of any given peg (pocket) to a location on another peg (pocket). Subjects may be required either to make actual moves (Owen *et al.*, 1990), or express planning ability by specifying the minimum number of moves required (Baker *et al.*, 1996b; Owen *et al.*, 1995). Problem difficulty varies from trivial, requiring one obvious move, to extreme, requiring at least nine moves in exact order. With increasing difficulty, moves must be made which do not directly place a given ball in its goal position, but are necessary to permit future moves. Some problems include counterintuitive moves, in which a ball must be moved temporarily out of its goal position, to permit intermediate steps (Ward and Allport, 1997).

Patients with prefrontal lesions are particularly poor at problems which demand such counterintuitive moves (Morris *et al.*, 1997a).

Several groups have used functional imaging to determine the neural correlates of planning in the TOL, in both normal subjects and patients. Computerised versions of the TOL have been studied with PET and single photon emission computed tomography (SPECT). When planning in the TOL has been compared to visuomotor controls, a consistent distributed network of brain activations has been found. This includes the left dorsal prefrontal cortex, left or right premotor cortex, anterior cingulate cortex, bilateral parietal cortex, medial parietal cortex (precuneus), prestriate cortex, and midline cerebellum (Baker *et al.*, 1996b; Dagher *et al.*, 1999; Dagher *et al.*, 2001; Elliott *et al.*, 1997a; Morris *et al.*, 1993; Owen *et al.*, 1998; Owen *et al.*, 1996a). Some of these studies have also observed activation of the right prefrontal cortex (Baker *et al.*, 1996b; Dagher *et al.*, 1999; Dagher *et al.*, 2001), and right or left cerebellar hemisphere (Baker *et al.*, 1996b; Elliott *et al.*, 1997a). Further, increased prefrontal activation was seen with more difficult problems (Baker *et al.*, 1996b; Dagher *et al.*, 1999; Dagher *et al.*, 2001; Owen *et al.*, 1996a), and in subjects who took longer to plan moves or made fewer errors (Morris *et al.*, 1993).

Although these studies indicate the network of brain activity required for performance on the TOL, they do not permit an analysis of the contributions of these separate regions to the overall task. Previous studies did not control for the generation, selection, and working memory for self-generated moves. To generate putative moves requires the identification of balls that can be moved, and the places into which they could be placed. A free ball and free target pocket are chosen, the move is mentally made, and its consequence imagined. If a putative move brings the

array closer to the goal, then it must be selected and placed in sequence. The correct moves are built up sequentially, and remembered in relation to the others until all the moves are known. In this respect, the TOL has many cognitive processes in common with the self-ordered task used by Petrides (1982).

For the current experiment, control tasks were developed that included some of these cognitive processes, but lacked a goal in the sense that they did not require "the construction and evaluation of a path from A to B" (Goel and Grafman, 1995). These control tasks were matched to the TOL for the generation and selection of moves, the working memory load for moves, and the execution of moves. Control for the working memory of self generated moves was particularly important. Owen *et al.* (1996a) showed that working memory for moves specified by the experimenter was associated with activation of prefrontal cortex at least as much as performance of the TOL. However, Deiber *et al.* (1998) have reported that there is more activation of the prefrontal cortex when subjects imagine such externally specified moves compared with self generated (that is, freely selected) moves. Two of the current control tasks required self generated moves because on the TOL the subjects also generate their own possible moves. Visuomotor and rest baseline conditions were also included to allow direct comparison with the earlier studies.

In the TOL, subjects are asked to determine the solution before executing their moves. In this context, the processes of planning the solution should be the same whether or not the subjects go on to execute the moves. In the present experiment therefore, a version of the TOL task was developed in which the subjects merely imagined the solution as well as a standard TOL task in which they also executed the moves. These were compared with control tasks requiring either just imagination or

imagination and execution of responses. This created two task pairs, which had in common the presence or absence of a specified goal array. Since the aim of the present study was to identify the components of planning (not just performance of the TOL) conjunction analyses were used to reveal the activation that was common to planning, that is irrespective of the way in which the TOL task was executed.

Methods

Subjects

Ten normal male right handed volunteers were studied, aged 23-34 with a mean of 27 +/- 4 years. They had no history of neurological or psychiatric illness, and took no regular medication. Ethical approval was given by the Ethics committee of the Institute of Neurology and permission to administer radioactive H_2O^{15} was given by the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK. The subjects gave written informed consent.

Presentation of stimuli

The format of presentation resembled the TOL as used by Owen *et al.* (1996a), with software written in Visual Basic 6.0 (Microsoft Corporation, USA). The problems were controlled from a personal computer (Gateway computers, Pentium II processor) operating Windows 95 (Microsoft Corporation, USA). The presentation and responses were made using a touch sensitive screen (Vision Master, Liyama Electric Co., Japan).

Two patterns of balls were presented, one above the other. The balls were red, green and blue, resting in three pockets that could hold one, two or three balls respectively. An example of the presentation is shown in Figure 9.1. Balls in the

lower array could be moved by touching the screen. A ball was moved by touching it and then an empty pocket. When touched, a ball would be highlighted in yellow until an empty pocket was touched or it was touched again to cancel the move. If an illegal move was attempted, such as moving a ball onto the background, no changes occurred. Subjects then either moved the ball to one of the other pockets or cancelled the move as above. Only the topmost ball in a given pocket could be moved, and pockets could not be "overfilled". When a trial was completed, the screen cleared for one second and the next trial began. Up to sixteen different trials could be presented without interruption.

Pretraining took place half an hour before scanning. The subjects were familiarised with the presentation format and also with responding on the touch sensitive screen, using "easy" TOL problems requiring one to three moves. The six conditions were then explained, demonstrated, and practised (eight trials maximum) until subjects were confident that they understood each condition. The sets of problems used in pre-training were not used in scanning sessions.

The TOL can be used to present 216 formally distinct problems requiring 0-9 moves to solve, each in six colour combinations. Of these 1296 visually distinct problems, 174 require four moves. 160 of these were divided between ten problem sets, each of 16 trials, to encourage novel planning for each trial. During image acquisition, all problems in plan conditions required a minimum of four moves. Subjects were allowed a maximum of ten moves or 30 s before the trial ended and the next problem was presented. The trials were presented from 30s before image acquisition and continued for up to 150s total duration.

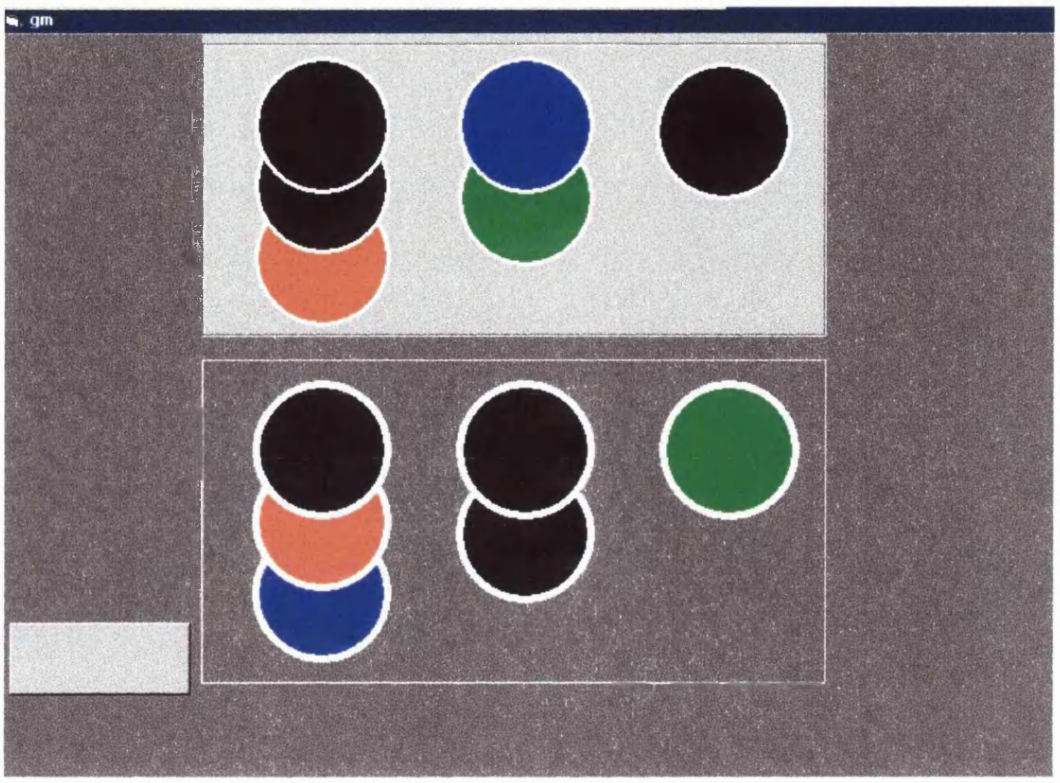


Figure 9.1. On each trial in the Tower of London task, the top display shows a target array of 'balls' in 'pockets'. Below a starting array is shown. Subjects must determine the minimum number of moves, ball by ball, to rearrange the start array to the target array.

Experimental Design

Twelve sequential measurements of regional cerebral blood flow were made, two in each of six conditions. The six conditions included two in which there was a specified goal (PLAN-MOVE and PLAN-IMAGINE), two formally similar but with no goal (PLAN-CONTROL-MOVE and PLAN-CONTROL-IMAGINE), a visuomotor control condition (VMC) and rest (REST).

PLAN-MOVE. The two arrays of balls were initially different. The subjects had to determine the best sequence of moves to change the lower configuration into the top configuration of balls (goal), in the minimum number of moves. They were asked to plan the solution "in their head" and then "execute the moves as smoothly as possible" by touching the balls and empty pockets in turn. Before imaging they were reminded to "think first then move".

PLAN-IMAGINE. The presentation of problems was similar to PLAN-MOVE. They were again asked to plan the solution "in their head". However, they were not required to execute the actual moves. Instead, they were asked to press a button on screen to indicate that they had the solution. The screen then cleared for 1 second and the next problem was presented. To ensure compliance with the imagination task, "catch trials" were included. These occurred in pretraining, and before the scanning window in the imaging session. On "catch trials" the screen did not clear after the button was pressed; instead the words "please show me" appeared and subjects were asked to execute their solution by touching the balls on screen in turn.

PLAN-CONTROL-MOVE. In plan-control conditions, the two arrays of balls were initially the same, so there was no goal to change one pattern to the other.

Subjects were asked to think of any four moves on the lower array of balls and, when they knew the sequence of these moves, to execute it smoothly and swiftly. The duration of each trial was yoked to the trials in the prior PLAN-MOVE condition, and the number of moves made matched the minimum number of moves required in PLAN-MOVE.

PLAN-CONTROL-IMAGINE. Two identical arrays were presented and subjects were required to think of four moves that could be made in the lower array. However, they were not to execute these moves, merely to press a button when they knew what these four moves would be. "Catch trials" were included in pre-training and before the scanning window to ensure compliance, as in the PLAN-IMAGINE condition. The duration of each trial was yoked to the trials in the PLAN-MOVE condition, and the number of moves made matched the minimum number of moves required in PLAN-IMAGINE.

VISUOMOTOR CONTROL. This was yoked to the PLAN-MOVE condition. The subjects repeated the actual moves made in the PLAN-MOVE condition, one by one, without planning or remembering moves. The two arrays were initially identical. A ball in the top array was highlighted together with an empty pocket. Subjects then touched the ball and the empty pocket in turn, and the ball moved. The next ball and pocket then lit up according to the timing of the moves made in PLAN-MOVE.

REST. The screen showed the two sets of pockets, empty, against the same neutral background. No moves were necessary.

The conditions were presented in a pseudo-random order. There was the constraint that the yoked conditions (PLAN-CONTROL--MOVE, PLAN-CONTROL-IMAGINE, and VMC) had to occur after the plan condition with which

they were yoked. However, all conditions occurred both early and late in the scanning session.

Data Acquisition

The behavioural data were recorded by the TOL program in Visual Basic. Data recorded included: the time from trial presentation to first touching a ball; the time taken to make each move; all individual moves made; and the number of error moves in PLAN-MOVE condition. Attempted illegal moves were not recorded.

The subjects lay supine in the scanner. Head movement was reduced by a padded helmet with chinstrap, fixed to the headrest. The screen position was adjusted to give full view of the screen and easy reach by the right arm. The visual display extended across approximately 15 degrees of vision. PET was performed using a CTI ECAT HR plus scanner (CTI, Knoxville, TN) in three-dimensional mode with inter-detector collimating septa removed. The axial field of view was 155 mm providing whole brain coverage including cerebellum.

Regional cerebral blood flow was measured using $H_2{}^{15}O$. Background activity was counted over 30s prior to each image. Six to ten mCi (mean 8.9 mCi) were delivered over 20s to the left arm. Image acquisition began 5s before the rising phase of the count curve, approximately 25s after injection, and continued for 90s. Correction for tissue and helmet attenuation was made using a transmission scan from 68Ga/68Ge sources at the start of the scanning session. The interscan interval was 9 minutes.

Corrected data were reconstructed by three dimensional filtered back-projection (Hanning filter, cut off frequency 0.5 cycles/pixel) and scatter correction. Sixty-three transverse planes were obtained with 128 x 128 pixel image

matrix, with a resulting pixel size of 2.4 x 2.1 x 2.1 mm, and a resolution of 6 mm at full width half maximum. T1- weighted structural MRI images were acquired for eight of the subjects on the same day.

Behavioural data analysis

The behavioural data were analysed using Microsoft Excel SR-1 (Microsoft Corporation). The number of moves per trial and the total number of moves made in the scanning interval were calculated for each condition. The mean time taken to initiate movement and complete each trial was calculated for each condition for trials during the scanning interval. Thinking time was the time taken from presentation of the arrays to initiation the first movement or to pressing the button to indicate that moves had been determined. Thinking times were subjected to a two-factor repeated measures analysis of variance with goal (plan vs plan-control) and execution (move vs imagine) as within-subject factors. Catch trials lay outside the scanning interval and were not included in these analyses.

Imaging data analysis

All analyses of images were made using Statistical Parametric Mapping software, SPM97d (http://www.fil.ion.ucl.ac.uk/spm), in the MATLAB 4 environment (Mathworks). The principles of SPM 97d are similar to the SPM99 used in previous studies. Images were realigned to the first image by rigid body correction for head movements between scans (Friston *et al.*, 1995b). All images were normalised to a standardised anatomic space (Talairach and Tournoux, 1988), by matching each image to a standardised template (Holmes *et al.*, 1998) using linear and non-linear spatial transformations (Friston *et al.*, 1995b). Each image was smoothed

with an isotropic Gaussian kernel (FWHM = 12 mm). The effect of global differences in cerebral blood flow between scans was removed by subject specific ANCOVA scaling of activity to a nominal mean global activity of 50 ml/100g/min (Friston *et al.*, 1990a).

There were two analytical models. First, six orthogonal covariates were specified corresponding to each of the six experimental conditions. I wanted to define brain regions activated by the presence or absence of a goal, regardless of method of execution (movement or imagination). Conjunction analyses were therefore used as defined by Price and Friston (Price and Friston, 1997; Price *et al.*, 1997) to identify areas in which there was a common simple main effect of plan versus baseline (analysis 1), plan-control versus baseline (analysis 2), or plan versus plan-control (analysis 3), regardless of whether the solutions were physically executed or imagined. The conjunction analyses were:

analysis 1: [PLAN-MOVE vs VMC] and [PLAN-IMAGINE vs REST]

analysis 2: [PLAN-CONTROL-MOVE vs VMC] and
[PLAN-CONTROL-IMAGINE vs REST]

analysis 3: [PLAN-MOVE vs PLAN-CONTROL-MOVE] and
[PLAN-IMAGINE vs PLAN-CONTROL-IMAGINE]

For activations to be attributable to the common difference of a plan (analyses 1 and 3) or plan-control (analysis 2), the magnitude of this effect must be similar. In factorial designs, the conjunction may be construed as a main effect in the absence of an interaction (for all the conjunction analyses interactions were excluded at $p<0.05$ uncorrected). The conjunction analyses were used to test hypotheses about regionally

specific conjoint condition effects, producing a statistical parametric map of the t statistic for each voxel.

The SPM{t} was transformed to a map of corresponding Z values. SPM97d did not include mechanisms for correction for multiple comparisons within reduced search volumes (regions of interest), even though there were prior hypotheses regarding the role of the prefrontal, premotor and parietal cortex in the TOL. Therefore, results are presented for voxels at which the Z statistic exceeded 3.09 ($p < 0.001$, uncorrected for multiple comparisons) in lieu of regions of interest.

In the second model, the times taken to make the first move or to press the button indicating that a sequence of moves had been determined (thinking time) in the plan and plan-control conditions were entered as covariates of interest. In analysis 4, data is presented for voxels in which thinking time significantly covaried with activity. Again voxels at which $Z > 3.09$ ($p < 0.001$ uncorrected) were considered significant.

Results

Behavioural results

For the PLAN-MOVE condition, subjects completed a total of 172 trials during imaging (mean 8.6 trials per scan, S.D. 2.5). Overall performance was good. During the PLAN-MOVE condition 148/172 (86%) of trials were solved in the minimum number of moves. Two subjects were error free. For the 172 four-move problems imaged for PLAN-MOVE condition, the subjects made a total of 700 moves (mean 4.07 moves made per problem). Errors were not made on catch trials, suggesting that subjects were properly imagining the solutions to the problems in

PLAN-IMAGINE. In the PLAN-CONTROL-MOVE condition, the subjects made varied patterns of four moves from trial to trial with little repetition.

The mean time to first movement (thinking time) was 7.5s (+/- 0.7s) for PLAN-MOVE and 7.3s (+/- 0.8s) for PLAN-CONTROL-MOVE, and the mean time to button press was 8.1s (+/- 0.6s) for PLAN-IMAGINE and 8.1s (+/- 0.7s) for PLAN-CONTROL- IMAGINE. By analysis of variance, there was no effect of plan/plan-control ($F = 0.5$, $df = 1,19$, p = n.s.) or movement/ imagine ($F = 1.1$, $df = 1,19$, p = n.s.) in time to first move, and no interaction ($F = 0.9$, $df = 1,19$, p = n.s.).

Imaging results

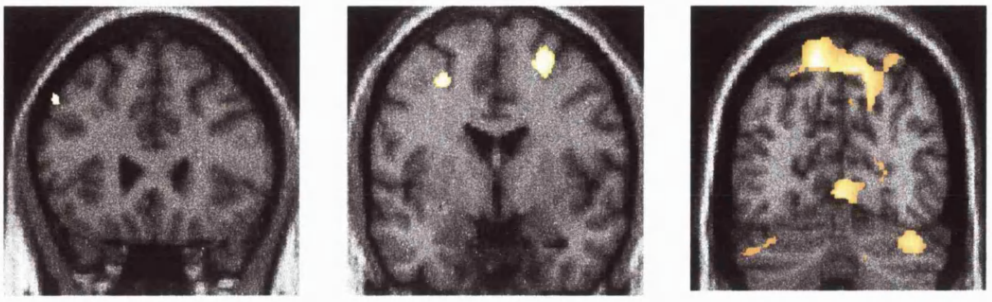
Plan vs baseline (analysis 1)

This conjunction analysis identified areas in which the activation was related to planning on the TOL. The contrasts [PLAN-MOVE vs VMC] and [PLAN-IMAGINE vs REST] share the common difference of planning the solution to the TOL. Areas of conjoint differences in activation for the task pairs are listed in Table 9.1. They included the left PFd and right PFo, bilateral dorsal premotor cortex, left motor cortex, parietal, prestriate and inferior temporal cortex, as well as in the insula. Subcortical activations were seen in the cerebellar vermis and hemispheres bilaterally. Figure 9.2a shows the distribution of the SPM{Z} superimposed on a standard T1 MRI image at the left prefrontal, premotor and parietal cortex. The parietal activation lay in and above the posterior part of the intraparietal cortex.

Plan-control vs baseline (analysis 2)

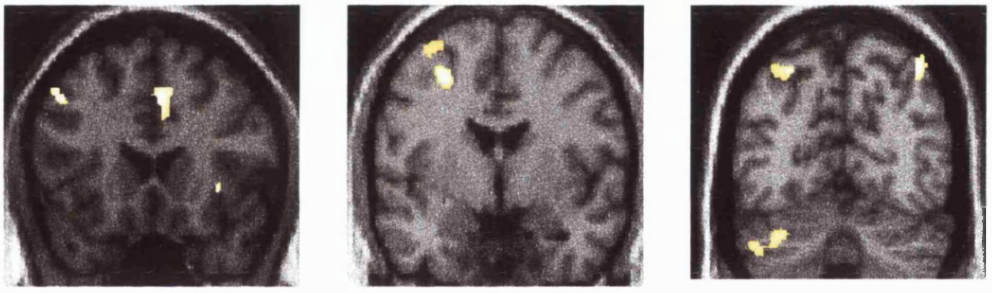
The contrasts [PLAN-CONTROL-MOVE vs VMC] and [PLAN-CONTROL-IMAGINE vs REST] share the common difference of generation and

A: plan



i, y =26 ii, y =-2 iii, y =-70

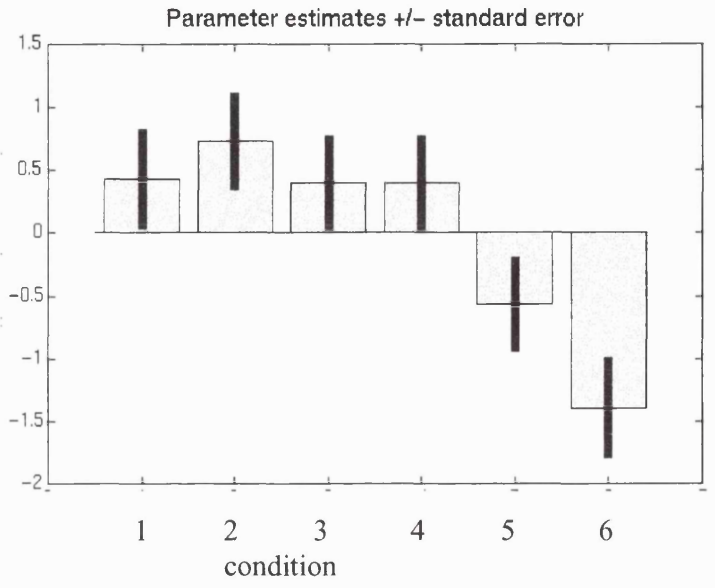
9.2B: plan-control



iv, y =20 v, y =-2 vi, y =-68

Figure 9.2. Significant rCBF increases shown as SPM{t}s for activations during plan (2A) and plan-control (2B) conditions, each compared with visuomotor and rest baseline conditions. Coronal planes are indicated by the corresponding y coordinate in standard anatomic space and all voxels shown exceed Z =3.09 (p =0.001). The top row, 2A i-iii, shows areas of significantly greater activation in plan conditions than baseline (analysis 1). Activations shown are: i. left dorsolateral prefrontal cortex; ii. bilateral premotor cortex; iii. bilateral intraparietal and right inferior temporal cortex. The bottom row, 2B iv-vi, shows areas of significantly greater activation in plan-control conditions than baseline (analysis 2). Activations shown are: iv. the left dorsolateral prefrontal and right anterior cingulate cortex; v. left premotor cortex; and vi. intraparietal cortex.

A



B

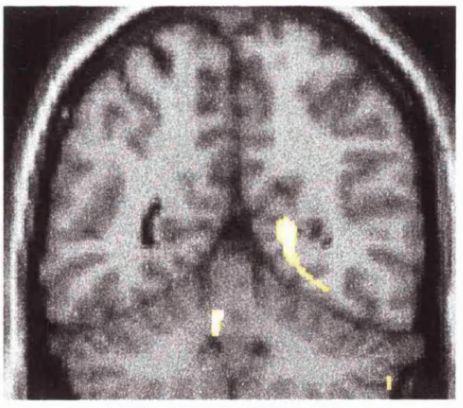


Figure 9.3 (a) Parameter estimates for the left dorsolateral prefrontal cortex (-50, 26, 42). The values indicate the parameter estimates from the general linear model of SPM analysis (standardised units) and indicate the relative activation under different task conditions. The six condition effects are: 1. PLAN-MOVE; 2. PLAN-IMAGINE; 3. PLAN-CONTROL-MOVE; 4. PLAN-CONTROL-IMAGINE; 5. VMC; 6. REST. The chart indicates that the activation of the left prefrontal cortex does not significantly differ between plan and plan-control conditions (1-4). (b) Regions of significant rCBF increases in analysis 3, shown as a SPM{t} overlaid on a coronal section through the plane of y = -54, illustrating the activation of the lingual and fusiform gyri when plan conditions were contrasted with plan-control conditions.

selection of moves and memory for selected moves. Areas of conjoint activation for the task pairs are listed in Table 9.2. There was again activation of PFd and PFo, bilateral premotor cortex, and intraparietal cortex. There was also activation of the anterior cingulate cortex and right insula. Subcortical activations were seen in the cerebellar vermis and hemispheres. There were no prestriate or inferotemporal activations. Figure 9.2b shows the distribution of SPM{Z} superimposed on coronal sections through prefrontal, premotor and parietal cortex.

Plan vs plan-control (analysis 3)

The contrasts [PLAN-MOVE vs PLAN-CONTROL-MOVE] and [PLAN-IMAGINE vs PLAN-CONTROL-IMAGINE] share the common difference of goal representation and evaluation of moves towards that goal. Areas of conjoint activation differences for the task pairs are listed in Table 9.3. There was no activation in the prefrontal cortex, but there was activation in the left superior parietal cortex; this lay posteriorly near the back of the intraparietal sulcus. Extensive activations were observed in the prestriate cortex and inferior temporal cortex, as well as in the right premotor cortex. Cerebellar activations were seen in the cerebellar nuclei and right paramedian lobe.

Figure 9.3a shows the parameter estimates for condition specific effects at the left dorsolateral prefrontal cortex. Figure 9.3b shows the SPM{Z} distribution superimposed on a coronal section through the lingual and fusiform gyri. These figures illustrate that there was no significant difference between plan and plan-control conditions in PFd. In other words, the presence of a goal (the critical feature of planning tasks) was not associated with increased activation of PFd.

Correlation with thinking time (analysis 4)

This analysis looks for the effect of planning time on activations during plan conditions [PLAN-MOVE and PLAN-IMAGINE]. The results indicate those areas in which prolonged thinking time in the plan and plan-control conditions was correlated with greater regional blood flow. There was a single peak of activation in the left frontal pole (-14, 68, 10, $Z = 3.66$, $p < 0.001$).

Discussion

It has commonly been assumed that because patients with prefrontal lesions are impaired on the TOL, and the TOL requires planning, planning is a critical function of the prefrontal cortex. In the present study some of the cognitive components involved in planning have been separated, and the activation of the dorsal prefrontal cortex was found to be accountable for by the processes of generating, selecting moves. Activation of the prefrontal cortex was not restricted to the presentation of problems in which the subjects must evaluate a path towards a specified goal.

Planning

Analysis1 identified the distributed network of activations during the planning tasks. This network was similar to that observed in previous studies and was activated irrespective of whether the subjects were required to execute their solution or not. There was activation in the left PFd (Baker *et al.*, 1996b; Elliott *et al.*, 1997a; Morris *et al.*, 1993; Owen *et al.*, 1998; Owen *et al.*, 1996a). The peak lay in the region identified by Petrides and Pandya (Petrides and Pandya, 1995) as area 9/46. However, there was also a peak of activation at the left frontal pole where the

activation increased with longer thinking times (analysis 4). Morris *et al.* (1993) also observed, using SPECT, a similar correlation between thinking time and left frontal activation.

There was activation bilaterally in premotor cortex, parietal cortex, and prestriate cortex (Baker *et al.*, 1996b; Elliott *et al.*, 1997a; Morris *et al.*, 1993; Owen *et al.*, 1998; Owen *et al.*, 1996a), the right insula (Baker *et al.*, 1996b; Elliott *et al.*, 1997a; Owen *et al.*, 1996a), ventral temporal cortex and caudate nucleus (Elliott *et al.*, 1997a). The whole cerebellum was imaged and activation was found in the midline cerebellum (Baker *et al.*, 1996b; Elliott *et al.*, 1997a; Owen *et al.*, 1998; Owen *et al.*, 1996a) as well as in the cerebellar hemispheres (Elliott *et al.*, 1997a). The agreement with earlier work supports the use of conjunction analysis to isolate planning irrespective of the way the task is presented.

Following Dehaene's definition of planning (Dehaene and Changeux, 1997), one can say that the subjects were required to detect and represent differences between the start and goal arrays of balls, to generate possible moves; to select the moves, to mentally make these moves, to evaluate these moves as steps towards the goal, and to hold earlier moves in working memory until the whole solution was known. All of these components are common to the conditions PLAN-MOVE and PLAN-IMAGINE.

The frontal, parietal and subcortical regions make different contributions to these multiple processes. This difference was demonstrated by Dagher et al (1999), who used PET to study regional activation during performance of TOL problems of variable difficulty. PFd and cingulate cortex showed a linear increase in activation with increasing problem difficulty. In contrast, the superior and intra-parietal cortex

was more active than rest during TOL performance, but here was no further increase with increasing problem difficulty. The caudate nucleus showed a 'U' shape response to task difficulty. However, the right parietal cortex did correlated with difficulty in a similar study using older subjects and patients with Parkinson's disease (Dagher *et al.*, 2001). In these studies, the differential activation of the prefrontal cortical was not attributable to visual or motor components of the TOL, nor to learning specific problems. Although the total number of movements made during the scanning window did not differ, there was a sharp decline in performance accuracy, below 50% for 5-move problems. This complicates the further interpretation of activation differences in terms of task component processes.

Whereas Dagher et al (1999, 2001) used variable task difficulty to understand the regional contributions to TOL performance, the present study used control conditions that were formally similar but differed in their cognitive demands. The aim of the subsequent analyses was to identify the neural correlates of these different cognitive components of planning.

Generation, selection and memory of moves

The plan-control conditions (PLAN-CONTROL-MOVE and PLAN-CONTROL-IMAGINE), had much in common with the plan conditions. The subjects had to generate moves, select and mentally make these moves, and hold these moves in memory until the whole sequence was determined. However, the plan-control conditions differed in that subjects did not need to think ahead to a particular end-state or goal, nor evaluate moves in the light of such a goal. By goal it is meant here a particular target or end-state of balls, rather than the general desire of subjects to comply with experimental procedures.

It could be argued that in the plan-control tasks the subjects generated a goal state in mind, and planned the moves towards it. However, debriefing subjects on their understanding and performance of the task suggested that this was not the case: each move was determined on the basis of the start array and previous moves without regard to a self-determined goal pattern. In other words, the chosen moves determined the end state rather than a chosen end-state determining the moves. Further, it would be very difficult for inexperienced subjects to know whether a self-generated pattern was exactly four moves away from the start array. Trial and error attempts to formulate end-states four-moves away from the starting position would require more than one guess for some trials. Trials would therefore take longer on average than planning the specified 4-move problems in plan conditions. The behavioural data show this was not the case.

It is also possible that rather than set a particular goal state in mind that was four-moves different, subjects may choose a series of intermediate goals, imagining a goal state one or two moves different, then 'planning' to move towards it. Such trivial one- or two- move problems however do not necessarily require planning, because they may be solved by a simple visio-spatial matching strategy without the need to think ahead. In addition, they do not activate the prefrontal cortex in normal subjects (Owen *et al.*, 1996a) and performance is not impaired by lesions of the prefrontal cortex (Johns, 1996; Owen *et al.*, 1990).

In analysis 2, the contrasts [PLAN-CONTROL-MOVE vs VMC] and [PLAN-CONTROL-IMAGINE vs REST] were tested conjointly. The conjunction for these comparisons revealed activations common to both plan-control tasks, that are irrespective of whether the subjects executed the moves or not. There was bilateral

activation of PFd, intraparietal cortex and premotor cortex, the frontal poles and anterior cingulate cortex.

In chapter 6, the free selection of actions was associated with activation of PFd, as well as the anterior cingulate cortex. However, the plan-control conditions also involved a working memory component. Working memory for four or five moves in the TOL was studied explicitly by Owen *et al.* (1996a). The subjects were asked to watch while the balls moved, and then reproduce this sequence at the end (an externally ordered working memory task). In comparison with their visuomotor control condition, there was extensive activation of the left PFd (area 46) as well as bilaterally in the frontal pole (area 10) and area 9. Therefore PFd is activated when subjects either generate and select moves, *or* when they are required to hold specified moves in memory.

In the plan and plan-control tasks the subjects also made mental moves: that is, they imagined making the moves that they selected. In making mental moves the subjects could either use representations of limb movements; or make saccadic eye movements between the current and desired locations; use shift covert spatial attention; or a combination of these. The imagination of specified repetitive finger moves has been associated with activation in the left PFd, anterior cingulate cortex/pre-supplementary motor cortex and parietal cortex (Deiber *et al.*, 1998).

When subjects make mental moves or remember them they may also make saccadic eye movements and this may facilitate their mental imagery. Subjects make saccades during mental imagery (Brandt and Stark, 1997) and there is interference between making voluntary saccades and mental imagery (Kosslyn *et al.*, 1995).

Similar voluntary saccades also occur during spatial working memory tasks (Hodgson *et al.*, 1999).

The role of gaze-control strategies in the TOL has been investigated by video-tracking natural scanning eye movements during the one-touch version of the TOL (Hodgson *et al.*, 2000). After initially reviewing the goal array, normal subjects then look predominantly at the start array, either from ball to ball or at a neutral midpoint in the array, before verifying the solution by looking again at the goal. On more difficult problem the subjects sometimes look back to the goal during the planning period (Hodgson, personal communication). During elaboration of the solution, the pattern of fixations depends on the moves being rehearsed by the subjects. Hodgson *et al.* (1999, 2000) proposed that the shifts in gaze strategy allow manipulation of information within mental imagery and reduce the working memory load during the TOL.

The use of eye movements to mentally move balls, or to facilitate the memory of moves may explain the activations seen in the occulomotor regions of the cerebellum (posterior vermis and flocculus) when the plan-control tasks were compared to baseline. There were not, however, corresponding activations in either the frontal eye-fields or supplementary eye-fields. The premotor and prefrontal activations found in analyses 1 and 2 are spatially distinct from the activations identified by functional imaging studies as regions for saccadic control (Anderson *et al.*, 1994; Paus, 1996; Petit *et al.*, 1997; Sweeney *et al.*, 1996).

However, subjects could also make mental moves without eye movements, by covert shifts of spatial attention. Kosslyn *et al.* (1997) have argued in relation to mental imagery tasks that parietal areas are involved in these shifts of spatial

attention. Both in plan-control and plan tasks there was activation in the intraparietal cortex.

Path to goal

The plan tasks, but not the plan-control, tasks required the subjects to construct and evaluate a path from the starting array to the specific goal array (Goel and Grafman, 1995). Thus, the particular goal had to be represented, the difference noted between the start and goal array, and the moves evaluated as steps towards that goal. The corresponding activations were identified by a conjunction analysis of [PLAN-MOVE vs PLAN-CONTROL-MOVE] and [PLAN-IMAGINE vs PLAN-CONTROL-IMAGINE] (analysis 3).

There was no additional activity in the prefrontal cortex for the plan tasks, over and above that seen for the generation and selection of moves, the making of mental moves and the working memory of moves (plan-control tasks). It could be argued that there might have been a small additional activation in prefrontal cortex for the plan vs plan-control conditions, but that PET is not sufficiently sensitive to detect such a difference. However, inspection of the parameter estimates for the left PFd gives no indication of such a difference (Figure 9.3).

There was extensive activation in the prestriate and inferotemporal cortex, extending along the lingual and fusiform gyri. Activation of the ventral prestriate and inferior temporal cortex has been found previously in studies of imagination of objects, pictures or maps when these are manipulated in mind. Kosslyn *et al.* (1995, 1997) proposed that the generation and use of visual images depends on a neural system that includes a visual buffer in prestriate cortex and a subsystem for encoding object properties and matching them to stored visual memories in the inferior

temporal gyri. Johnsrude *et al.* (1999) found activation in the posterior inferotemporal cortex when subjects mentally reoriented a remembered spatial array. The goal pattern in the TOL, or the representation of the difference between the starting position and the goal position, may be regarded as a visual mental representation or 'pattern'. This is also true for the representation of the difference between the goal and a sub-goal on the path to the goal.

When comparing plan with no plan conditions there were small regions of activation posteriorly in the intraparietal sulcus or neighbouring superior parietal cortex. Kosslyn (Kosslyn *et al.*, 1997) proposed that this cortex was involved in attentional shifts during mental imagery tasks. On the plan tasks the subjects had to evaluate the current position and move. This could be performed by shifting attention between the current state after a proposed move and the representation of the goal in memory. The present study does not allow us to test this hypothesis further.

Finally, in the comparison of plan with plan-control conditions there was activation of the dorsal premotor cortex, cerebellar nuclei and right cerebellar hemisphere. Both the dorsal premotor cortex (Stephan and Frackowiak, 1996) and the cerebellar hemisphere (Jueptner *et al.*, 1997b) are activated when subjects represent movements in their imagination. Kim *et al.* (1994) also reported activation in the dentate nucleus when subjects planned moves.

It is not clear why there was more activation in the premotor cortex and cerebellum in the plan than the plan-control conditions. The design of the conditions matched the plan-control tasks to the plan tasks in terms of the total time per trial and for the actual moves made. The behavioural data however indicated that they were also equal in the initial thinking time. Despite this close matching, the subjects may

have made more mental moves on plan tasks, because some moves would have been selected, mentally made, and then rejected if they did not contribute towards the goal. If additional generation and mental movements were occurring, but the initial thinking time was matched, then the processes of generation and mental moves must have occurred at a higher rate in the plan conditions. Activations of the cerebellum, parietal and premotor cortex during finger movements have been shown to be rate related (Jenkins *et al.*, 1997), and this could explain the persisting cerebellar, parietal and premotor activations in analysis 3 (plan v plan-control). However, Jenkins *et al.* (1997) also found that there was no relation between the rate at which subjects freely selected moves and the activation of the dorsal prefrontal cortex, and this may explain the lack of residual activation in the dorsal prefrontal cortex.

The advantage of using conjunction analysis is that it isolates regions that are common to planning, irrespective of whether the subjects did or did not execute the moves. This means that it is not sensitive to differences that occur for one task comparison (Price and Friston, 1997). The number of moves made in PLAN-MOVE was slightly greater than in PLAN-CONTROL-MOVE (4.07 vs 4.0 moves per problem) because of errors made on the plan task, but activations relating to this small difference will not survive the conjunction analysis. Similarly REST was used as one baseline for the Imagine tasks because it enabled the repetition of one of the conditions used in previous studies (Baker *et al.*, 1996b; Owen *et al.*, 1996a). For the comparison [PLAN-IMAGINE vs REST] the conditions differ by one move per trial, but the conjunction of [PLANMOVE vs VMC] and [PLAN-IMAGINE vs REST] (analysis 1) is not sensitive to this difference.

Clinical implications

The processes of generation and selection of moves, mentally making moves and memory for moves have been shown to activate a common cortical network including PFd, anterior cingulate, premotor and intraparietal cortex. In contrast, in a visually determined task, the processes of representing goals and comparing moves with the goal have been shown to activate the intraparietal, prestriate and fusiform cortex.

These results help to explain why patients with frontal lobe lesions are impaired on the TOL (Johns, 1996; Owen *et al.*, 1990; Shallice, 1982). This may not be because the patients cannot represent the goal or evaluate moves as steps on the path towards the goal. The prefrontal cortex is activated in association with the generation and selection of moves, by mental moves and the memory for moves. Patients with frontal lobe lesions may be impaired on one or more of these processes.

First, they may be poor at generating moves. Such an impairment would be analogous to the impairment of patients with prefrontal lesions on tests of verbal and design fluency. Patients generate fewer items than control subjects on letter fluency (Johns, 1996; Levin *et al.*, 2001; Stuss *et al.*, 1998); phonemic fluency (words rhyming with a cue word) (Jurado *et al.*, 2000); and semantic fluency (words belonging to a particular category) (Johns, 1996; Jones-Gotman and Milner, 1977; Tucha *et al.*, 1999). They are also less able to generate a random series of joystick movements (Johns, 1996).

Secondly the patients may act before they have selected and mentally made all the moves. Johns (Johns, 1996) examined 20 patients with neurosurgical frontal lesions on the TOL. The problems ranged in difficulty from two to seven moves. The

patients solved fewer problems in the minimum number of moves, and this was the case irrespective of the difficulty of the problem. Although the initial thinking time increased with problem difficulty, the patients with right sided lesions took less time to make a first move. This impulsive behaviour, with patients acting without knowing the whole solution, suggested that they may not have mentally made the moves before acting.

Thirdly, the patients may fail to remember all the moves they have planned. Patients with frontal lobe damage have been shown to be impaired on some spatial working memory tasks (Owen *et al.*, 1995), including moves on the Tower of Hanoi task (Morris *et al.*, 1997b). This is consistent with the current finding that PFd is activated as much in the plan-control conditions (requiring working memory for moves) as in the plan conditions. However, forward span for externally presented spatial locations or digits is not necessarily reduced following lesions to prefrontal cortex (Canavan *et al.*, 1989; D'Esposito and Postle, 2000; Miotto *et al.*, 1996; Owen *et al.*, 1990; Pigott and Milner, 1994). The memory load in the current study (4 moves) and duration of delay (around 8 seconds) are similar to the loads and delays used in these studies.

There may be other reasons for the impairment of patients with prefrontal lesions on planning tasks. Morris *et al.* (1997a) suggested that poor performance on the Tower of Hanoi task was due to impaired response inhibition in novel situations. The patients were impaired on the first four 4-move problems that contained goal-subgoal conflicts, but not on four subsequent 5-move problems. The authors proposed that performance on the new counterintuitive moves required inhibition of prepotent moves and that the apparent deficit in 'planning' was due to an inability to

deal with novelty in relation to goal-subgoal conflict. This suggestion is supported by the activation of PFd in normal subjects when resolving conflict between two responses (Banich *et al.*, 2000a; Zysset *et al.*, 2001).

For the subjects studied by Morris et al (1997), as problems with counterintuitive moves became familiar, the importance of response inhibition diminished. However, the patients with bilateral and right prefrontal lesions studied by Johns (Johns, 1996) were impaired on 4-move problems when these were spread over twenty trials varying in difficulty from two- to seven-move problems. The patients were no more error prone than controls on the most difficult problems, regardless of when they were presented. While novel counterintuitive moves may be particularly problematic for patients, in the current study there was activation of the left PFd even after many 4-move problems.

Johns (Johns, 1996) also reported that patients with lesions of PFo as the result of closed head injury sometimes attempted illegal moves, suggesting poor response inhibition. The orbitofrontal cortex was activated in a PET study of the TOL by Elliott *et al.* (1997b) when planning was compared with a condition in which the subjects simply guessed the number of moves to be made. The present study also found orbitofrontal activations when the plan tasks (analysis 1) and plan-control tasks (analysis 2) were compared with baseline. Others have shown that the orbital or inferior frontal cortex is activated under conditions that require the inhibition of responses (Jonides *et al.*, 1998b; Konishi *et al.*, 1999; Nobre *et al.*, 1999).

Summary

The findings suggest that the activation of the prefrontal cortex on the TOL may be due to the generation and/or selection of moves. Other imaging studies

suggest that forward memory span for a sequence of moves to spatial locations is not in itself sufficient to be associated with activation of PFd. Activation of PFd during planning was not attributable to the 'goal-directed exploration' of alternative moves (Dehaene and Changeux, 1997) or the evaluation of a path towards a specified goal. The activation of PFd during performance of the TOL planning task is therefore most likely to be associated with the generation and selection of responses.

Table 9.1. Coordinates of peak significant changes in rCBF in the conjunction analysis 1 [PLAN-MOVE vs VMC] and [PLAN-IMAGINE vs REST]

Region of activation	L/R	Brodmann's area	coordinate x	y	z	Z-value
PFd	L	9/46	-50	26	42	3.79
PFo	R	11	28	30	-28	3.91
Premotor cortex	L	6	-26	-2	50	4.22
	R	6	26	0	58	4.39
Anterior insula	R		34	20	0	4.19
Caudate nuclei	L		-18	-20	16	4.47
	R		18	-12	18	3.44
Intraparietal cortex	L	7	-8	-74	54	6.36
	R	7	14	-70	50	5.50
Medial parietal (precuneus)	R		2	-58	50	4.97
Prestriate cortex	L	18/19	-26	-76	38	3.86
	R	18/19	34	-80	28	3.99
Striate cortex	L	17	-16	-94	24	4.24
Cerebellar Vermis	--		0	-56	-24	6.96
Cerebellar hemisphere	L		-40	-56	-36	4.13
	R		38	-66	-26	5.27
	R		54	-56	-40	4.77

Table 9.2. Coordinates of peak significant changes in rCBF in conjunction analysis 2 [PLAN-CONTROL-MOVE vs VMC] and [PLAN-CONTROL-IMAGINE vs REST]

Region of activation	L/R	Brodmann's area	coordinate x	y	z	Z-value
PFd	L	9/46	-46	20	42	3.99
	R	9/46	36	26	32	4.49
PFo	L	11	-30	56	-12	5.48
	R	11	28	54	-12	5.30
Premotor cortex	L	6	-48	-2	50	4.76
	R	6	26	4	58	4.50
Anterior Cingulate cortex	L	32	-10	14	48	3.53
	R	32	6	24	36	4.27
Anterior insula	R		34	20	0	3.83
Intraparietal cortex	L	7	-24	-68	50	4.15
	R	7	50	-56	48	5.21
Cerebellar Vermis	--		0	-52	-10	5.23
	--		8	-78	-28	4.76
Cerebellar hemisphere	L		-40	-60	-36	4.21
	R		30	-44	-40	3.89

Table 9.3. Coordinates of peak significant changes in rCBF for conjunction analysis 3 [PLAN-MOVE vs PLAN-CONTROL-MOVE] and [PLAN-IMAGINE vs PLAN-CONTROL-IMAGINE]

Region of activation	L/R	Brodmann's area	coordinate x	y	z	Z-value
Premotor cortex	R	6	38	6	70	3.36
Intraparietal cortex	L	7	-10	-68	70	3.92
Prestriate cortex	L	18/19	-42	-60	6	4.26
	R	18/19	16	-68	12	4.57
Lingual/Fusiform gyrus	L	37	-30	-48	-8	3.53
	R	37	40	-46	-20	3.66
Cerebellar nuclei	L		-4	-56	-24	4.48
Cerebellar hemisphere	R		56	-56	-44	3.36

Chapter 10

General discussion

The challenge of the prefrontal cortex, revisited

In chapter 1, two very different conceptual frameworks were presented for the functions of the prefrontal cortex. **First**, a central role in working memory was proposed, based largely on the neurophysiological properties of cells around the sulcus principalis and lesion studies in monkeys (Goldman-Rakic, 1998). The contribution to working memory was subsequently redefined by the distinction between the processes of monitoring and manipulation in memory from the passive maintenance of information (D'Esposito *et al.*, 2000c; Petrides, 2000; Smith and Jonides, 1999). A more specific role in monitoring and manipulation was supported by functional imaging studies and the effects of lesions in humans and monkeys.

Second, the prefrontal cortex was proposed to mediate 'willed action' in humans (Frith, 2000; Norman and Shallice, 1980) or the control of voluntary action through the selection of contextually appropriate responses. This view was supported both by functional imaging studies of voluntary action, including speech, and the consequences of focal lesions in humans and monkeys. A supervisory attentional system had been proposed earlier on the basis of a functional analysis of cognitive and behavioural tasks in normal subjects and patients (Norman and Shallice, 1980). The functions of this supervisory attentional system were later shown to be dependent on

the integrity of the prefrontal cortex in humans, and were associated with activity of the prefrontal cortex during functional neuroimaging studies.

It was proposed in chapter 1 that a common framework for understanding the functions of the prefrontal cortex must consider the anatomy of the prefrontal cortex, the basic properties of neurons and the consequences of lesions. It must also be applicable to previous experimental paradigms and generate specific testable hypotheses.

But, how could a framework encompass working memory, willed action, the neurophysiological properties of monkey cells and the cognitive deficits that may occur in patients with lesions of the frontal lobe? A potential solution emerged out of the convergence of ideas from studies of response selection and visual selective attention.

Response selection

In humans, there is activity of PFd when subjects choose freely among motor responses or among verbal responses (chapter 6; Deiber *et al.*, 1991; Frith *et al.*, 1991; Hyder *et al.*, 1997; Jahanshahi *et al.*, 2000; Pujol *et al.*, 1996; Phelps *et al.*, 1997; Thompson-Schill *et al.*, 1998; Ojemann *et al.*, 1998; Buckner *et al.*, 1995; Klein *et al.*, 1995). The selection of one item from many alternatives is associated with more activation of prefrontal cortex than selection of one item from just a few (Desmond *et al.*, 1998; Thompson-Schill *et al.*, 1997). The selection of a unique set of responses to solve a novel problem is also associated with activation of PFd (Morris *et al.*, 1993 #126; Baker *et al.*, 1996; Owen *et al.*, 1996; Owen *et al.*, 1998; Elliott *et al.*, 1997; Dagher *et al.*, 1999). There is also activation associated with the selection between conflicting responses, when the context determines which response is correct (Taylor

et al., 1997; George *et al.*, 1994; Carter *et al.*, 1995). Moreover, it is the imposition of attentional control of responses that is associated with activation of PFd (Banich *et al.*, 2000b; MacDonald *et al.*, 2000).

Selection of items can also occur in working memory. There are different forms of selection within different working memory paradigms. These may not be equally important in terms of prefrontal cortical activity, and may differ between monkeys and humans. Nevertheless, it is useful to distinguish selection within working memory from the passive maintenance of information over delay intervals.

First, consider the monkey delayed response task studied by Goldman-Rakic (1987), in figure 1.3. During the delay period, the monkey must retain an internal representation of the location of the reward. At the end of the delay, the monkey must select between responses to the left or right locations. That selection depends on the existence of the correct internal representation of the reward location. However, the mnemonic and selective components of the task are, in principle, separable. It is possible that monkeys with lesions to PFd fail this task not because they cannot remember the stimuli, but because they cannot use this information to guide the correct response.

Second, some studies require the selection between different items in memory, whereas others require that all items be reported back in the order in which they were presented. For example, in chapters 4 and 5, PFd was activated when subjects selected one location out of three in order to make a response. In contrast, forward span for spatial locations when the whole sequence was replayed was not associated with activation of PFd (Owen *et al.*, 1996b).

Third, some tasks require that a stimulus be attended to in relation to others. This requires more than simple attention to one stimulus. For example, on the self-ordered task the patterns or locations already chosen must be attended to in relation to the remainder (Petrides and Milner, 1982). On the n-back task, the current n- items are selectively attended to, with new items added to the list of recent items and older items no longer selected. Both tasks are associated with activation of the prefrontal cortex (Braver *et al.*, 1997; Cohen *et al.*, 1994; D'Esposito *et al.*, 1998; Jansma *et al.*, 2000; Martinkauppi *et al.*, 2000; Nystrom *et al.*, 2000; Perlstein *et al.*, 2001; Rama *et al.*, 2001; Schumacher *et al.*, 1996; Smith *et al.*, 1996) and are impaired by disruption of prefrontal cortical function (Oliveri *et al.*, 2001).

Fourth, during manipulation items, several items must also be attended to in relation to others. To construct the new (manipulated) response set, the original items must be selected sequentially and considered in relation to the other items and according to the manipulation rule. Manipulation of spatial or non-spatial stimuli is associated with greater activation of PFd than maintenance without manipulation (D'Esposito *et al.*, 1999b; Owen *et al.*, 1996b; Postle *et al.*, 1999a; Smith and Jonides, 1999).

Fifth, in experiments with multiple trials it is necessary for a subject to distinguish between the information relevant to the current trial from the information presented in previous trials. Impaired discrimination between stimuli on past and present trials leads to interference from trial to trial. The delayed response deficits following lesions of PFd are caused by interference from recent trials (Diamond and Goldman-Rakic, 1989). In fMRI studies of human response selection, selection

related activity in PFv was greater when stimuli in previous trials interfered with the current probe (D'Esposito *et al.*, 1999c; Jonides *et al.*, 1998b).

It is proposed that selection between alternate remembered items and the selection between alternate responses are mediated by a common mechanism in prefrontal cortex. The mechanisms of selection must also incorporate the context in which the selection is made. In working memory tasks, the context of selection of remembered items is determined by the monitoring or manipulation demands, or the type of probe cue. A loss of context sensitivity of response selection may contribute to the deficits of patients with focal frontal lesions. These patients may make inappropriate responses or decisions rather in both 'real-world' and laboratory situations (Burgess *et al.*, 1996; Ferrier, 1878; Golden, 1976; Johns, 1996; Lhermitte, 1983; Luria, 1969; Owen *et al.*, 1990; Rogers and Monsell, 1995; Rogers *et al.*, 1998; Shallice, 1982; Stablum *et al.*, 1994; Vendrell *et al.*, 1995). There is now direct evidence for the encoding of context by neurons in the prefrontal cortex. Some neurons show context specific stimulus selectivity of firing (Asaad *et al.*, 2000) while others encode the general rule governing the appropriate responses to multiple stimulus types (Wallis *et al.*, 2001).

If the prefrontal cortex determines the selection of remembered items or actions according to context, how is the selection to be put into effect? A neural mechanism of selection has been identified in studies of visual attention, and this may generalise to the motor system and memory.

Attentional selection

The term 'attention' is widely used. James wrote that "Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out

of what seem several simultaneously possible objects or trains of thought.... It implies withdrawal from some things in order to deal effectively with others" (James, 1895). In the language of cognitive psychology, attention determines the allocation of processing resources to an item or event. In a system of limited global capacity, attention to an item is necessarily selective (Desimone and Duncan, 1995; Kastner and Ungerleider, 2000).

Attention is sometimes used to describe the consequence of increased processing allocated to a single stimulus in a display, perhaps because it is brighter or louder. The 'attention' in this case has been 'captured' or driven 'bottom up' by the stimulus itself (Theeuwes *et al.*, 2000). Attention may also be used to describe the voluntary or goal directed imposition of differential processing resources to those stimuli that are relevant. This goal directed allocation of processing resources is sometimes known as 'top-down' attentional control. Bottom-up and top-down mechanisms may interact. For example, goal-directed control of processing (top-down) may change as a result of stimulus driven processing of one part of the visual field (bottom-up). These interactions are facilitated by the extensive reciprocal interconnections between brain regions.

Attention is not an all-or-nothing phenomenon. The top-down influences on processing *bias* the activity related to one particular stimulus, or change the degree to which other stimuli will cause interference. Similarly, the supervisory attentional system (Norman and Shallice, 1980) was proposed to operate by the modulation of the activity of schemas. The schema that is finally executed is said to be 'selected', but the selection is a result of biased activation, not the flip of an 'on-off' switch.

Studies of selective visual attention have demonstrated that the multiple representations of different stimuli within a cortical region are mutually inhibitory (Chelazzi *et al.*, 1998; Chelazzi *et al.*, 1993; Desimone, 1998; Reynolds *et al.*, 1999). This mutual inhibition will enhance the effect of bias of any given stimuli, so that a relevant representation is selected above alternatives. The bias signal itself may act in different ways. It may increase baseline activity, increase the stimulus-response gain, or shift a non-linear stimulus-response curve to the left. The result remains preferential activity of the neural representation for that item.

The term '**attentional selection**' emphasises both the mechanism and consequence of this top-down modulation of representations. It makes reference to the top-down 'attentional' modulation of cortical processing (of a stimulus, a movement or a memory) and the effect of 'selection' of a neuronal representation (of objects, locations, actions or memories). In the visual system, attentional selection has been shown directly as a 'spotlight' of visual attention, enhancing focal cortical activity (Brefczynski and DeYoe, 1999). The modulatory inputs from prefrontal to infero-temporal cortex are sufficient to bias neuronal activity in a stimulus specific manner, in the absence of direct visual input (Tomita *et al.*, 1999). This same mechanism has been proposed to extend to other sensory domains, and to actions and memory (Miller, 2000; Miller, 1999).

An attentional selection hypothesis of prefrontal cortical function includes a mechanism of signal bias that is well described in the visual cortex. This mechanism is proposed to apply to motor response selection as well as sensory selection. It is further proposed that stimulus and/or response selection occurs in many working memory studies.

Selection within working memory

PFd

The distinction between maintenance and attentional or selective processes in working memory has been emphasised by Baddeley (Baddeley, 1993). He drew the paradoxical conclusion that not all working memory studies need involve memory. Rather, the central executive was concerned with attention. This was not a slight change in terminology, but indicated a profound shift in the meaning of 'working memory' from a memory system towards an attentional (selective) system.

The first two experiments (chapters 4 and 5) contrasted passive maintenance during a delayed response task with the selection between remembered items in order to make a response. In both experiments, it was intended to keep the apparent simplicity of the delayed response task. Although the delayed response task has many cognitive and motor constituents, each trial and its stimuli can be considered to be (almost) independent of the others, and the remembered information does not need to be changed during the delay. Our tasks differed from the monkey versions in several ways. It was taught explicitly, rather than learned by trial and error. In addition, in chapter 4, the delay related processes of memory trials and non-memory trials were conditional on the first stimulus, rather than all trials following the same format. In chapter 5, all trials were the same at presentations of stimuli and during the delay, but response demands differed according the probe cue.

Spatial cues were chosen in order to reduce the likelihood of verbally encoding the stimuli, or naming of objects or faces. In contrast with the n-back task, each trial was intended to be independent of its neighbours. It could be argued that there could have been interference between successive trials. In the first experiment

this was reduced by the inclusion of control trials. In both studies, the dots could have appeared anywhere in the display. Many hundreds of locations were possible, reducing the probability of recurrence of locations.

Models of working memory have suggested 'process specificity' and 'domain specificity' in the functional organisation of PFd and PFv. It is proposed that the processes of monitoring and manipulation include serial selection of stimulus representations. If the delay period included monitoring or manipulation, then it would have undermined the distinction between delay activity and response selection. Therefore, the subjects were not required to monitor one location in relation to others, and it was not necessary to manipulate the stimuli or their order. Domain specificity predicts that spatial material would be associated with activity of PFd. The first two studies therefore also directly test the domain specificity working memory hypothesis.

The results were very clear and consistent. Selection of one item out of three was associated with activation of area 46 of PFd in both experiments. Area 46 is of particular interest because even small lesions restricted to this area in monkeys are sufficient to impair delayed response performance (Butters *et al.*, 1971; Hoshi *et al.*, 2000). There was also activation more posteriorly in area 9/46, and in parietal cortex. This activity related to selection occurred whether the selection was made according to a line that went through the target's location, or by a number that specified its position in the sequence.

In contrast, memory for three spatial locations, with or without their temporal order, was not associated with activation of area 46 of PFd. Inspection of the temporally realigned data, for fitted (figures 4.4, 4.5) or adjusted (figures 5.4, 5.5) data suggests that there was not even a weak trend towards delay related activation

here, nor activation early in the delay period. At reduced statistical threshold in the first study, there was activation in the posterior part of the middle frontal gyrus, lying either in area 8 or area 9/46. There was however activation of area 8 around the posterior part of the superior frontal sulcus. This has been noted previously in studies of spatial working memory (Courtney *et al.*, 1998b).

It is possible that there was weak delay related activity in other voxels of PFd, not detected in these experiments, even with the reduced threshold or regions of interest analyses. Even if this was the case, area 46 was dominated by selection related activation. Large activations associated with response selection have been reported previously, but discussion has usually focused on the much smaller delay related activity, rather than differences at response selection (Belger *et al.*, 1998; D'Esposito *et al.*, 2000c; Jha and McCarthy, 2000; Postle and D'Esposito, 1999; Rypma and D'Esposito, 1999; Rypma and D'Esposito, 2000; Zarahn *et al.*, 1999). This is perhaps because of the debate over domain specificity and process specificity in the working memory literature.

Delay related activity in the frontal cortex has been identified, distinct from stimulus and response related activity, in other studies of working memory, even without manipulation or instructions to rehearse stimuli. However, delay related activity was often not sustained. Rypma and D'Esposito (1999, 2000) studied the maintenance of two or six letters, over 16 seconds. Activation of PFd was dominated by response related activation. Smaller effects were seen at encoding, and during the delay. The delay related activation was not load sensitive, and tended to be lower in the second part of the delay period than in the first. Interestingly, subjects who were slower to response to the probe cue had more extensive activation of PFd at response,

and more extensive activation of PFv during the late delay period. In other studies, forward memory for five letters (D'Esposito *et al.*, 1999a; Postle *et al.*, 1999a) or four letters (D'Esposito *et al.*, 1999c) over 8-12 seconds was associated with minimal or no delay related activity of PFd in many subjects, despite significant encoding and response related activation. It is possible that with shorter delays, BOLD activity may be incorrectly attributed to delay related neural activation, even when is truly attributable to late neural activity related to perception and encoding of stimuli.

Jha and McCarthy (2000) used face stimuli rather than letters, over 15 second delays. In contrast to Courtney et al (1997), Jha and McCarthy did not ask subjects to rehearse the image of the face. Activation of PFd was again dominated by encoding the stimuli and the response. There was some delay-related activation, but this was only observed earlier in the delay period and when multiple faces were presented before the delay. In a second experiment using long delays of 24 seconds, it was clear that delay related activity declined to near zero before the probe stimulus enabled response selection.

The functional dissociation between anterior and posterior regions of the frontal cortex was emphasised by Smith and Jonides' (1999). In chapter 5, the anterior (area 46) and posterior (area 8) frontal cortex was compared directly. These regions did differ significantly in their maintenance- and selection-related activation, more so on the left. Smith and Jonides (1999) also suggested laterality effects: right activation predominant for spatial information and left for verbal information. In chapter 4, the maintenance related activation was bilateral in area 8, but selection related activation in area 46 was right sided. In chapter 5, the maintenance related activation of area 8 was greater on the left, the selection related activation was bilateral, and the difference

was greater on the left. Therefore, the laterality effect proposed by Smith and Jonides was not supported by the current data.

The dissociation between anterior and posterior regions of the frontal cortex also exists in monkeys. For example, Rao et al (1997) assessed the integration of object feature and location information. Integrative cells were predominantly anterior, whereas cells sensitive to location alone were more posterior in the bow of the arcuate sulcus and posterior third of sulcus principalis. Many of the cellular recording studies that supported domain specificity had recorded mostly from the posterior third of sulcus principalis and area 8 [Wilson, 1993 #940; Scalaidhe, 1997 #938; Scalaidhe, 1999 #937; Goldman-Rakic, 2000 #936; Levy, 2000 #935; Romo, 1999 #941]. Activity in these posterior areas is specifically related to the maintenance of spatial items in memory not response preparation (Funahashi *et al.*, 1993; Sawaguchi and Yamane, 1999a). Domain specificity has not been demonstrated more anteriorly in areas 46 versus 47.

PFv

The role of PFv in working memory has been discussed in relation to theories of domain specificity and process specificity (Goldman-Rakic, 1998; Smith and Jonides, 1999). Domain specificity predicts that working memory of spatial items would not be associated with activation of PFv. In contrast, process specificity predicts that spatial working memory would be associated with PFv activation, even without manipulation.

The version of process specificity put forward by Petrides (Petrides, 1995a; Petrides *et al.*, 1995) suggests that PFv mediates the retrieval of information from posterior memory systems. Such retrieval was proposed to be necessary for

performance of additional on-line processing e.g. manipulation. In the current studies, PFv was activated in association with response selection (chapter 4, right; chapter 5, bilateral). It is possible that at the time of response selection the subjects retrieved a mental image of the initial stimuli. Consistent with this possibility is the co-activation of prestriate and medial parietal cortex at response selection. Both of these regions have been associated with mental imagery and memory for visual stimuli (Fletcher *et al.*, 1995; Kosslyn *et al.*, 1993; Kosslyn *et al.*, 1997).

Other process specificity models have suggested that PFv mediates passive maintenance of information, regardless of stimulus modality (D'Esposito *et al.*, 1999b; D'Esposito *et al.*, 2000c; Owen *et al.*, 1999). This is not supported by the current studies. In chapters 4 and 5, passive maintenance was not associated with activation of PFv. In chapter 5, the closest activation was in ventral premotor cortex (or the frontal eye fields), but this could not be confused with PFv.

The tasks used in chapters 4 and 5 were similar to the memory task for a sequence of spatial locations studied using PET (Owen *et al.*, 1996b; Owen *et al.*, 1999). Owen et al (1996, 1999) found activation of PFv in both studies. There are several possible reasons for the different results. **First**, the PET method could not differentiate activation related to delay from response selection. The activity in their study may have been attributable to selection related activity. In chapters 4 and 5, selection was associated with activation of the inferior frontal gyrus (right, chapter 4; bilateral, chapter 5). Activation of the left PFv has also been associated with selection of responses during a semantic retrieval task (Thompson-Schill *et al.*, 1997).

Second, the tasks used by Owen et al (1996, 1999) required the recall of the whole sequence of items, rather than the selection of one item among several. The

demands on PFv may differ between recall of a sequence of stimuli and the recognition of a sequence, or selection of a single response based on the sequence. A difference of this kind has been demonstrated for PFd (Ferreira *et al.*, 1998; Pochon *et al.*, 2001).

Third, our results may represent false negatives. The ventral and orbital frontal cortex is prone to distortion and dropout in EPI images, increasing at high magnetic fields. Distortion and dropout of PFv were not obvious in the BOLD images acquired, but subtle effects could introduce greater variance in fMRI studies than PET, increasing the risk of type II error.

PFv has also been linked to the inhibition of responses, rather than selection or maintenance of information. The spatial tuning of cells in frontal cortex is enhanced by inhibition of neighbouring cells and cells that would have different spatial tuning in the absence of inhibition (Rao *et al.*, 1999; Rao *et al.*, 2000). This resembles the mutual inhibition between object-specific cells in visual association cortex (Chelazzi *et al.*, 1998). The inhibition of a response could result from biased activation (attentional selection) of a subset of response representations, or the representations of stimuli used to guide a response. Inhibition can therefore result from the selection of alternate responses. The failure of response inhibition following damage to prefrontal cortex has been linked to the failure of selection of appropriate alternative responses (Kimberg and Farah, 2000).

However, inhibition has also been proposed to result from the activation of an inhibitory control centre in PFv, distinct from 'positive' response selection (Diamond, 1990; Konishi *et al.*, 1999). Evidence comes particularly from studies that require the suppression of a prepotent response e.g. a go/no-go task. Inhibition of verbal

responses has also been proposed to contribute to the activation of PFv during non-spatial working memory tasks (Smith and Jonides, 1998). In chapters 4 and 5, many spatial locations were used, and the targets were evenly distributed across the screen over the course of the experiment. This reduced the prepotency of any given response. Where prepotent responses exist, the incorrect responses have been reinforced by experience and will occur in the absence top-down control bias.

The bias that inhibits a prepotent response may be the same as that which selects between responses. It depends on the memory for the recent stimuli and awareness of the current context (Miller and Cohen, 2001). However, it remains uncertain how the process of selection mediated by PFv differs from that mediated by PFd.

The generalisation of attentional selection

In chapter 6, it was proposed that attentional selection was a generic function of the prefrontal cortex. Free selection of an action, or a colour component of a visual display, was proposed to arise from the top-down bias of specific motor or sensory representations. The regions of the prefrontal cortex are extensively interconnected with sensory and motor association cortex in frontal, parietal, occipital and temporal lobes. They therefore have the potential to modulate cortical activity in many different domains, according to the current goal or context.

There were three subsidiary hypotheses. **First**, that the same regions of the prefrontal cortex are activated when selecting actions as when selecting visual stimuli. **Second**, these regions are the same as the region activated when selecting items from memory (chapters 4 and 5). **Third**, that despite common activation of PFd, there is

modulation of cortical activity in distinct domain specific regions in non-prefrontal cortex.

Four tasks were devised, in a two-by-two factorial design. One factor contrasted the effects of free selection (dependant on attentional selection) with externally specified responses (in which the response is directly related to the stimulus). The second factor contrasted tasks based on actions (one of four fingers) with tasks based on colours (one of four colours). A response here means the target or goal of the trial. It is suggested here that what is selected is the action or the colour. The response is not merely the finger movement on the button. All trials included such a movement, to indicate the chosen action/colour, or obedience to the external specification of action/colour.

The results confirmed that the prefrontal cortical activation associated with free selection was similar for action and colour tasks. The broad activation patterns were closely overlapping, and the peaks lay within 12 mm of each other, bilaterally in area 46. Moreover, these peaks were within 5 mm and 11 mm respectively of the right and left PFd peaks associated with selection from memory in chapters 4 and 5. This provides evidence for the generalisation of selection in PFd to multiple motor, sensory and mnemonic domains.

The domain-specific modulation of non-prefrontal cortex was sought by the interaction contrasts. All tasks required a finger movement to indicate the chosen action/colour. In the colour tasks, and when the action was externally specified, this finger movement was directly related to the arrow or colour boxes on the display. Only when the action was freely chosen would the attentional selection hypothesis predict modulation of medial or lateral premotor cortex. Such modulatory influence

was found adjacent to the central sulcus ($p<0.001$ uncorrected), but not in premotor cortex. It is possible that the representation of the action was mediated by cells in motor cortex. Alternatively, there may have been modulation of the representation of expected sensory feedback in primary sensory cortex. Attentional modulation of SI and SII has been demonstrated by functional imaging in humans (Johansen-Berg *et al.*, 2000; Macaluso *et al.*, 2000; Meyer *et al.*, 1991), although not consistently (Mima, 1998; Mauguiere *et al.*, 1997).

However, neurophysiological recording in monkeys suggests that cells in premotor cortex encode the target of an action (Shen and Alexander, 1997). The absence of a significant interaction between selection (free vs externally specified) and modality (action vs colour) in premotor cortex may be because the selection in this experiment was between four alternative actions. The differential activation of one action and inhibition of others may have resulted in too small a net increase in the metabolic activity of the population of premotor cells, resulting in no significant change in BOLD signal.

It is possible that subjects selected the 'action' according to the spatial location of the buttons or fingers, rather than the action to be made. This would nonetheless be a process of free selection, but of location. The results would still support the hypothesis of generalisation of attentional selection to multiple domains. However, there is no evidence in favour of such location-based selection, such as a location-specific free selection effect in parietal cortex.

There was an interaction between selection and modality in the prestriate cortex. Free selection of colour, but not action, resulted in a greater activation of this region than the respective externally specified tasks. The modulation occurred in

inferolateral prestriate cortex, the expected location of colour sensitive area V4 (Tootell and Hadjikhani, 2001). Attentional modulation of V4 has been demonstrated in V4 of the monkey cortex (Reynolds *et al.*, 2000). Our results confirm this observation in the human brain, and suggest that this modulation is driven by modulatory inputs from the prefrontal cortex.

Interactions between cortical regions

The previous experiments suggested that the prefrontal cortex mediates a general process of attentional selection of non-prefrontal representations, whether mnemonic, visual or motor. In chapter six, there were modality specific free selection effects in ventral prestriate cortex (colour selection), and in cortex adjacent to the central sulcus (action selection). It is proposed that the modality specific effects in non-prefrontal cortex were driven by top-down modulatory influences from the prefrontal cortex. The effects were not large, perhaps because the selection was differential between multiple colours or actions. A main effect of attention to action or colour would provide a stronger enhancement of the action or colour 'target' regions.

A main effect of attention to action was studied in chapters 7 and 8. The contrast of attended action with unattended action (ATTEND vs MOVE) was a replication of the study by Jueptner et al (1997). The pattern of results in the statistical parametric map was similar. However, the fMRI method appeared to be more sensitive: several regions were significant in the current fMRI study ($p<0.05$ corrected) that had only been found as trends ($p<0.01$ uncorrected) in the earlier PET study. These areas included premotor cortex and SII, the proposed targets of attention to the action and sensory feedback respectively.

The attentional selection hypothesis predicts that selection of a motor representation, say in premotor cortex, would be associated within increased activation of prefrontal cortex (the source of modulatory influences) and the premotor cortex (the target of the modulatory influences). The influence of the prefrontal cortex over premotor cortex represents effective connectivity (Friston *et al.*, 1997a), which may be measured using fMRI data. More specifically, the change in movement related coupling was measured under different conditions.

In chapters 7 and 8, the effective connectivity between prefrontal cortex and premotor cortex was measured by structural equation modelling of fMRI data. Two attentional modulations were used. By analogy with the study of sensory attention by Meyer et al (1991), there were three attentional states: neutral, attention towards action, and attention distracted away from action. The distractor task was an attentionally demanding visual search paradigm, which in previous studies was associated with activation of prefrontal but not premotor cortex (Coull *et al.*, 1998).

To interpret the effect of attention towards action, it was necessary to compare attention to action (ATTEND) and attention away from action (DUAL). The neutral condition (MOVE) may have included partial attention to action, diminishing the effect of the instruction to attend to the next move. The effect of the distractor task would then be expected to be opposite to the effect of attention to action. In contrast, if the effect of the distractor task was in the same direction as the effect of attention to action, then the change in effective connectivity would be attributable to a non-specific effect of attentiveness, and not to changes in attentional selection of action representations.

The method used to detect changes in effective connectivity differed from the application of structural equation modelling applied to PET data (Coull *et al.*, 1999; Horwitz *et al.*, 1999; McIntosh, 1999; McIntosh and Gonzalez-Lima, 1991; McIntosh *et al.*, 1994; Nyberg *et al.*, 1996). In the current method, all fMRI data from the interconnected regions were included in a single model. However, the model also included moderator variable to characterise the change in effective connectivity under different attentional conditions. The use of moderator variables was introduced by Buchel and Friston (1997, 2000), to study the attentional modulation of coupling within the visual system.

The moderator variables were more complex than those used by Buchel and Friston (1997, 2000) in that the time course for the distractor task was orthogonalised with respect to the time course of attention to action. This was necessary because the two attentional tasks were not independent: it was not possible for a subject to both attend to action and perform the visual conjunction search. The result of the orthogonalisation was that attention to the distractor task was nested in the periods of 'not-attending-to action'.

The effective connectivity between prefrontal and premotor cortex in healthy subjects was increased by attention to action, but not by attention to the distractor task. In young subjects (chapter 7), the distractor task diminished the effective connectivity while in older subjects (chapter 8) the distractor task had no significant effect. Attention to action also increased the coupling between the prefrontal cortex and the supplementary motor area (chapter 8). Moreover, these effects were not attributable to the effect of common parietal inputs to prefrontal and premotor cortex (chapter 7).

The results are consistent with the proposed attentional selection of action representations by prefrontal cortex. The effects are significant in relation to the subject-to-subject variability (random effects analysis). Therefore, it is possible to directly compare two populations, such as patient vs control, or young vs old. Differences may be attributed to a true population differences i.e. effect of disease of ageing, and not due to large effects in a subset of individuals. This approach was taken in chapter 8, when considering the impact of Parkinson's disease on attention to action.

Clinical implications

The clinical implications of the attentional selection hypothesis were considered in chapters 8 and 9. In chapter 8, the paradigms and methods developed to assess attention to action and cortico-cortical connectivity in the young (chapter 7) were applied to patients with Parkinson's disease and age matched controls. Chapter 9 studied a test that is commonly used with frontal lobe patients, together with variants of the task, to try to characterise the component cognitive processes that are dependent on the prefrontal cortex.

A functional disconnection in Parkinson's disease

The patients with Parkinson's disease had abnormalities within specific cortical regions, and abnormal effective connectivity among regions of the extended motor system. The supplementary motor area (SMA) showed an abnormal increase in activation relative to control subject, in a simple motor sequence task. However, the SMA did not increase its activity when subjects attended to their actions. Relative impairment of the SMA in Parkinson's disease has been reported previously, in tasks

that required attention to action, such as trial and error learning or execution of complex sequences (Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1992; Samuel *et al.*, 1997a; Thobois *et al.*, 2000), fMRI (Haslinger *et al.*, 2001; Sabatini *et al.*, 2000). On other motor task comparisons, SMA activity has been normal or increased (Catalan *et al.*, 1999; Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995; Nakamura *et al.*, 2001; Praamstra *et al.*, 1996; Sabatini *et al.*, 2000).

The motor related coupling between prefrontal cortex and the premotor cortex or SMA was not enhanced by attention to action, in the normal way (figure 8.5). Although the activation of the prefrontal cortex itself was not significantly different between the two groups, the prefrontal cortex was not able to modulate the activity of premotor cortex and SMA, to mediate attention to action. This might suggest why Parkinson's disease is associated with higher activation of SMA in some tasks and with lower activation in other tasks.

A functional disconnection between the SMA and other regions was proposed in Parkinson's disease by Dick et al (1986). By this the authors meant that the anatomical connections exist but that afferents from other cortical regions (e.g. prefrontal cortex) do not influence the activity of the SMA. Our results support this hypothesis. There are still behavioural effects of attention to action, but the mechanism remains uncertain.

A functional disconnection of the prefrontal cortex may occur in other cognitive tasks. In addition to akinesia, rigidity and tremor, Parkinson's disease is associated with cognitive abnormalities, particularly on tasks or cognitive functions that are associated with impairments of the frontal lobes. These tasks include the Stroop task and word fluency (Rinne *et al.*, 2000; Stam *et al.*, 1993), or the Tower of

London task, attentional set shifting and spatial working memory (Lange *et al.*, 1992; Owen *et al.*, 1997; Owen *et al.*, 1993; Robbins *et al.*, 1994).

The pattern of deficits changes during the course of disease progression. For example, spatial working memory is more impaired in severe disease despite medication, whereas set-shifting may be impaired at all stages of the disease (Owen *et al.*, 1992; Owen *et al.*, 1993b; Owen *et al.*, 1997; Postle *et al.*, 1997). The pattern of deficits is also not identical to that found in patients with frontal lobe lesions (Owen *et al.*, 1993). The variation of effects over time, and the distinction from patients with frontal lobe lesions, may be due to the uneven distribution of cortical and subcortical dopamine depletion in Parkinson's disease (Agid *et al.*, 1987; Scatton *et al.*, 1983; Scatton *et al.*, 1982). It may also be due to the differential rate of progression of neurodegeneration, dopamine depletion and compensatory mechanisms in these different cortical and subcortical structures (Dymecki *et al.*, 1996; Kaasinen *et al.*, 2000; Kaasinen *et al.*, 2001).

The cognitive tasks outlined above depend on the interactions among many brain regions. These interactions could be impaired by dysfunction within a given region, or by impaired connectivity between regions. This connectivity may be direct, i.e. cortico-cortical connectivity. Alternatively it may be indirect, via cortico-striatal-thalamo-cortical loops of the type proposed by Alexander et al (1986, 1990). In Parkinson's disease, particular attention has been paid to impairment of the caudate nucleus and the internal segment of the globus pallidus as contributors to impaired cognitive function.

Parkinson's disease is not always associated with reduced activation of the prefrontal cortex, measured by PET (Owen *et al.*, 1998). Indeed, some parts of PFd

may even be more activated in patients than controls during the performance of complex cognitive tasks (Dagher *et al.*, 2001). However, reduced activity of the caudate nucleus has been suggested to impair performance of frontal tasks by impairing the function of the frontal cortical-striatal-thalamo-cortical loops (Alexander *et al.*, 1986; Dagher *et al.*, 2001; Owen *et al.*, 1998). If the subcortical outflow tract of the prefrontal cortex is damaged, then the functions of the prefrontal cortex will not be properly expressed, even if the activity within prefrontal cortex is preserved.

There is no direct evidence for this in the current data. In chapter 8, the putamen was less active in patients than in control subjects during performance of the motor task. Abnormalities of basal ganglia function were not detected in other contrasts. This negative result may be a type II error. The neurovascular responses in the basal ganglia may be different from the cortex, increasing the risk of false negative changes in BOLD. Also, the neurovascular response to increasing task difficulty may not be monotonic. Whereas increasing task demands increased activation of PFd linearly, the activity of the caudate nucleus may change in a U-shape manner (Dagher *et al.*, 1999). Our particular attentional tasks and control conditions may have been associated with activity on opposite limbs of the 'U', such that contrast comparisons did not reveal a difference.

In structural equation modelling the inference about effective connectivity between regions is restricted to the systems level. No inference can be made about the nature of the synaptic connection, whether excitatory or inhibitory whether monosynaptic or polysynaptic. Therefore it is possible that the functional disconnection between the prefrontal cortex and the premotor regions is due to

abnormalities in subcortical connections, abnormalities in direct cortico-cortical connections, or a combination of these.

Planning and the frontal lobe

The Tower of London task is one of many tasks used commonly to assess the function of the frontal lobes (Rabbitt, 1997). It has been applied to patients with surgical lesions to the frontal lobe, neurodegenerative syndromes including Parkinson's disease, depression and schizophrenia (Dagher *et al.*, 2001; Elliott *et al.*, 1997a; Elliott *et al.*, 1998; Johns, 1996; Morris *et al.*, 1995; Owen *et al.*, 1990; Owen *et al.*, 1998; Pantelis *et al.*, 1997; Shallice, 1982). These patient groups are usually, but not always (Dagher *et al.*, 2001) impaired on the task, especially for more difficult problems.

The task has some similarity to the self-ordered task used by Petrides and Milner (1982). Subjects must self-select moves from a range of possible moves, and bear in mind previously chosen moves when selecting the next. The growing sequence of chosen moves must be remembered over the time it takes to complete the selection process. However the task is distinguished as a planning task by virtue of the specified goal state that subjects must consider when selecting their moves.

The subjects must bear in mind the goal state. It is perhaps surprising that normal subjects rarely look at the goal pattern while solving the problem (Hodgson *et al.*, 2000). Instead, they rely on a mental image or construct of the goal. In chapter 9 the presence of a specified goal in the Tower of London was associated with activation of parietal cortex and the lingual gyrus, when contrasted to a formally similar task with no such specified goal. The presence of a goal was not associated with greater activation of the prefrontal cortex.

The selection and working memory for four moves was associated with equal activation of the prefrontal cortex, whether or not a goal was specified, and whether or not the chosen moves were to be executed. The tasks used in chapter 9 cannot distinguish the relative contribution of the self-selection of moves and the working memory for these moves.

The impairment of Tower of London task performance following damage or degeneration of the prefrontal cortex may arise for several reasons. **First**, when several moves are possible given the goal and start array, patients may be impaired at selecting one putative move from the others. This resembles the impairment of response selection following TMS (Jahanshahi and Dirnberger, 1999; Jahanshahi *et al.*, 1998) or surgical lesions to the prefrontal cortex (Johns, 1996). Lesions also impair the generation of multiple responses to cues (Johns, 1996; Stuss *et al.*, 1998). Our plan-control conditions required serial selection of moves from legitimate possible moves: there was as much activation of PFd as when planning the solution to a standard TOL problem.

Secondly the patients may act before they have selected and mentally made all the moves. For example, Johns (1996) reported that patient with right sided prefrontal lesions took less time to make their first move, but were subsequently impaired at completing the whole problem, despite the instruction to move only when the whole solution was known. This impulsiveness was greater following lesions to PFv and PFo than PFd. However, it is not clear whether this results from guessing moves because of reduced sensitivity to reward feedback (Bechara *et al.*, 1998; Elliott *et al.*, 1997b), or to an inability to inhibit selected moves until the whole sequence is known.

Thirdly, the patients may fail to remember all the moves they have planned. However, forward span for a series of four or five moves on a spatial span task is minimally impaired following lesions to PFd (Owen *et al.*, 1990), and is not associated with activation of PFd in normal subjects (Owen *et al.*, 1996b). Therefore it is unlikely that the patient deficit is due only to an inability to maintain selected moves for a few seconds.

Owen et al (1996) tried to control for memory by using a control condition in which a series of TOL moves were specified by the computer, one by one. Subjects replayed these moves after presentation. However, memory and execution of externally specified movements is associated with different patterns of cortical activation than memory and execution of self-selected movements (Deiber *et al.*, 1996; Deiber *et al.*, 1991). Therefore, the selection and memory for self selected moves was chosen as a control condition in chapter 9. This control condition was associated with as much activation of PFd as planning the solution to a standard TOL problem (figure 9.3a).

Fourth, the patients may be unable to bear one move in mind in relation to previous moves. This is at the heart of the monitoring tasks for moves e.g. the self ordered task, or for recurrent stimuli e.g. the n-back task. In both the plan tasks and plan-control tasks used in chapter 9, the subjects needed to bear in mind the earlier moves in order to make the later moves.

In summary, performance of the Tower of London task is associated with activation of the prefrontal cortex in normal subjects, and is impaired following lesions to prefrontal cortex. However, the activation can be accounted for by the cognitive components of selection of putative moves, or consideration of each self-

selected move in relation to previous moves. The critical element of a planning task – the presence of a specific goal array - was not associated with additional activation.

Evaluation of attentional selection

Principal advantages

If the attentional selection hypothesis is to be adopted and tested in further experiments, then it should have clear advantages over alternatives. In particular, the formulation of prefrontal cortical function in terms of generic attentional selection must be useful in comparison with the established theories of working memory, central executive, and the supervisory attentional system. I believe that there are several distinct advantages:

First, the attentional selection hypothesis is applicable to working memory paradigms and free selection. Attentional selection of items maintained in working memory is required to monitor and manipulate items, and to select a response from among alternatives. The same mechanism enables free or constrained response selection, for limb, eye or speech responses. It can also account for the selective attention to a sensory stimulus, such as one of several visually presented items.

Until recently, it could have been argued that the role of the prefrontal cortex in free selection of responses was working memory for previous responses. However, this is no longer tenable. Selection even of unique responses is also associated with activation of the prefrontal cortex, and TMS impairs selection in a task with no working memory component.

Second, attentional selection is based on a mechanism that was first characterised in the visual system, using single and multiple cell recordings. The

mechanism is therefore based on basic physiological properties of neurons. A demonstrable physiological mechanism was one of the proposed requirements for a common framework of prefrontal cortical function (see introduction).

The mechanism of attentional selection is applicable to many modalities. The prefrontal cortex has extensive interconnections with motor, sensory and memory related structures. It receives information from the multiple modalities, enabling the selection of an appropriate goal-oriented response (action) or to change the processing of selected visual, auditory or touch sensory stimuli.

Third, the attentional selection hypothesis is consistent with the properties of the supervisory attentional system. The attentional selection of actions, stimuli or remembered information is analogous to the selection of schemas by top-down bias from the supervisory attentional system. The supervisory attentional system was developed in response to the functional analysis of human behaviour during different tasks. Later it became near synonymous with the functions of the prefrontal cortex.

Fourth, attentional selection is equally applicable to monkeys and humans. It is not dependent on anthropocentric task descriptions such as planning or manipulation, yet it is applicable to such tasks in humans. It is possible to test the predictions of attentional selection experimentally in humans and monkeys. Some of the predictions have been tested in this thesis, but there are outstanding issues.

Outstanding issues

There are several outstanding problems that need to be addressed regarding the attentional selection hypothesis. Some of these are theoretical issues, while others are experimental results that may seem not predicted by the hypothesis. For the hypothesis to be tested experimentally, it must be clear in its predictions. 'Selection',

like 'attention', risks being used too loosely to retain any useful meaning. The single term has be used in connection with many different processes and phenomena. Although "Everyone knows what attention is" (James, 1895) the mechanism of attention, or perhaps of multiple attentional processes, is still the subject of extensive research and debate,

It should be clear what the object of attentional selection is, i.e. what it is that is selected. In describing the variety of working memory paradigms, I have tried to make clear the variety 'selection' processes that occur (e.g. in the section 'response selection' above). These different selection processes may not all be equal in their demands on the prefrontal cortex, and may not be mediated by the same mechanism. For example, attending to one remembered stimulus in relation to others (monitoring), requires attentional (selective) and relational processes. This may not be equivalent to the wilful selection of one action schema during voluntary action. Both can be described in attentional terms, and both are mediated by the same regions of the prefrontal cortex. However, it is conceivable that these are two different processes that are mediated by functionally distinct but anatomically overlapping neuronal sub-populations.

Brefczynski and Yoe (1999) demonstrated that the activity of visual stimulus specific neuronal sub-populations could be modulated by attention. In their study the retinotopic nature of the visual cortical neurons is clear. But, what is the nature of the response representation during response selection? For example, in chapters 7 and 8, subjects were asked to "think about their next move: to specifically attend to the forthcoming movement". It was possible that they attended to the movement itself, aware of the preparation to move the particular finger. However, they may also have

attended to the location of the finger, in terms of its position on their hand or its position on the keypad. They may also have expected the specific sensory consequences (feedback) of moving the next finger.

It was proposed that when subjects select a response, they select the goal or target of the response. For example, if subjects had to reach past an obstacle to press the button, they might reach over, under or around the side of the obstacle. In this case, the target of the response is the button to be pressed, rather than the specific trajectory necessary to reach it. Shen and Alexander (1997) have shown that cells in premotor cortex encode the target of a movement in this sense. In the working memory paradigms in chapters 4 and 5, it was proposed that the critical process was the selection of one remembered location as the target for the joystick movement, not the joystick movement itself.

In the computational models developed by Cohen et al (Cohen *et al.*, 2000; Cohen *et al.*, 1996; Cohen *et al.*, 1990; Cohen and Servan-Schreiber, 1992; Miller and Cohen, 2001), the prefrontal cortex represents the context, and biases the stimulus-response associations. Neither the stimulus nor response is directly biased (selected), but rather the strength of a connection between them. The bias is sustained throughout the context, just as the context representation is sustained by prefrontal neuronal firing in monkeys (Wallis *et al.*, 2001).

This raises two further issues. **First**, the results of event-related fMRI studies of humans, such as chapter 4 and 5, suggests that the activity of area 46 mediating response selection is transitory not sustained. The sustained representation of context may be distinct from the transient imposition of context specific response bias. Functionally distinct sub-populations of neurons in the prefrontal cortex could

mediate these different processes. Alternatively, dynamic neuronal firing patterns and changing effective connectivity could enable the same cells to mediate both sustained context representation and transient attentional selection of responses. This has not been demonstrated experimentally. A third alternative is that the functional module of 'context/prefrontal cortex' in the computational models (Cohen *et al.*, 2000; Cohen *et al.*, 1990; Cohen and Servan-Schreiber, 1992) and the rule specific cells in prefrontal cortex (Wallis *et al.*, 2001) are not directly equivalent to the human prefrontal cortex.

Second, if the stimuli and responses are represented by different neurons, then the proposed bias of stimulus-response associations is a change in effective connectivity between them. In an fMRI study of attentional modulation of visual processing in humans, the prefrontal cortex was shown to exert a significant modulatory effect on the connection between visual cortex (V5) and the response of the posterior parietal cortex. (Buchel and Friston, 1997). The location and cellular mechanisms of this change of effective connectivity could not be inferred from structural equation modelling. However, the prefrontal cortex could in principle modulate the efficacy of stimulus-related afferents to response neurons, either pre- or post- synaptically, or by modulating the activity of interneurons.

In addition to these theoretical considerations, there are a number of experimental results that are initially unexpected. For example, Oliveri et at (2001) studied the effect of TMS to PFd on visual and spatial n-back tasks. TMS to PFd during the interval between stimuli impaired response accuracy and speed for both visual-object and visual-spatial tasks. This supported the process-specificity theories of PFd function rather than domain-specificity theories. However, TMS of PFd at the

time of response selection did not impair response accuracy. This would seem to argue against the role of PFd in response selection from memory.

This task was not a typical n-back. First, the same three stimuli were used for each run, resulting in high interference from trial to trial. Second, the response on each trial was delayed for two seconds from the presentation of a stimulus to the execution of the response. The button to be pressed could not be known until this two-second interval had passed, because the button corresponding to the nth-back stimulus was varied from trial to trial. If the selected response was the button pressed, then the results of Oliveri et al (2001) argue against the attentional selection hypothesis.

However, I suggest that the target of the response was not the button to be pressed, but the nth back location or the nth back object. This location or object was the goal of the response. Now, this response selection could be made during the two-second interval: TMS during the interval did impair accuracy and speed of the response selection as measured from the eventual button press. The transformation from the selected target (location or object) to the pressing of the matching button would be expected to depend on parietal and premotor structures (Murray *et al.*, 2000; Wise and Murray, 2000) and not the prefrontal cortex.

In previous event related fMRI studies of human delayed response, there was evidence of delay related activity for spatial or object stimuli in PFd, even anterior in area 46 in some subjects. These studies were sometimes confounded by instructions to rehearse the stimuli, to keep the image in mind, and it was speculated that rehearsal may involve re-selection of the stimuli recurrently during the delay. Other studies used limited stimulus sets, and the delay related activation was confounded by the

need to select the current trials' stimuli in preference to other recent stimuli to minimise interference.

However, it is possible that there are some cells in area 46 that are primarily related to maintenance of information. In the monkey, when the cellular coding of 'what' and 'where' was studied adjacent to the sulcus principalis, the majority of anterior cells (area 46) were integrative for 'what' *and* 'where' stimuli (Rao *et al.*, 1997). Although the 'where' only cells were predominantly posterior in areas 9/46 and 8, there were some 'where' only cells anterior in area 46. The functional specialisation of areas 8 and 9/46 for maintenance and area 46 for selection must therefore be considered to be a matter of degree rather than an absolute.

The hypothesis at present proposes a generic function of attentional selection mediated by the prefrontal cortex. It specifically proposes that the same generic function is applicable to multiple sensory, motor and mnemonic modalities. It does not include laterality differences between the left and right prefrontal cortex. Laterality effects have been proposed in terms of the modality specific activations during working memory (D'Esposito *et al.*, 2000a; Smith and Jonides, 1999). In addition, the selection of motor or speech responses is more commonly associated with activation of left PFd (chapters 7 and 8) (Deiber *et al.*, 1991; Jahanshahi *et al.*, 2000; Jueptner *et al.*, 1997b).

These laterality effects may only be relative differences, exaggerated by the dichotomy between activated and not-activated in thresholded SPMs. Few studies directly compare left and right activations, to prove a hemispheric difference in selection related activation (chapter 5). Domain based laterality effects in attentional selection would be expected in the human brain. The attentional selection is

dependent on the interconnections of prefrontal cortex with the rest of the brain. If there is asymmetry in regional functional specialisation in temporal, parietal and premotor cortex, then there will be corresponding asymmetry of attention selection in prefrontal cortex. The generic mechanism however can still be the same.

Further work is required to test the predictions of the hypothesised role of PFd in the attentional selection of responses. This includes further testing of the proposed generalisation of attentional selection to the motor system. For example, there is sufficient somatotopy in premotor cortex and SMA to expect to be able to detect regionally specific modulation of motor representations when attending to hand or foot actions. In addition, responses made with the limbs and eyes could be compared. Functionally specific regions for limb (premotor and parietal) and eye (frontal eye-fields and parietal) movements are well characterised from previous human and monkey studies, and are likely to be the target of attentional selection for these different motor response modalities.

The current analysis of effective connectivity using structural equation modelling of fMRI time series is dependent on extremely low frequency ($\cong 0.01$ Hz) modulation of covariance of BOLD responses. It would be interesting to test the attentional modulation of coherence of EEG responses in the range of frequency corresponding to neural excitation (10-100 Hz). A change in effective connectivity might be seen as an increase in coherence at one or multiple frequencies. ERP response latencies might also be able to provide further support for the directionality of modelled cortico-cortical connections.

The effects of transient disruption of prefrontal cortical function by TMS could be used to test the hypothesis that prefrontal cortex has common areas for

selection of motor responses, sensory stimuli or remembered items. For example, TMS could be applied during the delay period or at response selection, in the paradigms used in chapters 4 and 5. TMS to PFd and area 8 would each be expected to produce different effects when given in the delay period or at response selection. It might not be sufficient merely to apply TMS to those locations appearing on the thresholded SPMs in chapters 4 and 5, for several reasons. First, within a networks of regions mediating maintenance and selection systems, the loss of function in one region may be compensated for by continuing activity in another (Price and Friston, 1999). Second, the contralateral prefrontal cortex may not be sufficiently active to appear on the thresholded SPM, but activity may nonetheless be sufficient to enable performance of the task. Third, the effects of temporary disruption by TMS may be due to the local effects of TMS or due to the induction of remote abnormalities (known as diaschisis). Diaschisis following focal lesions may be task specific (Price *et al.*, 2001). Despite these cautions, a TMS effect at PFd, only at the time of response selection, and not during the delay period, would support a role for PFd in response selection rather than maintenance.

Summary

The different regions of the prefrontal cortex receive extensive afferents from each other and the rest of the brain. Neurons here may encode the current context, goals and specific sensory cues and may integrate information across multiple modalities. There are also efferents back to sensory, (pre-)motor and association cortex.

Against this background, it is proposed that the prefrontal cortex (particularly PFd) may selectively bias the neuronal representations of sensory stimuli, actions, and remembered information. This enables a subject to select between remembered items to make an appropriate response in working memory paradigms. The same mechanism enables the free selection of action, and the free selection of visual sensory cues. The selection is associated with increased effective connectivity between the prefrontal cortex (at least PFd) and the domain specific non-prefrontal regions.

The supervisory attentional system and central executive of working memory hypotheses are both closely associated with the functions of prefrontal cortex. The properties of the supervisory attentional system and the central executive can be reformulated in terms of attentional selection. This formulation is applicable to monkeys and humans, and can be used to explain the selective cognitive deficits following focal frontal lesions. The work presented here supports James' assertion in 1895 that "Selection is the very keel on which our mental ship is built".

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