The role of the prefrontal cortex in strategic processes, as revealed by spatial span

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Preface

The following work was conducted at the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK during the period 1998 - 2001 under the supervision of Dr Adrian Owen and Dr John Duncan (both MRC Cognition and Brain Sciences Unit). This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration. Furthermore, this dissertation has not been submitted, in whole or in part, for any other degree, diploma or qualification at another institution. Throughout this dissertation, I have attempted to reference any idea or finding which is not my own. Finally, this dissertation does not exceed the limit of length prescribed by the Biology Degree Committee.

The work in chapters 3 and 6 have been published or submitted in the following papers:

Bor, D., Duncan, J., and Owen, A.M. *The Role of Spatial Configuration in Tests of Working Memory Explored with Functional Neuroimaging.* Scandinavian Journal of Psychology, 2001. **42**(3): p. 217-224.

Bor, D., Duncan, J., and Owen, A.M. *Prefrontal cortex and strategy use in human working memory.* Nature Neuroscience (submitted)

This thesis is dedicated to three people:

Firstly, to my mother for her deep unselfishness, love and support.

Secondly, I dedicate it to my father - who I love far more than he ever realised and whose memory I strive to honour by my character and achievements.

Finally, of course, I dedicate the thesis to Rachana, for her continued devotion, support, love, unbridled silliness and - above all - her bravery.

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My main debt of gratitude for this thesis goes to my two supervisors. Adrian Owen has acquitted himself unbelievably well in his task as my primary supervisor, particularly considering I was his first official PhD student. Very luckily, I immediately found his strong creativity and drive quite infectious. From the start, he showed a nurturing support, somehow putting up with my constant, naïve ideas - with a sleight of hand creating the illusion that this was an equal collaboration between the two of us. As I gained some much needed experience, he always appeared positive and willing to listen to my suggestions for experiments, despite their still occasionally outlandish nature, while shaping them with panache, based on his very sound judgement, and excellent sense of "the bigger picture." What I will value most from my three years of working with Adrian, however, is his personality. I cannot imagine working for a more fun, friendly supportive person, while also relying heavily on his outstanding ability to deal with people, as mine left a lot to be desired.

John Duncan has been the ideal second supervisor, providing regular insights from his great experience and wisdom, showing by example how to be a rigorous, passionate scientist, and offering his praise freely. At the same time, his remarkable gentleness, warmth and apparent utter inability to show anger or frustration to anyone have been a source of inspiration. He has provided excellent academic and personal support, and I can't help but see him as a good friend.

As well as having the keen sense of great luck in my choice of supervisors, this feeling extends clearly to my department, the Medical Research Council Cognition and Brain Sciences Unit. From the start, it was made clear to me that the fantastic

resources within the unit were fully available to me, while excellent, new personal equipment were immediately provided for me. The level of technical, and academic help in the unit has been outstanding, making the task of thanking people within the unit appear an almost endless one. However, I would like to thank the following people particularly for their help over the last three years. I have found invaluable help on countless occasions from the local SPM "guru," Matthew Brett, who has probably taught me more about neuroimaging than everyone else put together. Others who have provided much needed guidance in this area were Ingrid Johnsrude, Rhodri Cusack and Matt Davis. In terms of help with programming, I would not have learnt much without the help of Nick Cumming and again Rhodri Cusack, who were also extremely useful in troubleshooting my many programming problems. The statistical staff - Ian Nimmo-Smith and Peter Watson - provided many invaluable hours helping me with my statistical analyses. I owe a particular debt of gratitude to Iain Morrison, of the computing support staff, who has on many occasions gone above and beyond the call of duty to solve my various hardware and software problems. Thanks also go to the patient and volunteer panel staff, Ann Lickorish and Jackie Harper, for providing such a professional service.

The two PET studies and the fMRI study in this thesis were all carried out at the Wolfson Brain Imaging Centre, UK, and I would like to thank all the staff there for helping me carry out these three studies.

The large scale behavioural study of chapter 7 was made possible by a Glaxo-Wellcome grant secured by Richard Wiseman, of the University of Hertfordshire, who also carried out much of the administrative and organisational details of the project. I would like to thank him for all his help with this experiment, as well as to the staff at the London Science Museum for their assistance.

None of these studies would have been possible without the enthusiasm and patience of all the volunteers and patients who took part in the experiments, and I would like to thank them all for their involvement. In addition, my PhD placement and this thesis could not have happened without a grant from the Medical Research Council, and I am grateful to them for giving me this opportunity.

On a personal level, I would like to thank my family, particularly my mother and my partner Rachana, for tedious proof-reading as well as deep emotional support in the face of my large set of faults over the years.

“There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact.”

Mark Twain

Contents

Thesis Summary

There is growing evidence that the frontal lobes are involved in higher-order processes such as organisation of behaviour, goal-management, and strategic processing. However, for strategy at least, there has been little success in localising such a process to regions within the frontal lobes, since most experiments in support of this have used patients with large-scale frontal lobe lesions. This thesis will describe a set of experiments where the association between strategy use and the frontal lobes will be limited to the lateral prefrontal cortex. A particular, well-characterised strategy, that of chunking, will be centred on. In addition, the thesis will describe attempts at showing impairments on such tasks in patients.

Initially a summary of the relevant literature and a description of general methods relating to the experiments of this thesis are given in chapters 1 and 2 respectively.

Chapter 3 discusses a neuroimaging study using Positron Emission Tomography where a variant of a standard working memory task, that of spatial span, is given to subjects. While previous studies have shown an association between spatial span and the ventrolateral prefrontal cortex, this version is associated instead with the dorsolateral prefrontal cortex.

In chapter 4, a follow-up Positron Emission Tomography study will be described, where two variants of the spatial span task are directly compared within subjects. The versions differ in the level of organisational structure of the spatial arrays. More activity in the dorsolateral prefrontal cortex is observed for the span task with the more structured array compared to a control than the span task with the less

structured array. This experiment replicates the results of the previous chapter, while demonstrating that subtle differences in a working memory task can elicit associative changes within the lateral prefrontal cortex.

Chapter 5 describes a behavioural study using similar spatial span tasks to the previous neuroimaging chapter, in order to explore possible behavioural differences that may correspond to the established differences in activation patterns of chapter 4. The results suggest that the crucial difference is that for the more orderly spatial array span task, there is a greater strategic component to the task.

Chapter 6 outlines a study involving frontal lobe patients, where the spatial span versions of chapter 5 are presented to this patient group as well as closely matched controls. The results indicate that frontal lobe patients are impaired on such working memory tasks, contrary to the prevailing opinion about this patient group. In addition, there is a slight trend for the patients to be further impaired at the more structured version of the span, in line with the neuroimaging results of chapter 4.

Chapter 7 describes an event-related functional Magnetic Resonance Imaging study, where two versions of the spatial span task – this time using the identical structured array of possible stimuli – are presented to subjects. The versions differ in the level of structure of each span within the array. Highly structured or highly unstructured spans are presented in an interleaved manner to subjects in the scanner. The results indicate that there is significantly greater lateral prefrontal involvement relating to the highly structured span trials, directly compared to the unstructured span trials. This provides more direct evidence for a connection between strategic processing and the lateral prefrontal cortex. In addition, it seems clear that such strategy would mean some form of chunking in this case, as the structured spans are highly amenable to being perceived as regular shapes, e.g. squares, triangles, etc.

Chapter 8 provides confirmatory evidence that chunking is occurring in such trials. A large scale behavioural experiment involving many different spatial span versions is run. Identical span sequences (of the form of the structured spans of the previous chapter) in two key conditions differ only in the facilitation of the chunking of stimuli into regular shapes. The high facilitation condition produces a significantly greater performance than the low facilitation condition, providing clear evidence that the chunking process is occurring during some kinds of spatial span, most notably the structured spans of the previous chapter. Other results generally relating to factors relevant to spatial span performance are also discussed.

Finally, in chapter 9, the results of all experimental chapters are summarised. The results are then discussed in terms of potential extensions to current models, and diversions from them. Speculations from the evidence from this thesis and other sources are made on the possible role of the lateral prefrontal cortex. Finally, limitations of current work and future directions are outlined.

Chapter 1: General introduction

1.1 - Introduction

In this chapter, an outline of the anatomical features of the prefrontal cortex (PFC) will be given. This will then be related to function, initially by insights obtained by the anatomical details, then by an historical perspective on behavioural observations made in both humans and monkeys. There will follow a description of more recent theories linking this brain region to specific psychological processes, either within or outside of the framework of working memory. Finally, an overview of the remaining chapters of this thesis will be given.

1.2 - The anatomy of the prefrontal cortex

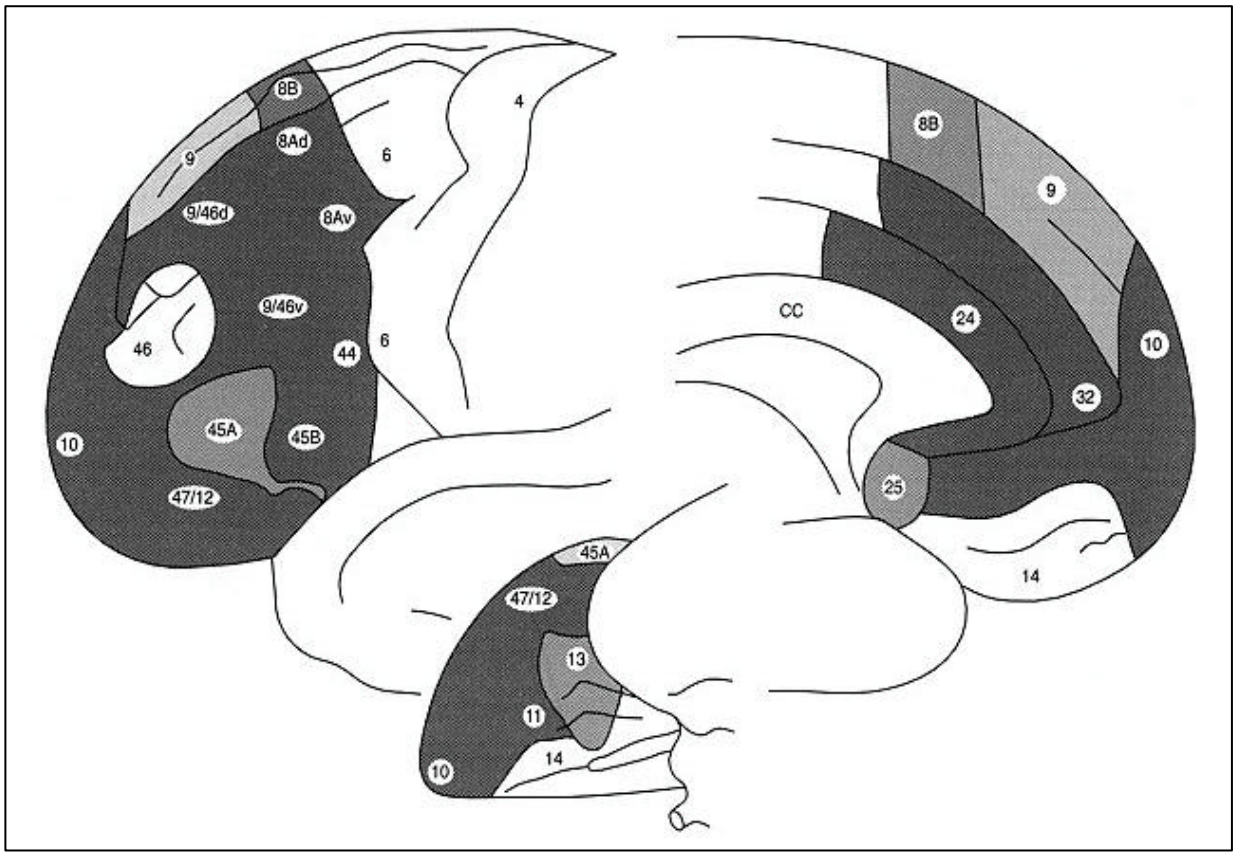
The frontal lobes are segregated from more posterior regions in the brain by the central sulcus. Non-frontal regions include primary and secondary sensory areas processing visual, auditory and tactile stimuli. Lying anterior to the motor and premotor cortices in the frontal lobes, is the PFC.

1.2.1 - Anatomical subdivisions within the prefrontal cortex

In the early part of the twentieth century, Brodmann carried out studies, using architectonic markers, to differentiate regions in the neocortex (Brodmann 1905; Brodmann 1909). As part of these studies, Brodmann anatomically subdivided the

PFC in the monkey (Brodmann 1905), and later in the human (Brodmann 1909). These so-called "Brodmann areas" have been highly influential ever since, although initial discrepancies in labelling between human and monkey architectonic maps and later developments in histological staining has led to an extensive revision of this scheme, most recently by Pandya and colleagues (Petrides and Pandya 1994; Pandya and Yeterian 1998). Figure 1.1 presents schematic views of the lateral, medial and ventral surfaces of the human frontal lobes, with modern clarifications of Brodmann areas labelled. Of particular note to this thesis is the lateral surface of the PFC, posterior to the frontal polar regions. As figure 1.1 demonstrates, these broadly comprise a ventrolateral region, involving Brodmann Areas (BA) 45 and 47, as well as a dorsolateral region, involving BA 46, 9 and 9/46. However, it is important to note that even within the modern labelling of BA 9/46, there are further clear subdivisions to be made (i.e. 9/46v and 9/46d). Also of relevance to this thesis is the anterior cingulate, found on the medial surface in "bands" anterior and dorsal to the corpus callosum (BA 24 and 32).

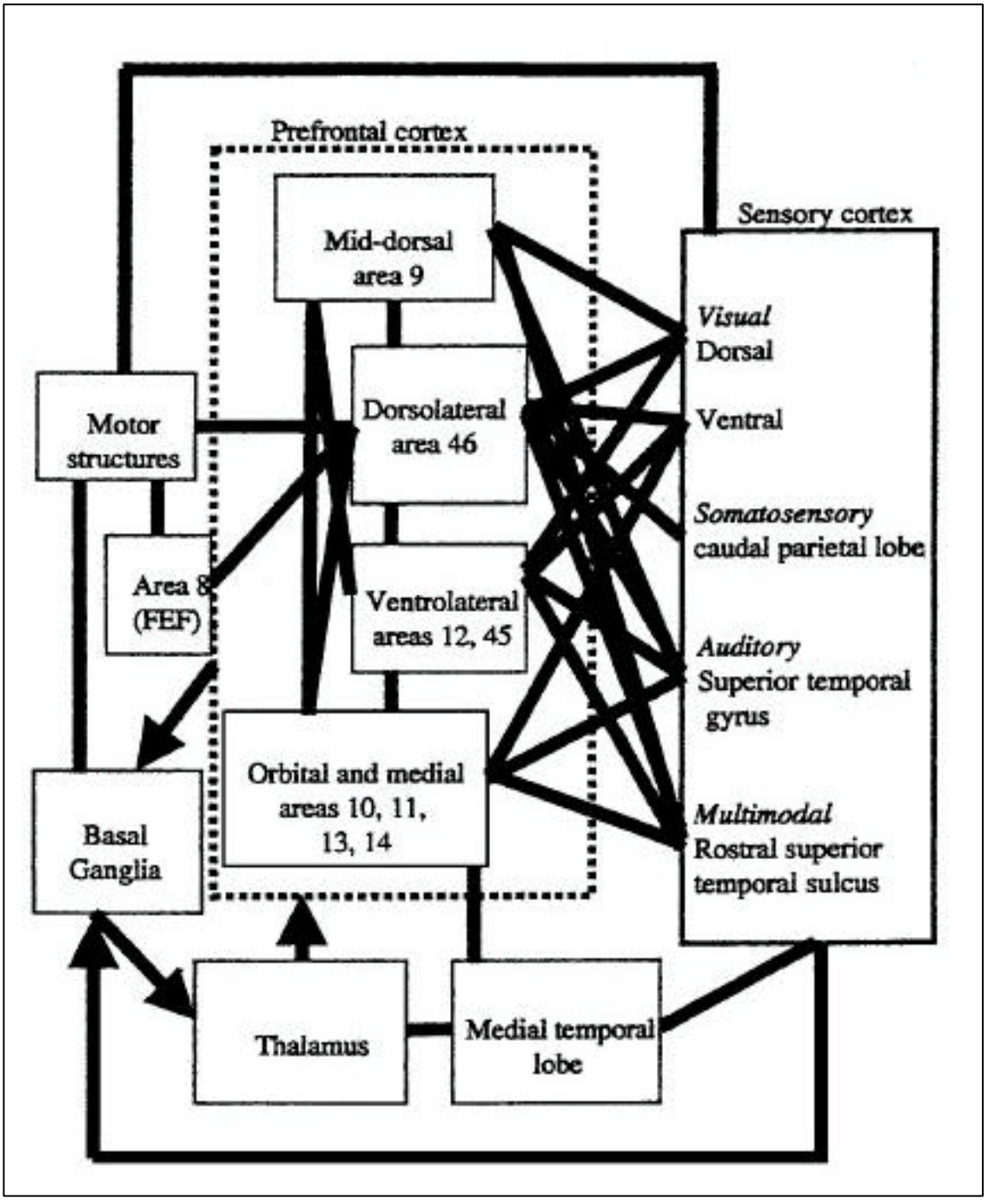
Figure 1.1 - Cytoarchitectonic maps of the lateral (left figure), medial (right figure) and ventral (bottom figure) surfaces of the human frontal lobes. Adapted from Petrides and Pandya (Petrides and Pandya 1994).



1.2.2 - Extrinsic and intrinsic prefrontal cortex connections

Retrograde and anterograde tracers can be injected directly into parts of the living monkey brain. The chemical then travels to connected regions via axonal paths. The monkey is then killed and special means, usually the fluorescent nature of the tracer, are used to determine the neuronal connections with the original area. Using this technique, it has been shown that the monkey PFC has extremely dense connections, both throughout the rest of the brain and between local regions. Subdivisions within the PFC have partially unique, though overlapping, patterns of connections, suggesting that there is some regional specialisation within the PFC. Figure 1.2 provides an illustration of the extent of extrinsic and intrinsic connections of the PFC, while demonstrating that almost all pathways are reciprocal.

Figure 1.2 - Schematic diagram showing some of the extrinsic and intrinsic connections of the PFC. Those connections which are not reciprocal are indicated by arrows. Taken from Miller and Cohen (Miller and Cohen 2001).



1.2.2.1 - Sensory connections

Of PFC regions, the lateral PFC has the greatest level of connectivity with sensory areas. This region receives visual, auditory and somatosensory information from the occipital, parietal and temporal cortices (Goldman-Rakic and Schwartz 1982; Petrides and Pandya 1984; Pandya and Barnes 1987; Barbas and Pandya 1989; Seltzer and Pandya 1989; Pandya and Yeterian 1990; Barbas and Pandya 1991; Petrides and Pandya 1999). In addition, many PFC regions, particularly the DLPFC and ventrolateral PFC (VPFC) receive converging inputs from at least two sensory modalities (Jones and Powell 1970; Chavis and Pandya 1976).

1.2.2.2 - Motor connections

Although no regions within the PFC appear to have direct connections with primary motor cortex, the DLPFC (particularly involving BA 46) does have direct connections with an extensive array of secondary motor regions, including the supplementary motor area, the pre-supplementary motor area, the cingulate, premotor cortex, cerebellum, superior colliculus and the frontal eye fields (Goldman and Nauta 1976; Bates and Goldman-Rakic 1993; Lu, Preston et al. 1994; Schmahmann and Pandya 1997). Many of these secondary regions are in turn intimately connected with the primary motor cortex and the spinal cord, providing clear pathways for the PFC potentially to influence behaviour. Of further note is extensive interconnections between PFC and the basal ganglia, with the main output from this region projecting to the PFC.

1.2.2.3 - Connections with emotion and memory centres

The main efferent and afferent projections with regions relating to emotion and memory occur within the orbital and medial PFC. Other PFC regions largely have access to these pathways via connections to these two prefrontal areas. The orbital and medial PFC are connected to long term memory regions such as the hippocampus, and related medial temporal lobe areas, as well as areas processing motivation and emotion, including the amygdala and hypothalamus (Van Hoesen, Pandya et al. 1972; Porrino, Crane et al. 1981; Amaral and Price 1984; Goldman-Rakic, Selemon et al. 1984; Barbas and Pandya 1989; Barbas and De Olmos 1990).

1.2.2.4 - Intrinsic connections

The PFC has very dense interconnections, both between major regions, and within sections of those regions (Pandya and Barnes 1987; Barbas and Pandya 1991). This is particularly true of the lateral PFC, with the VPFC having a set of connections with the DLPFC, while both regions have connections with orbital and medial areas.

1.2.3 - Anatomical summary and functional insights from anatomical features

The lateral PFC is separate from, but closely connected with, almost all sensory areas, sometimes with multiple senses projecting to the same regions of the PFC. This suggests that the lateral PFC is amodal and capable of combining information from multiple inputs. In addition, the PFC is quite distinct from the primary motor cortex, indicating that this area isn't itself involved in movement. However, via multiple

indirect routes through more sophisticated motor domains such as the supplementary motor area, and regions involved in automating behaviour such as the basal ganglia, the PFC appears capable of exerting considerable influence on behavioural output. Medial and orbital PFC regions have connections with important long term memory and motivational regions, and these PFC regions in turn have dense interconnections with lateral PFC. Thus, PFC functions may be influenced by and may in turn control both motivational and emotional states, as well as information from past experiences. With highly dense parallel intrinsic connections throughout the PFC, information may be exchanged with relative ease throughout the whole region.

Three key implications come out of this:

1) **The PFC appears unique in being connected to all sources of information, both externally via the senses, and internally, via long term memory and motivational states.** The PFC, therefore, is the prime candidate for any form of processing that requires multiple sources of information. However, it is important to note the *reciprocal* nature of almost all extrinsic connections with these informational inputs. This suggests that in addition the PFC is capable of exerting influence on sensory inputs, emotional and motivational states, as well as modifying the information stored in memory.

In terms of sensory inputs, the limited capacity of sensory systems requires that only a tiny subset of data available from the environment can be processed to a sufficiently high degree. The PFC may be able to make a more "informed decision" in relation to current goals as to which sections of the environment require a more detailed analysis, and which sections can be ignored, since it may have information available on all current sensory information, as well as internal states and goals.

In relation to motivational states, a flexible, intelligent means of knowing when to turn metabolically expensive states such as fear and anger "on" and "off" would increase the chance of survival considerably, while potentially making behavioural choices more energy efficient. Such decisions can sometimes best be made via sophisticated analyses of sensory inputs, normally combined with information from memory, which the PFC is in an excellent position to accomplish. For instance, if a starving primate has discovered a rich, though highly transient, food source (e.g. a carcass fresh from a hunt), and spots a herd of elephants charging from afar, fleeing may be highly detrimental to that animal's survival if a more careful analysis of the situation can be made. It may well be that the trajectory of the elephants will pass the primate a considerable distance away from it, and that these elephants have always taken that route in the past. Therefore a suppression of the fear and desire to flee, based on a more systematic analysis of information from vision and memory, may save that animal from starvation at no danger to itself.

Reciprocal connections to memory systems also allow the PFC control over whether current information is "useful" enough to be maintained over time, and recalled when relevant to future states. In other words, such structure may provide an executive role for the PFC in the remembering (and forgetting) of mnemonic information.

2) The PFC seems suited to highly complex, adaptable processing requirements. The PFC, although not apparently "hardwired" to directly process any specific skill such as the management of visual input or motor responses, nevertheless has a comprehensive network of interconnections. Such a region may allow for the integration of dynamic information from many sources, as discussed above. At the

same time, this area may mediate high level processing by the manipulation of data between internal sub-regions. Further anatomical evidence to suggest that the functional role of the PFC involves higher-level, complex cognitive processing, comes from phylogenetic differences between humans and other mammalian species. It is commonly believed that amongst mammals, humans are the most intelligent while chimpanzees come closest to us in this regard. Studies of the proportion of cerebral cortex occupied by the PFC have suggested that humans have the largest fraction, followed by chimpanzees, with the macaque monkey, for instance, having considerably less than the chimpanzee (Blinkov and Glezer 1968; Preuss 2000).

3) The lateral PFC may be the main region for behavioural response selection, particularly in complex situations. In simple or highly familiar situations, response selection requires little more than an inflexible program (e.g. a chunk of long term memory) to link sensory input to motor output. In novel or difficult situations, however, the synthesis, comparison and manipulation of information from multiple sources (perhaps multimodal sensory data in addition to comparison with mnemonic information) is normally paramount to the success of the current goal. With close, yet indirect links with the motor system, the PFC may control complex behaviour via access to all possible information (see point 1), and consequent analysis of that information (see point 2). In addition, input from motor cortex enables the PFC to further refine behaviour requiring complex or serial forms of motor output.

Largely absent from the above discussion is the question of what possible reason there could be for utilising such an energy-hungry means to move from sensory input to behavioural output? If a highly primitive animal's behaviour is examined,

input-output paths are largely “hardwired.” This has a distinct energy advantage to the animal, since little or no processing is required to form responses relating to basic motivational needs. However, the cost is in terms of flexibility, causing the moth, for instance, to die in a candle flame. Presumably, natural selection strongly favoured behavioural flexibility over metabolic cost in mammals. Fundamental to that flexibility is the ability to set up a multitude of internal goal states beyond simply basic biological motivations, such as food, fighting, fleeing and procreation, although still relating to maximising chances of survival and reproduction (at least in non-human species). All of the above processes suggested by anatomical considerations for the PFC - integrating information, controlling behavioural responses, and providing an adaptable surface for analysing this hub of data - allow the PFC to realise complex, non-automatic goal states. Indeed the most plausible suggestion for the functional role of the PFC (particularly the lateral PFC) from the above anatomical considerations seems to fall under the umbrella of accomplishing internal goals whenever a non-automatic response would be beneficial. An intriguing question following on from this is whether PFC regions are also involved in creating, choosing, modifying or generally managing such goal states. I will return to this question later in this chapter and in the general discussion.

1.3 - Early behavioural observations relating to the prefrontal cortex

For a discussion of more recent literature, please refer to the section on current theories (1.4).

1.3.1 - Behavioural observations in humans

In the middle of the nineteenth century, the famous case of Phineas Gage produced critical behavioural clues about the frontal lobes (Harlow 1868). Following a traumatic brain injury to the PFC, Gage appeared to make a remarkable recovery. However, on closer examination and over time it became apparent that various subtle behavioural deficits were manifest. Gage was unable to plan for the future, he was severely impaired at following the usual social rules, or decide on important courses of action (Harlow 1868).

Somewhat later, Penfield and Evans (Penfield and Evans 1935) reported on three similar patients, who all exhibited symptoms of organisational dysfunction akin to those of Phineas Gage. One woman, following the surgical excision of much of her frontal lobes, was still quite capable of cooking individual dishes, but was unable to plan and prepare a complete family meal.

More experimental accounts later attempted to use specific tasks to provide a handle on the nature of impairment. For instance, Porteus and Kepner (Porteus and Kepner 1944) demonstrated that frontal lobe patients are impaired on maze learning. More recently, Milner (Milner 1963) used the Wisconsin card sorting test - a dynamic and complex task where the goal keeps changing following sufficiently improved performance - to show that frontal lobe patients are severely impaired on such tasks.

1.3.2 - Behavioural observations in monkeys

The first monkey lesion studies on the frontal lobes seem highly in accord with observations from the clinical cases in humans, cited above. For instance, Bianchi described one such monkey with an ablation to the whole frontal lobes, who would

grab a door handle, but then would not open the door because it appeared to become distracted by staring at the handle (Bianchi 1922). After looking at the handle, instead of eventually opening it, the monkey would sit on it. Bianchi described the impairment as an inability to "co-ordinate the different elements of a complex activity."

Although such early monkey work was characterised by anecdotal behavioural observations, Jacobsen (Jacobsen 1936) was the first to perform systematic tests on monkeys with frontal lobe lesions. Jacobsen demonstrated that such monkeys were incapable of performing the delayed response task - a task involving the retention in memory of a stimulus location over a short delay. Jacobsen suggested that the monkey's behaviour following the lesion, "instead of being directed by a balance of immediate, recent and temporally remote stimulation, is dominated by present external stimuli and the stable habit systems derived from earlier training."

Other experimental work was initiated at the same time on a similar test: the delayed alternation task, which requires the monkey both to retain a stimulus location over a delay and then to respond to the alternative location. It was shown that monkeys with frontal cortex lesions are also impaired on this task (Jacobsen and Nissen 1937).

Further work demonstrated that other brain regions in the monkey fail to elicit such a deficit: neither lesions to the temporal cortex (Jacobsen and Elder 1936; Mishkin and Pribram 1956; Orbach and Fantz 1958), the postcentral gyrus (Breslaw, Barrera et al. 1934), nor the motor and premotor cortices (Jacobsen and Haslerud 1936; Pribram, Kruger et al. 1955; French and Harlow 1962) elicited impairments in delayed response performance.

In addition, later monkey work further refined the critical site of lesion for this task. For instance, Pribram et al. (Pribram, Mishkin et al. 1952) demonstrated that lesions to the lateral surface of the frontal cortex were sufficient to cause deficits on the delayed response task. Later still, Gross and Weiskrantz (Gross and Weiskrantz 1962) showed that an impairment in the delayed response task could follow a lesion of just the cortex around the sulcus principalis.

1.4 - Current theories of prefrontal cortex processes and functional divisions

Both the early monkey and human literature that have investigated the PFC suggest a high-level cognitive role for this region, relating to organisational processing. Perceptual, mnemonic or motor processing seems largely unaffected by lesions to the PFC, as the monkey that can still grab or sit on the door handle (Bianchi 1922), or the woman who can make individual dishes, but not a large meal (Penfield and Evans 1935), illustrates. The early monkey literature also suggested that the critical region for such functions was the mid-lateral surface of the PFC (Gross and Weiskrantz 1962). However, two key questions remain, requiring more modern techniques and theories. First, is there a parcellation of higher cognitive function within the lateral PFC, such that regions within this have different specialist roles in the organisation of behaviour, for instance? Secondly, what precisely is impaired when monkeys with frontal lesions are unable to perform the delayed response task, or humans with damage to their frontal lobes are unable to learn to navigate through mazes? For example, the core deficit may be one of planning a new response, repeating the

inappropriate old response, or maintaining attention during the task. Indeed, terms such as "planning" and "organising behaviour" are vague and need more precise characterisation. The rest of this chapter will describe modern attempts at answering these two questions.

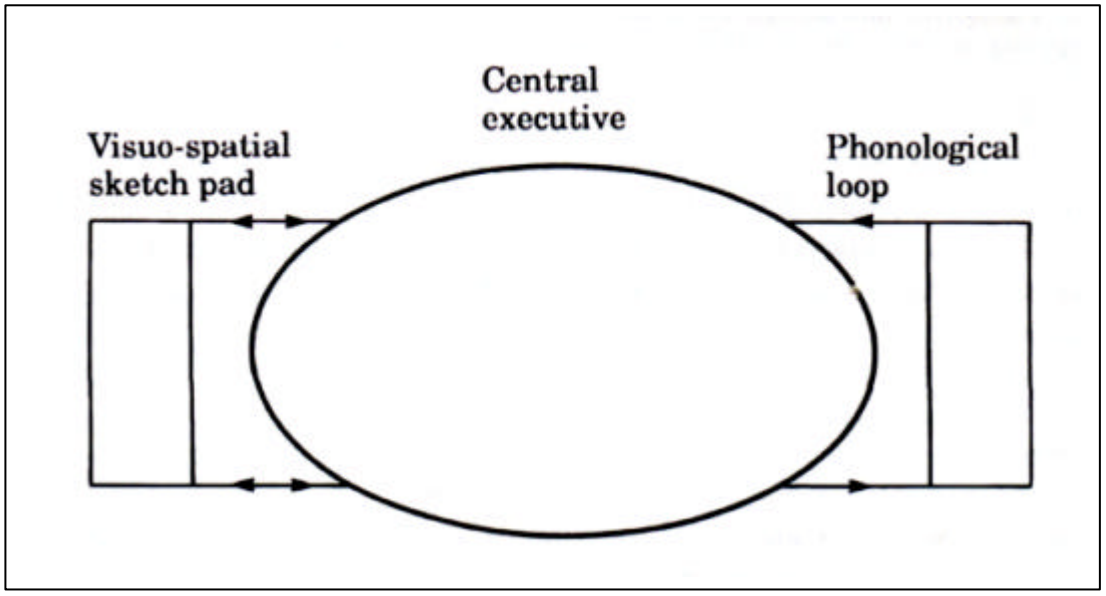
1.4.1 - The prefrontal cortex and working memory

Cognitive models of short term memory in the 1960's and early 1970's emphasised a single "module" capable of both holding and manipulating information temporarily in order to facilitate general cognitive tasks such as learning and reasoning (Atkinson and Shiffrin 1968; Craik and Lockhart 1972). However work by Baddeley and Hitch (Baddeley and Hitch 1974) indicated that there were at least two separable systems, one relating to the executive processes applied to short-term memory and another relating to the storage of that data. In addition, there was evidence to suggest at least two different short term memory stores, based on modality. For instance, in a recent example of such evidence, Robbins et al. (Robbins, Anderson et al. 1996) found that performance on a complex visuospatial task (assessing chess positions) was disrupted by a simultaneous spatial task (tapping a predefined sequence of keys), though not by a simultaneous verbal task.

Baddeley and Hitch proposed an alternative model of short term memory, attempting to incorporate such findings (Baddeley and Hitch 1974; Baddeley 1986; Baddeley 1992; Baddeley 1997; Baddeley and Della Sala 1998; Baddeley 2000). The original model involved two "slave" systems, the phonological store to hold verbal material online, and the visuospatial sketchpad to store visual information in short term memory. These systems are considered "slaves" to the third module, the "central

executive" which is partially involved in managing and "co-ordinating" information from these stores (see Figure 1.3 for a schematic illustration of the working memory model). In addition to this role, the central executive is critical for "attentional control" as well as the "manipulation" of information in order to perform "complex cognitive tasks" (Baddeley 1992).

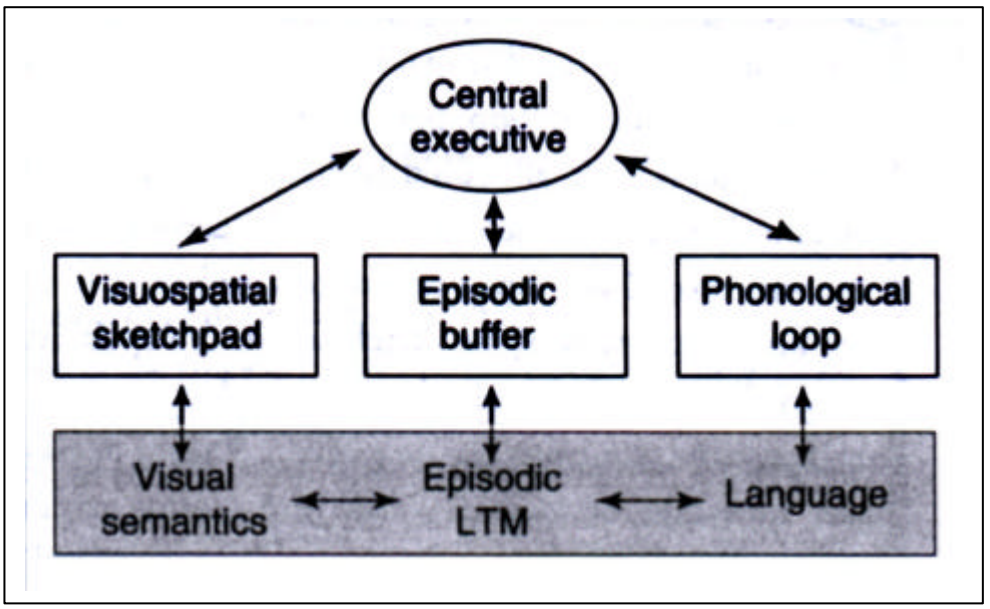
Figure 1.3 - A simplified version of Baddeley's original working memory model, taken from Baddeley (Baddeley 1997).



Baddeley has associated the frontal lobes with the central executive (Baddeley and Della Sala 1998), an hypothesis that clearly is consistent with behavioural observations mentioned in section 1.3, as well as anatomical considerations in section 1.2. However, of much relevance to experimental results of later chapters in this thesis is a recent revision made by Baddeley on his own model (Baddeley 2000). Although we regularly, highly effectively, bind temporary information from different

modalities (e.g. using lip-reading to aid auditory comprehension of speech), there is no means by which the original model can explain such a process. Due to these and other concerns with the original model, Baddeley suggested a fourth component to the model: the episodic buffer (Baddeley 2000). See figure 1.4 for an illustration of how this new module fits into the general framework of the model. The episodic buffer is thought to be a third storage system, distinct from the other two slave systems in that it is capable of integrating and storing information from a variety of different sources. Although the central executive still controls this module, it nevertheless is itself able to perform rudimentary manipulations on the data stored within it, in order to create "new cognitive representations, which in turn might facilitate problem solving" (Baddeley 2000). Baddeley assumes that this module as well would be subserved by some region of the frontal lobes.

Figure 1.4 - The current version of Baddeley's working memory model. Shaded areas represent "crystallised" systems capable of long-term knowledge, while unshaded areas represent "fluid" capacities, such as attention and temporary storage. Taken from Baddeley (Baddeley 2000).



Support for the connection between the central executive and the PFC comes from various sources. For instance, in human neuroimaging literature, a relatively early study (D'Esposito, Detre et al. 1995) found that no PFC activation was present in association with either of two simple tasks alone, but when the tasks were performed together, the DLPFC was activated in response. It was concluded that the DLPFC may underlie the central executive (D'Esposito, Detre et al. 1995).

Recently Prabhakaran et al. (Prabhakaran, Narayanan et al. 2000) compared a working memory task where the verbal and spatial information was either integrated, or where such data were unintegrated. The lateral PFC was activated more for the integrated condition. Baddeley (Baddeley 2000) suggests that this provides evidence

for the episodic buffer residing in the lateral PFC, since widely differing features are clearly being integrated in this case.

Neuroimaging studies seeking to find neural correlates of the phonological loop and visuospatial sketchpad have implicated more posterior regions, particularly the inferior parietal cortex (Paulesu, Frith et al. 1993; Coull, Frith et al. 1996), for these modules, although Broca's area has also been suggested (Paulesu, Frith et al. 1993; Coull, Frith et al. 1996).

In addition to increasing general evidence implicating the PFC with working memory functions, two rival working memory theories that have fractionated the lateral PFC according to function have been prominent during the last decade. It should be pointed out, however, that these theories refer to "working memory" in a slightly broader way than Baddeley's specific theory.

1.4.1.1 - The domain-specific model of the lateral prefrontal cortex

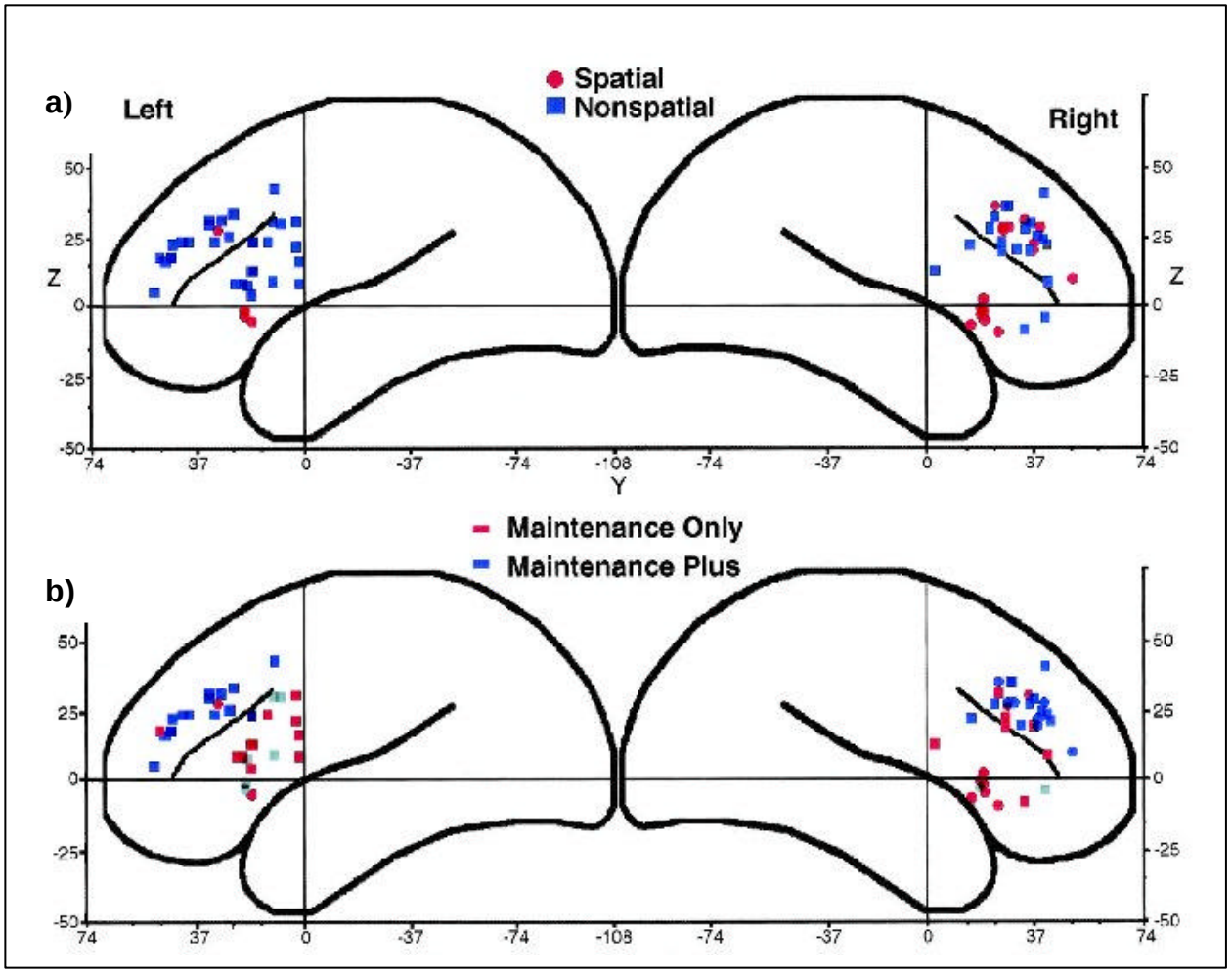
The first theory discussed is partially based on an influential model describing the parallel processing of the visual system (Underleider and Mishkin 1982; Goodale and Milner 1992; Milner and Goodale 1995). This model states that from very early on in the stream (arguably immediately after the retina) two pathways emerge, segregated by function: one is a ventral stream, carrying object-centred visual information ventrally to temporal lobe structures; the second stream contains locational information, which is primarily processed in dorsal brain regions, particularly within the parietal cortex (Underleider and Mishkin 1982; Goodale and Milner 1992; Milner and Goodale 1995). Goldman-Rakic has taken this model and extended it further, suggesting that the endpoints of the parallel stream lie within the lateral prefrontal cortex (Wilson, Scalaidhe et al. 1993; Goldman-Rakic 1998). Specifically, the VPFC

is said to be involved in object-based working memory processing, while it is claimed that the DLPFC is involved in spatial-based working memory processing.

Evidence to support such a model largely comes from monkey electrophysiology. For instance, Wilson et al. (Wilson, Scalaidhe et al. 1993) presented two types of delayed response trials, either based on location or pattern, while recording either in the inferior convexity (VPFC) or the principle sulcus (DLPFC). They found that the VPFC fired selectively during the delay for the patterns, while the DLPFC fired selectively during the delay for the locations.

Although this domain specific theory has enjoyed considerable popularity over the last decade, there is mounting evidence to suggest both that such a theory could not extend to humans, and that the picture even in monkeys is not as clear-cut. For instance, Rao et al. (Rao, Rainer et al. 1997) demonstrated that both monkey DLPFC and VPFC neurons can code for either location, object, or a combination of both. In addition, D'Esposito et al. showed in a review of 24 human working memory neuroimaging papers that there was no division whatsoever within the lateral PFC, according to whether the working memory task was spatial or not (see figure 1.5a).

Figure 1.5 - Plots of the Talairach coordinates (Talairach and Tournoux 1988) taken from the 24 working memory neuroimaging papers reviewed in D'esposito et al. (D'Esposito, Aguirre et al. 1998). The top panel (a) shows peaks of activation split into spatial or non-spatial categories, while the bottom panel (b) is split instead into basic working memory tasks involving the active retrieval of items in short term memory ("maintenance only") and more demanding tasks involving the manipulation of such items ("maintenance plus"). In both panels, the black line in the middle of the frontal lobes indicates the boundary between the middle and inferior frontal gyrus, so that anything above the line would be classed as DLPFC while anything below the line would be classed as VPFC. Figure taken from D'esposito et al. (D'Esposito, Aguirre et al. 1998).



1.4.1.2 - The 2-stage model of the lateral prefrontal cortex

In contrast to the domain specific theory described in 1.4.1.1, Petrides (Petrides and Pandya 1994; Petrides 1998) put forward a model for the lateral PFC based on process, rather than content. According to this hypothesis, the VPFC "subserves the expression within memory of various first-order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long-term memory" while the DLPFC is involved in second order working memory processes, where multiple sources of information needed to be "monitored or manipulated on the basis of the requirements of the task or the subject's current plans" (Petrides 1998). This model was originally proposed based on monkey lesion studies. For instance, Petrides (Petrides 1995) found that monkeys with DLPFC lesions were impaired when they had to monitor which of three stimuli they had previously selected, although they were not impaired when they had to choose which of three stimuli had been previously presented to them.

Recently, far more support for this model has come from human neuroimaging. As figure 1.5b illustrates, most tasks given in the scanner that involve some form of monitoring or manipulation activate the DLPFC, while most tasks involving lower-level working memory demands, requiring maintenance of information only, activate the VPFC. Some neuroimaging studies have sought more directly to validate this model. For instance, Owen et al. have shown using PET that while a standard working memory task, such as the spatial span task, only activates the VPFC, tasks involving a manipulation component, such as a searching task (Owen, Evans et al. 1996), or a 2-back task (Owen, Herrod et al. 1999) activate the DLPFC.

However, the 2-stage model of the lateral PFC suffers from various problems as well. Due to the under-specified definitions of the two processes, it is unclear whether such a model could be falsifiable. In addition, it has never been made clear how the two processing "domains" interact. For instance, it is unclear whether DLPFC processes require lower-level VPFC processes, or whether a task sufficiently complex is processed in the DLPFC and not the VPFC. Another problem concerns a common confounding factor in both neuroimaging and monkey lesion studies. It is possible that tasks that are more difficult per se, regardless of computational mechanism required for success, will activate the DLPFC, while simpler working memory tasks will activate only the VPFC. Since, almost by definition, tasks involving a greater monitoring or manipulation component will also be more difficult, most findings purporting to support Petrides' 2 stage model may instead be supporting this alternative interpretation.

1.4.2 - Alternative theories of the lateral prefrontal cortex

1.4.2.1 - The prefrontal cortex and cognitive demand

Given the frequency with which more difficult tasks of various kinds tend to activate the lateral PFC, as discussed in the last paragraph, it has been proposed both within working memory (Cohen, Perlstein et al. 1997; Jonides, Schumacher et al. 1997) and more generally (Duncan and Owen 2000), that the lateral PFC is simply responsive to cognitive demands per se. Jonides et al. (Jonides, Schumacher et al. 1997), for instance, found using PET that varying the working memory load in an n-back task from 0 to 3 produced a proportionate drop in behavioural performance and a corresponding increase in lateral PFC activation, particularly within the DLPFC.

Cohen et al. (Cohen, Perlstein et al. 1997) obtained broadly similar results using functional Magnetic Resonance Imaging (fMRI), also with a verbal n-back task.

It could be argued that such activation patterns reflect mnemonic, rather than executive, demands. However, there is evidence to suggest that in virtually any cognitive domain a significantly harder task will activate the lateral PFC more. Duncan et al. (Duncan and Owen 2000) carried out a review of neuroimaging studies containing contrasts involving harder compared with easier versions of the same task in a wide array of cognitive demands. Such processes included perception, working memory, novelty and response conflict. The results indicated that whatever the task involved, three regions would commonly be activated. As well as the anterior cingulate, both the VPFC and DLPFC would almost always increase in activation in response to more difficult tasks.

In line with this hypothesis, Duncan et al. (Duncan, Seitz et al. 2000) used PET to compare a hard versus an easy version of three different types of fluid intelligence tests: spatial, verbal and perceptual. For each domain, the main area of activation was the lateral PFC (including both the VPFC and the DLPFC).

Although such an account of the lateral prefrontal cortex is useful in relation to other theories, and in capturing much of the neuroimaging data, it lacks specificity on a mechanistic level.

1.4.2.2 - The prefrontal cortex and the management of task/goal states

A more promising, specific suggestion in the literature concerning the lateral PFC returns to implications made in the anatomical section (see section 1.2.3). A clear suggestion from the anatomy of the PFC in the monkey is that it carries out processes in the pursuit of current, non-automatic goals, particularly if such goals are complex.

Although this explanation is not new, recent monkey electrophysiology studies have provided a fresh perspective for this theory (Rao, Rainer et al. 1997; Rainer, Asaad et al. 1998; Rainer, Asaad et al. 1998; Asaad, Rainer et al. 2000; Fuster, Bodner et al. 2000; Freedman, Riesenhuber et al. 2001; Miller and Cohen 2001; Wallis, Anderson et al. 2001). For example, Asaad et al. (Asaad, Rainer et al. 2000) gave monkeys three interleaved tasks - a spatial delayed response task, an object-based delayed response task and a conditional association task. They found that the activity of many PFC neurons was influenced by the task being performed. This modulation was in certain cases so extreme that some neurons were unresponsive to two of the tasks, while highly responsive to the third. Asaad et al. conclude that one PFC function "is the acquisition and implementation of task context and the 'rules' used to guide behaviour (Asaad, Rainer et al. 2000).

In humans, Duncan has made more explicit the relationship between managing goal states and the frontal lobes by suggesting that "impaired goal weighting lies at the root of the frontal lobe syndrome" (Duncan 1990). The emphasis on "weighting" is influenced by accounts of patients who appear aware of the current goal, understand how to achieve that goal, yet nevertheless somehow become distracted and fail to achieve it. For instance, Baddeley (Baddeley 1986) reports a patient, R.J, who following bilateral frontal lobe damage, was asked to measure out a piece of string in order to cut it at a later time. Without having measured the string, R.J. immediately began to cut it. When told not to, he replied, "Yes I know I'm not to cut it" while he continued to cut the string. It is as if R.J had inappropriately given the "cut-string" goal a very high weighting, while inappropriately given the "measure-string" goal a null weighting.

In order to characterise such a deficit more explicitly, while also extending it to the normal population, Duncan et al. (Duncan, Emslie et al. 1996) gave a simple letter detection task, with a switching element towards the end, to both healthy controls and patients. Although all subjects fully understood the task, frontal lobe patients were severely impaired at performing the switching element of the task compared both to posterior cortex lesion patients, and matched healthy controls. Intriguingly, healthy controls at the low end of the IQ scale were also highly impaired at this aspect of the task. They claimed that the critical details of the task just "slipped their minds" during the experiment, despite realising this error later. Duncan characterised such a deficit in low-IQ rated normals and frontal lobe patients as "goal neglect" (Duncan, Emslie et al. 1996).

1.4.2.3 - The prefrontal cortex and strategy

From early reports of frontal lobe patients (see section 1.3.1), it has been very clear that these patients suffer from organisational dysfunction. One obvious aspect of organising one's behaviour is to hold in mind the current goal, particularly if such a goal is dynamic or complex. However, carrying out a single goal is a relatively rare state in human behaviour. Far more common is the requirement to juggle a set of goals, some relating to current circumstance, while others may relate to a future occasion, hours or days away. In addition, single goals may well have a large set of sub-goals. My current goal of writing up my PhD thesis requires me to choose the next point, retrieve the appropriate words in order to create a sentence to communicate that point, sequentially make a set of finger movements in order to type the words, consider how that point relates to the previous one and the next, and how in the wider context it relates to the section, and the thesis as a whole. It is not sufficient merely to

hold online all these sub-goals simultaneously, since in order to carry out this task, I need to know when to give weight to which sub-goal and ignore others, as well as to apply existing strategies about writing style. Ideally, in addition I should be seeking to form new strategies at every level, from developing ways around my word processor program's idiosyncrasies to painting as coherent a picture of my research and ideas as possible. This way the goal will be reached more effectively with less effort.

This example should make clear that functional organisation requires both the management of a potentially large number of goals *and* the formation and maintenance of strategies to optimise specific goals, or even to switch resources between the goals effectively.

Strategy has been implicated in frontal lobe function, largely from studies involving frontal lobe patients (Owen, Downes et al. 1990; Shallice and Burgess 1991; Miotto, Bullock et al. 1996; Owen, Morris et al. 1996; Morris, Rowe et al. 1999; Burgess, Veitch et al. 2000). For instance, in a relatively true to life example, Shallice et al. (Shallice and Burgess 1991) gave three frontal lobe patients what they termed a "six element test" consisting of two sets of three tasks: dictating a route, mathematical problems and picture naming. Crucially, maximum scores would have been gained if the subjects equally attempted all 6 tasks in the time limit. Therefore the strategic element consisted of managing one's time for each task and switching to different tasks according to the rules. Despite the fact that a stopwatch was available to the subjects at all times, the frontal lobe patients performed significantly worse than the controls, appearing unable to develop any effective strategy in order to maximise their score. One patient, for instance, only attempted 2 of the 6 tasks in the time limit.

In a later study, which compared frontal lobe patients with other lesion groups, Owen et al. (Owen, Morris et al. 1996) reported a double dissociation between strategy

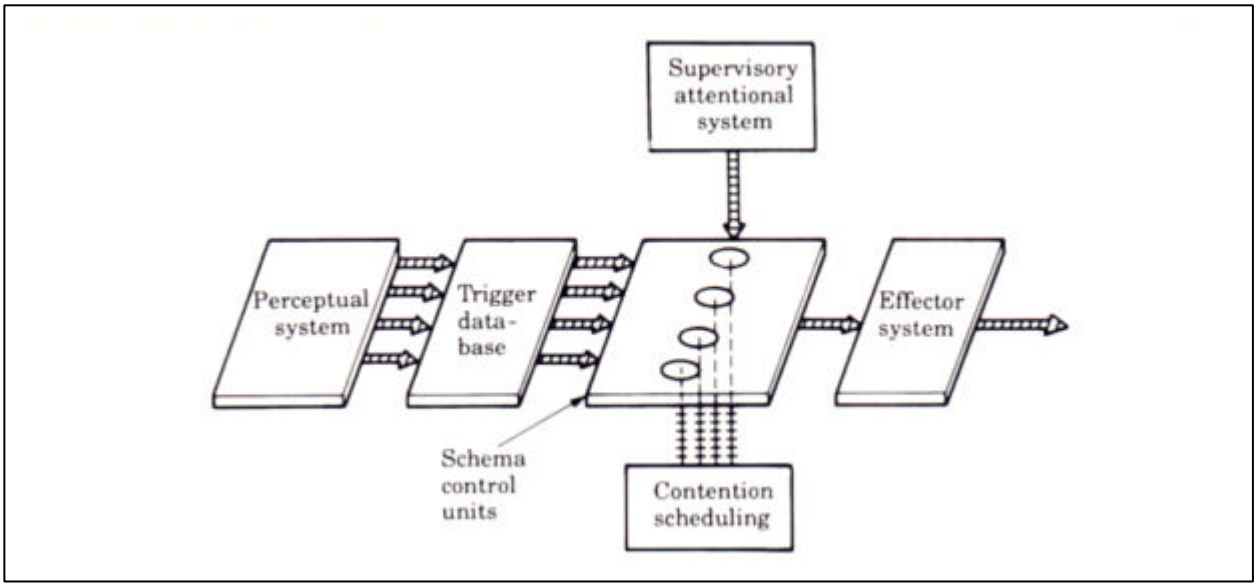
and memory. They found that while frontal lobe patients were impaired at forming or maintaining an obvious searching strategy that would significantly improve performance on a spatial working memory task, temporal lobe lesion and amygalo-hippocampectomy patient groups were not impaired in finding such a strategy, but were impaired in the mnemonic aspect of the task. The frontal lobe patients showed no such mnemonic deficit.

1.4.2.4 - The prefrontal cortex and the Supervisory Attention System

Norman and Shallice (Norman and Shallice 1986; Shallice and Burgess 1991; Shallice and Burgess 1998) outlined a model that attempted to explain both the "goal neglect" and strategic deficits of frontal lobe patients. According to the model (see figure 1.6), there are two broadly differing routes from perceptual input to output. For the first route, perceptual inputs trigger appropriate well-learned skills in the form of schemas, which in turn create specific outputs (either involving a behavioural response or further thoughts). When the current environment suggests two competing schemas, a system referred to as "contention scheduling" automatically chooses between the two schemas by comparing them based on predefined weights; whichever schema has the greatest weight or importance, is activated. However, when the situation is novel or complex, there is no clear mapping between the perceptual input and existing schemas. At this stage, the supervisory attention system (SAS) exerts influence on response. Specifically in relation to schemas, the SAS can create, trigger and evaluate such schemas (Shallice and Burgess 1991). Shallice and Burgess have more recently described such processes in a more general way, relating to plan formation and evaluation, as well as the articulation of goals (Shallice and Burgess 1998). This model has been very successful in explaining errors relating to automatic behaviour.

For instance, I recently changed offices and for the first day regularly went to my old office accidentally. This could be explained by the previously most appropriate schema automatically being activated, without the SAS imposing a new schema on behaviour. In addition, the SAS closely reflects frontal lobe function, as revealed by frontal lobe patients who seem unable to update previously established behavioural responses to novel features of a task, such as in the Wisconsin card sorting test (Milner 1963).

Figure 1.6 - A simplified version of the Norman and Shallice model (Norman and Shallice 1986; Shallice and Burgess 1991; Shallice and Burgess 1998), comprising the SAS. The route from perceptual input to output, via the effector system, can occur with little or no influence from the SAS if there is a clear mapping between input and existing schemas. However in novel or complex situations, the SAS exerts control over behaviour, possibly by forming new schema units. Diagram taken from Baddeley (Baddeley 1997).



1.4.3 - Summary of theories of prefrontal cortex function

The most influential framework for models of PFC function appears to be Baddeley's working memory model (Baddeley 1986; Baddeley 1992; Baddeley 2000). Two key areas of the model are linked to the lateral PFC: the central executive and the episodic buffer. While the central executive is critical for attentional control and the manipulation of information, the episodic buffer is thought to integrate information from multiple sources.

Specific theories attempting to fractionate the lateral PFC according to domain (Wilson, Scalaidhe et al. 1993; Goldman-Rakic 1998), or process (Petrides 1994; Petrides 1998) have only been partially successful, at best. While the domain-specific theory has not found supporting evidence in human neuroimaging studies, the 2-stage processing model has lacked specificity.

Work outside of working memory has emphasised the role of the frontal lobes in maintaining task-based information, or in strategic processes. It has also been suggested that the lateral PFC is simply responsive to cognitive demand of any kind.

What is readily noticeable from this set of theories is the high degree of conceptual overlap. For instance, Baddeley (Baddeley 1997) has admitted that the SAS may well be an appropriate model for his less well characterised idea of the "central executive." Petrides' 2-stage processing model incorporates the idea of strategic processes within his suggestions for the role of the DLPFC. Duncan's (Duncan 1990) conception of "goal weighting" appears also to resemble the influence of the SAS on competing "goals" as represented by schemas. The reason for such common features between these theories seems to be a rough, general consensus about

rather abstract processes that are hard to capture by descriptions of specific mechanisms.

1.5 - Outline of remaining thesis chapters

What was clear in the review of the frontal lobe literature above, both in anatomy, historical work and current theories, was the common links between the PFC and complex goals, as well as the processing of plans or strategies. However, strategy use has not been associated with any specific region within the frontal lobes, since evidence so far has only been provided by patient lesion studies. This thesis will provide initial evidence that a well-established working memory paradigm, that of spatial span, can under certain modifications, elicit DLPFC activation instead of VPFC activation. The reason for the difference in prefrontal activation patterns will be explored via behavioural studies, the first of which will implicate strategy use as the key difference, and the second of which will suggest a particular form of strategy, that of chunking. Thus at least one form of strategy will be associated not just with the frontal lobes, as suggested by patient studies, but with the DLPFC. A later neuroimaging study will establish in a more controlled way an association between the lateral PFC and strategy use. In addition, contrary to previous findings, a frontal lobe patient study will suggest that this patient group is impaired on this type of working memory task.

Chapter 2 will describe the methods utilised in this thesis. The physical mechanism, design considerations and analysis details of both PET and fMRI will be elucidated. Methodological details of neurological patient studies will be outlined, as well as general considerations relating to behavioural experiments.

Chapter 3 will describe a PET study that provides preliminary evidence that varying the level of spatial order of the locations of stimuli in a standard working memory task can change the observed activation from the VPFC to DLPFC.

However, the conclusions of chapter 3 are based only on an implicit, between groups design. To address this, in chapter 4 an experiment is described which uses PET *within* a single group and provides similar results. In that study, two different types of a spatial working memory test are presented to each subject. The two versions differ in the level of spatial regularity of the stimuli, which is assumed to call upon different levels of strategic involvement.

In chapter 5, a small behavioural study addresses the issue of whether the two types of spatial span task of chapter 4 do indeed differ in terms of levels of strategic involvement. Very similar spatial span tasks to that used in chapter 4 are given to healthy subjects, to test whether there is a behavioural difference between such tasks. Although the performance data fail to confirm this, subjective reports clearly indicate that the crucial difference between the two span tasks is that of strategy.

In chapter 6, the same tasks given to healthy subjects in the behavioural study of chapter 5 are given either to frontal lobe patients, or carefully matched controls in another behavioural experiment. Previous studies have indicated that such patients have no basic working memory deficit (D'Esposito and Postle 1999), at least where span tasks are employed. However, this study clearly demonstrates that frontal lobe patients do indeed have a deficit, if the task is made sensitive enough. In addition, the evidence from this chapter indicates a small, differential impairment in these patients between the two spatial working memory tests.

Chapter 7 follows up the two PET studies (chapters 3 and 4) using fMRI. Spatially structured and non-structured span trials are compared, using the same

spatial grid of possible locations, thus further controlling for visual similarity, while also attempting to maximise the difference in the spans themselves. The structured spans show significantly greater activation in the lateral PFC, compared with the non-structured trials, possibly as a result of the structured spans eliciting greater strategic involvement.

In chapter 8 a large-scale behavioural study looking at many spatial span parameters is carried out. Some parameters are designed to pertain directly to possible strategic mechanisms that differentiated performance on span conditions in previous chapters. In particular, using very similar trials to that of the spans in the fMRI study, a behavioural difference between two conditions designed to maximise and minimise strategic chunking suggest that this is a relevant strategic process to such working memory tasks.

Finally in chapter 9, a general discussion will attempt to show how the new data of the experimental chapters provides clues as to the involvement of the lateral PFC in one underlying psychological mechanism of strategy processing. There will follow a conceptual discussion about what processes may be required to perform "intelligent," high-level organisational tasks, of the kind it appears the lateral PFC is involved with. Finally, limitations of the current work and possible future lines of research will be outlined.

Chapter 2: General methods

2.1 – Introduction

In this chapter, general methodologies relating to the experimental chapters in the thesis will be discussed. Most experiments in this thesis involve neuroimaging, so this will be centred on. General methodological considerations and advantages of neuroimaging will be described. There will follow a brief outline of the physical mechanisms of both PET and fMRI, as well as issues of experimental design, neuroimaging preprocessing and analysis of fMRI and PET data. The chapter will end with analytical details relating to the non-imaging methods used in this thesis, including behavioural experiments on normal controls and on frontal lobe patients.

2.2 – Neuroimaging

In human cognitive research, before neuroimaging existed, any attempt at mapping a cognitive function to a brain region involved the examination of deficits in patients with localised lesions. However, such lesions are commonly large, and can overlap two possibly separable functional areas. In addition, brain damaged patients can often have multiple non-contiguous regions of damage, while the site of lesion could hinder apparently healthy brain areas far away by disruption to a network. For this reason, only the crudest possible localisation has been possible through this technique in patients alone. Neuroimaging has held the promise of far finer spatial resolution in the attempt to map the brain according to function.

Over the past 20 years, the emergence of neuroimaging techniques (Posner and Raichle 1994; Friston 1997) has revolutionised cognitive neuroscience, shifting the emphasis from the mechanism and form of psychological processes and frameworks, largely as revealed by deficits in patients, to the mapping of such processes to brain regions in healthy subjects. Functional neuroimaging, particularly PET and fMRI, involves the association of markers thought to relate to brain activity with certain psychological functions. Although such an approach is undoubtedly very powerful, there are two major concerns with these techniques:

1) Neuroimaging can only ever reveal *associative* data, i.e. neuroimaging can only demonstrate that a certain brain region is correlated with a certain cognitive process. It is impossible to demonstrate that such an activated region is necessary for a given psychological function on the basis of neuroimaging data alone, or that it is even involved in such processing. Only in combination with other data, such as human lesion studies, or animal studies can inferences about involvement be made.
2) It is not yet clear whether the markers of brain activity do indeed relate in a direct way to regional neuronal involvement. In the case of PET, as will be discussed below, regional cerebral blood flow (rCBF) is measured, which *is thought to* relate in turn to local neuronal activity, although this has not been demonstrated conclusively. For fMRI, blood oxygen levels are measured, which again are thought – though not yet conclusively shown – to be dependent on neuronal activation.

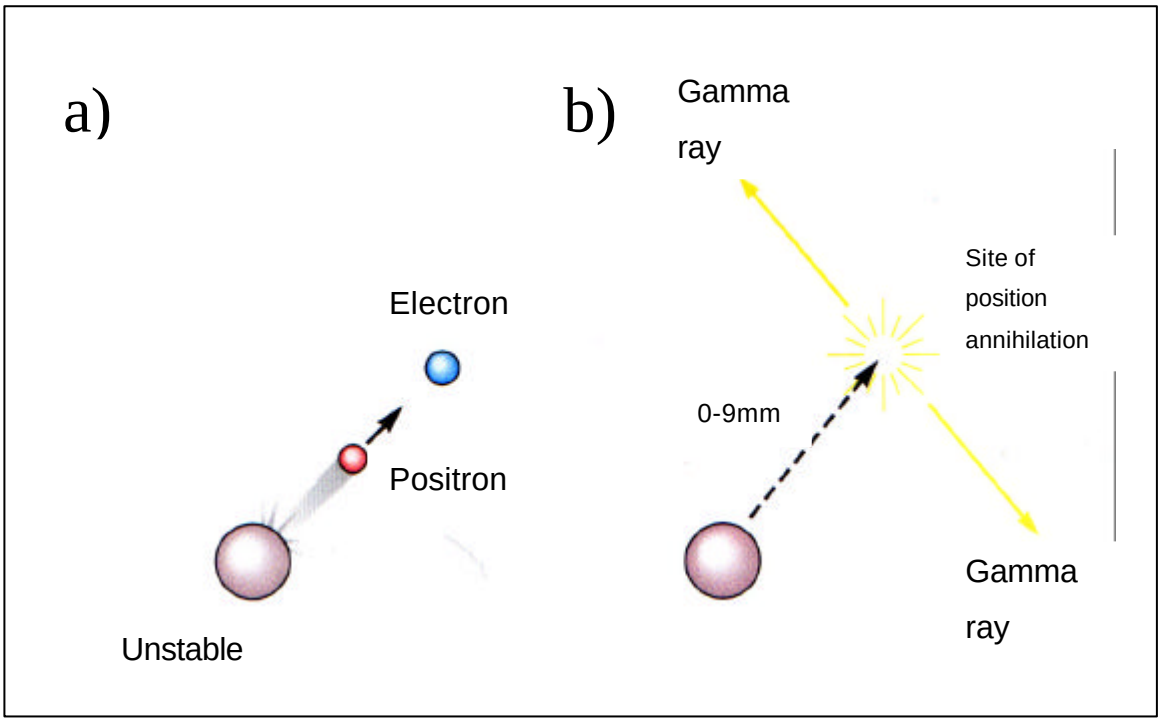
2.2.1 – Mechanism of measurement in neuroimaging techniques

2.2.1.1 – Mechanism of measurement in PET

The first stage in PET imaging involves the introduction into the brain of materials labelled with radionuclides that emit positrons. In current functional imaging using PET, a radioactive isotope of oxygen (^{15}O) is most commonly used, as part of the water that is injected into the subject's blood-stream via a catheter. Such non-standard compounds can be biologically processed as normal. The half-life of the substance in part determines the temporal resolution of the scan, with ^{15}O having a relatively short half-life, allowing for scans of about one minute, making it particularly amenable to functional imaging. Another substance commonly used, ^{18}F-deoxyglucose, has a far longer half-life, creating a temporal resolution of the order of 30 minutes.

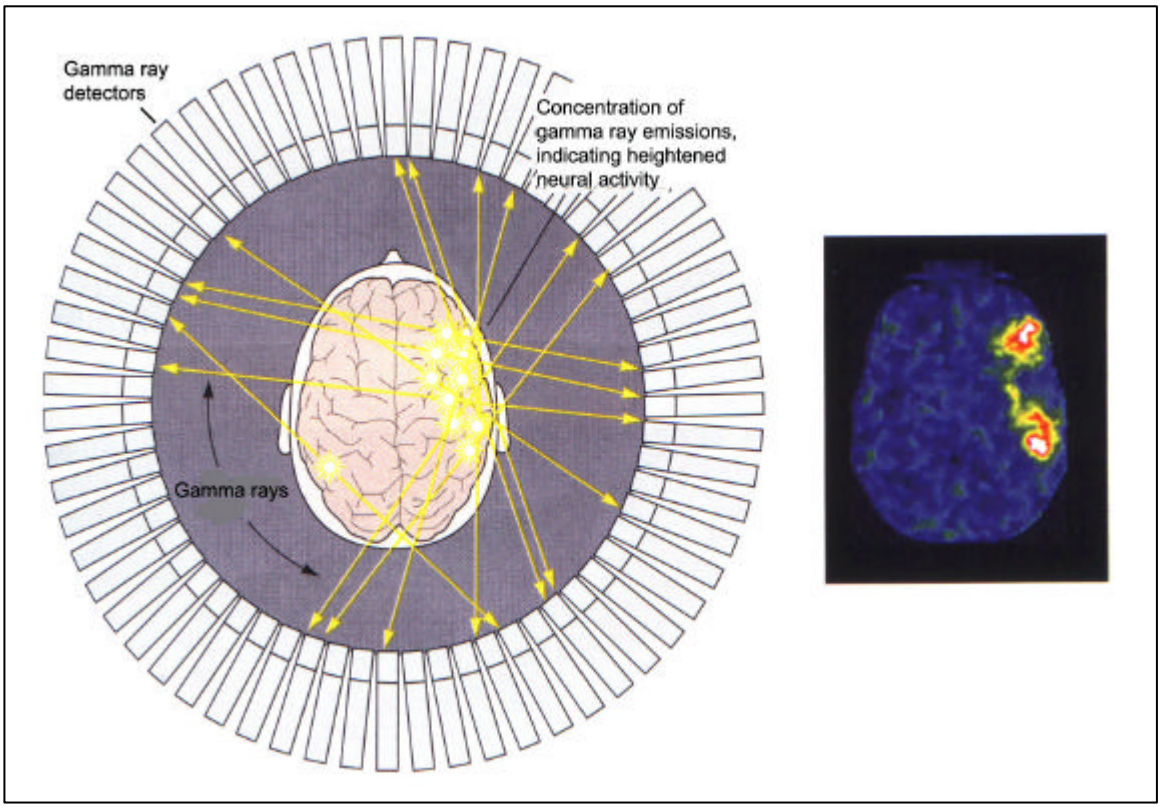
When these unstable isotopes break down via beta radiation, the "extra" proton decays into a neutron and positron (see figure 2.1a). The positron travels away from the original nucleus at very high speeds, eventually colliding with an electron up to approximately 5 mm away, thus limiting the spatial resolution of scans to this distance. The collision annihilates both particles, and in the process two gamma ray photons are emitted at 180 degrees from each other (see figure 2.1b).

Figure 2.1 – Illustration of emission sequence from unstable isotope to detectable gamma ray. Figure 2.1a shows how the unstable radionuclide decays, emitting a positron at extremely high speeds. Figure 2.1b indicates how the positron soon collides with a resident electron and the result is the emission of two photons 180 degrees from each other. Adapted from Kandel and Schwartz (Kandel, Schwartz et al. 2000).



The PET scanner can detect these gamma rays via arrays of detectors, which encircle the subject's head (see figure 2.2). If two simultaneous detections are made within a plane, this data is recorded and the source can be extrapolated from the pattern of such recordings in 3 dimensions.

Figure 2.2. – Illustration of gamma ray detector system as part of the PET scanner. When two simultaneous emissions are detected, this is registered as real signal and the location of activity is calculated from this.



Since higher concentrations of blood in a local region will also contain higher levels of the radionuclide, an increased detection of gamma rays in the scanner indicates increases in rCBF. Increases in rCBF are thought in turn to reflect increases in neural activity due to populations, since neuronal populations can only increase in activation in concert with greater metabolic activity.

2.2.1.2 – Mechanism of measurement in fMRI

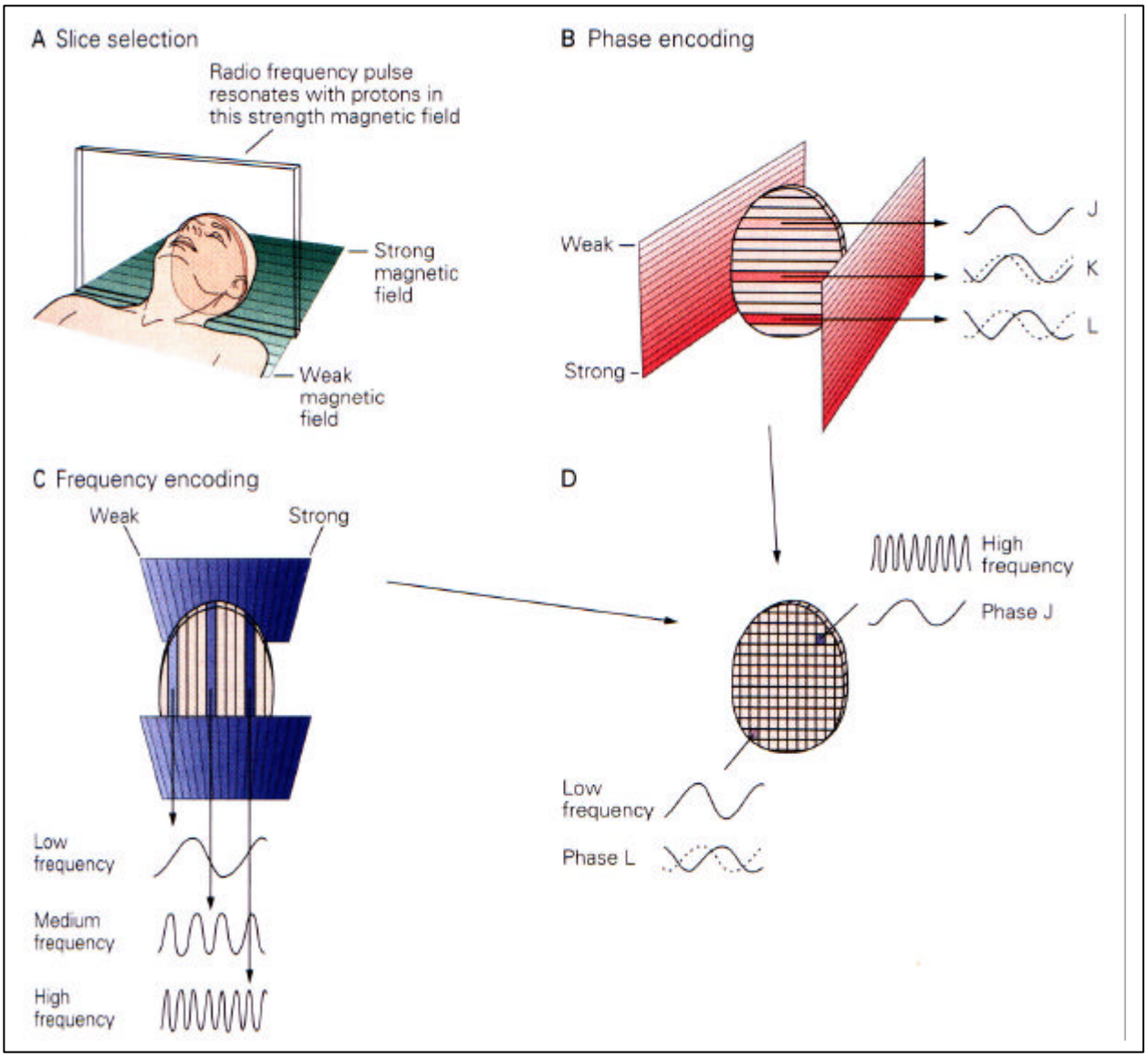
Due to the magnetic properties of hydrogen ions (protons), and the presence of hydrogen ions in every water molecule, it is possible to make measurements of aspects of cerebral blood in the Magnetic Resonance Imaging scanner. When a subject is placed in this scanner, all hydrogen ions in the subject's head are aligned towards the high, static magnetic field that the MRI scanner produces. The magnetic field is continuously gradated in terms of field strength. Scans are produced in a particular plane, directed by the level of field strength, which will be homogeneous within that plane (see figure 2.3a). A radio-frequency pulse specific to a band of field strength momentarily disrupts the alignment of hydrogen ions in a particular direction, normally perpendicular to the original direction of field. For each scan, which is effectively a two dimensional array of information, concentrations of hydrogen ions are detected by gradations of radio-frequency in one dimension and gradations of the wave phase (relative alignment of waveforms with each other) in the other dimension (see figure 2.3b and 2.3c). Thus, individual pixels in each slice can be detected by their unique phase and frequency properties, while slices are distinguished by field strength.

For functional MRI methods, the ratio of oxygenated to deoxygenated blood is used as an index of neuronal activation. This ratio is detectable due to the fact that

oxygenated blood has a different effect on the phasing of protons to deoxygenated blood. Local increases in neural activity are thought to cause an initial deoxygenation of blood, followed by an increase in blood supply which causes a more enduring oxygenation in local blood supplies (Friston 1997). It is the increase in oxygenated relative to deoxygenated blood that is thought to reflect increases in neural activity.

Temporal resolution is determined in large part by the length of time it takes to create one whole functional image, typically two to three seconds, although statistical techniques can increase the resolution to approximately half a second. Spatial resolution is determined by the magnetic field strength of the scanner and is normally of the order of 2-3 mm.

Figure 2.3 – An illustration of the mechanism used to pick up signal in an MRI scanner. A) The image is created slice by slice, with all ions in each slice selected by a radio-frequency pulse which resonates hydrogen ions in a particular magnetic field strength. B) Along one axis of each slice, the pulse is graded by the phase of the waveform, so that hydrogen ions at one end of the slice will be at a slightly later wave stage than those at the other end. C) Along the second axis of the slice, the pulse is graded by frequency, so that hydrogen ions are magnetised to a higher frequency at one side of the slice, compared with the other. D) Therefore, each pixel in each slice will have unique properties, based on phase and frequency. Taken from Kandel and Schwartz (Kandel, Schwartz et al. 2000).



2.2.2 – Design Issues with functional neuroimaging

Common functional imaging designs (Friston 1997) usually contrast a few conditions of psychological interest with a carefully matched control. Whatever increased activation is observed when the control signal is subtracted from the activation associated with the psychological condition may be taken as activity specific to the cognitive process isolated by that psychological task (Fletcher, Shallice et al. 1998; Owen, Herrod et al. 1999; Hopfinger, Buonocore et al. 2000; Lee, Robbins et al. 2000). For instance, a working memory task might be contrasted with a control task where the visuomotor aspects of the task are the same, but the working memory demands are minimal.

Other ways of comparing psychological processes include factorial designs where two orthogonal issues are compared in a 2 x 2 matrix of type of task (Schumacher, Lauber et al. 1996). For instance, a hard versus easy working memory condition might be given in both the spatial and verbal domains. In addition, parametric designs are sometimes used (Cohen, Perlstein et al. 1997; Jonides, Schumacher et al. 1997), where a single factor is varied across conditions. For instance, 5 different levels of difficulty of a working memory task may be given to subjects to attempt to ascertain what brain regions correlate with difficulty (Jonides, Schumacher et al. 1997).

2.2.2.1 – Design issues in PET

The subject is placed lying face up, with his/her head in the scanner, and, for the water bolus methodology (involving the most common radioactive tracer: ^{15}O), a drip is inserted into the subject's arm.

Environmental distracters as a result of the PET equipment are minimal, compared to fMRI (see below). The scanning procedure is silent, while the subject is largely outside of the scanner, thus avoiding problems of claustrophobia. For stimulus delivery, auditory stimuli can be presented through headphones, while visual stimuli can be presented on a monitor placed close to the subject's head. This can double as a touch-screen monitor, allowing the subject to make more intuitive motor responses. In both PET studies reported here, a touch-screen monitor was used.

A normal functional imaging PET experiment consists of approximately 12 scans, separated by 8 minutes in order to allow the radioactive tracer from the previous condition to have "washed out" of the cerebral system. Each scan normally lasts between 60 and 90 seconds, and involves only one condition. It is known that the subjects' head position in the scanner tends to drift slightly across scans in particular directions (Brett, Bloomfield et al. 1999), and this can lead to systematic changes in signal. To minimise this confound, it is desirable to counterbalance the order of conditions between subjects.

Due to the effective maximum of only 12 data-points per subject, it is normally advisable to have a small number of conditions (e.g. 3) repeated as many times as possible across the scans. It is also advisable to test at least 12 subjects in order to provide sufficient statistical power to detect changes in rCBF between conditions.

2.2.2.2 – Design issues in fMRI

Unlike in PET, almost the whole body of the subject is placed within the bore of the scanner, again face up. Although the procedure is non-invasive, it is potentially considerably more dangerous than PET, and steps need to be taken to ensure the

subject has no metal on him/her (since this could be extremely dangerous due to the high magnetic field of the scanner). In addition, the scans themselves are extremely loud and ear protection needs to be provided.

The noise of the scanner makes it problematic to present auditory stimuli to the subject although methods have been devised to circumvent this problem; sparse imaging, where the stimulus presentation and scanning are carried out at two separate stages for each trial, is one example. In addition, the fact that the subject is almost entirely within the fMRI machine means that easy sight of a monitor, and the ability to touch such a monitor to make responses, are impossible. Instead, the setup used in the fMRI experiment reported in this thesis involved an angled mirror just above the subject's head, so that a back-projected screen at the opening of the scanner bore was visible. Responses are normally made with a specially created button box.

Unlike PET, there is virtually no restriction on the number of scans collected, so that instead of 12 scans, it is common to collect over 500 scans per subject. In addition, there need not be any delay at all between two scans, so that data can be collected continuously over long periods, typically up to 20 minutes. Such a wealth of data-points creates two clear advantages over PET. First, fMRI analyses can be carried out in single subjects due to the greater statistical power. However, to make valid inferences about the population it is still necessary to carry out a group analysis (on at least 12 subjects, normally). Second, individual psychological events such as the encoding phase of a single spatial span trial (see chapter 6), can be distinguished, due to the high temporal resolution of fMRI.

2.2.3 – Neuroimaging Analysis

All neuroimaging preprocessing, analyses and graphical presentations in this thesis were carried out using the SPM 99 software (provided by the Wellcome Department of Cognitive Neurology, London, UK), except chapter 3, which used SPM 96 (provided by the Wellcome Department of Cognitive Neurology, London, UK). SPM is a widely used tool for neuroimaging analysis.

2.2.3.1 – Preprocessing

The raw data in both PET and fMRI can suffer from various problems. For instance, head movement during or between scans can severely reduce the signal when comparisons between scans are made during the analysis. In addition, the shape and size of brains can differ markedly, making direct comparison between subjects in a group analysis difficult. Various mathematical procedures are therefore carried out on the raw data before analysis, in order to minimise such problems:

1) **Slice timing correction** (only relevent for fMRI) – As mentioned in 2.2.1.2, each fMRI image is created by taking a set of slices. These slices are collected in the same order (for instance, from the bottom to the top of the brain) for every single image. Therefore, one part of the brain may always be scanned a second before another. Due to the fact that a single image is taken as a single time point, the hemodynamic response will be consistently displaced by one second between these two brain regions. In order to correct for this displacement, and to make a single image appear more properly as a single time point, the hemodynamic response at each slice is modified so as to appear from the same time point as, say, the middle

slice. This is normally carried out as a "shift" forward in time on each slice, via sinc interpolation algorithms.

2) **Image realignment –** In both PET and fMRI, subject head movement in the scanner means that images are not properly aligned with each other – sometimes to a substantial extent. This stage generates movement parameters for each image so that they are realigned appropriately to a reference image, usually via a mean of all the images in the series.
3) **Normalisation –** In order to compare different subjects, with varying brain sizes and shapes, as well as to be able to extrapolate to different studies, each image needs to be warped so that it closely matches a standard template. The warping process usually involves various linear and non-linear transformations in the three dimensions and three planes of rotation, again via sinc interpolation algorithms. The template is normally that of the Montreal Neurological Institute, which is generated from an average of 305 normal brains, although specialised ones do exist for fMRI studies. All templates roughly correspond to the atlas of Talairach and Tournoux (Talairach and Tournoux 1988), which shows how specific co-ordinates for activations on the normalised brains correspond to brain regions.
4) **Smoothing –** In order to increase the signal to noise ratio, the intensity values at each voxel are locally averaged, which has the effect of "blurring" the signal. A Gaussian smoothing kernel applied in three dimensions to each image is the most usual method to achieve this.

2.2.3.2 – Analysis

In both PET and fMRI, the most common way of analysing functional data is based on the General Linear Model (GLM). However, while in PET, the separate images can be taken as independent, since the radioactive tracer should have totally decayed between scans, in fMRI, with continuous scanning normally carried out, the signal can clearly overlap between images. Therefore fMRI analyses in addition take into account details of the time-series.

In GLM, the statistical test is carried out between the actual data and a predicted model. If the fit between the predicted and actual data is good, then the conclusion is that there is a relationship between the actual data (voxel intensity values) and task-related factors (such as working memory processes). Consider a primitive case where there is only one independent variable (say working memory load), then the model can be expressed as a linear relationship:

$$Y(j) = \beta * x(j) + c + E(j)$$

where Y is the dependent variable (i.e. the intensity for a given voxel), j refers to a given scan, β is the parameter estimate of x (or the gradient of the line, if the equation were represented graphically), x is the independent variable (e.g. working memory load), c is the constant (or intercept on the graph), and E is the error term. If there is a good fit between the psychological factor and voxel values, then the gradient of the line (i.e. β) would be significantly greater than zero. This can be statistically tested by calculating a t-statistic, which is:

$$\text{gradient of the slope } (\beta) \text{ / standard error of the slope.}$$

So a high gradient (or β) compared to low standard error would produce a significant association between voxel activation and some psychological factor.

The model can be extended to more than one independent variable easily. For instance, for two independent variables – (executive function and memory load, say), the formula would be:

$$Y(j) = \beta 1^* x1(j) + \beta 2^* x2(j) + c + E(j)$$

where β1* x1 refer to executive function, for instance, and β2*x2 refer to memory load. For executive function, one would expect β1 to be high compared to the standard error of the slope, while β2 would not be significantly different from zero. Meanwhile, one would expect β2 to be high relative to the standard error for memory load, but β1 not to be different from zero. Such contrasts can be made more explicitly, with t-scores for one independent variable subtracted from another on a voxel-by-voxel basis. After the subtraction, whatever t-scores at any voxel survive the threshold used (see below), those are taken to be significantly more active for one variable compared to another.

2.2.3.3 – Reporting of results

If all voxels are taken together in a single contrast, approximately 100,000 separate statistical tests may have been made. The reporting of all activations from this as being valid would fail to correct for the multiple comparisons made, and would greatly increase the chances of a type I (or false positive) error being reported. Various ways

have been suggested to make multiple corrections for neuroimaging data. I will discuss the two main approaches, both used in this thesis:

1) **Correcting for multiple comparisons using 3D Gaussian random field theory (Worsley, Evans et al. 1992; Worsley, Marrett et al. 1996) –** the first step in this approach is to calculate the number of resels in a given contrast image. A resel is a cluster of voxels, the size of which is determined by the extent of spatial smoothing used (see 2.2.3.1). Then a mathematical function called the Euler Characteristic (EC) curve is calculated from the number of resels. For a given t score, there will be a corresponding, unique EC value for that image. For the EC value of 0.05, for example, there may be a corresponding t-score of 4.1. If only those clusters of activation that have a t-score of 4.1 or greater are included, there is a 0.05 probability that each of these clusters occurred by chance.
2) **Correcting by false detection rate (FDR) (Benjamini and Hochberg 1995) –** Instead of taking the whole contrast image as a basis for calculating false positives, this method uses the number of activations (beyond a certain statistical threshold determined by the level of activation in the image) as the set used to apply a correction. The correction used is a simple Bonferronni-type correction. If there are no significant clusters, then this FDR method will produce the same level of correction as the random field theory correction described above. However, the greater the number of activations, the greater power gained by this correction compared with the random theory correction above. In other words, if there are a large number of activations, then for a given correction level (say that 0.05 of the clusters will be false positives by chance), the t-score threshold will be lower for this method of correction, and more clusters of activation will be taken to pass the threshold.

If there is an a priori assumption about a brain region being associated with a condition prior to scanning, then a relaxation in statistical threshold can be applied for that specific area. For instance, using 1) above, the same multiple comparison approach can be applied to a specific brain region rather than the whole brain. This way, since the resel count will be far lower, so will the threshold applied to that region (Worsley, Evans et al. 1992; Worsley, Marrett et al. 1996).

Once a threshold has been decided, the results that pass this criterion are usually presented in a table with level of significance linked to co-ordinates of the most active peak within the given cluster. These co-ordinates refer roughly to those given in the atlas of Talairach and Tournoux (Talairach and Tournoux 1988), where x is given as minus numbers to the left and positive numbers to the right (ear to ear) of the anterior commisure, y is given as positive anterior to the anterior commisure, and negative posterior to this (nose to back of head), while z is given as negative ventral to the anterior commisure, and positive when dorsal to the anterior commisure (neck to top of head).

In addition, a graphical 3D map can be generated from the voxels (see figure 2.4 for an example), by plotting them using their co-ordinates on three planes of a model brain that shares the size and shape of the template brain. Such a “glass brain”, although statistically relatively accurate, makes it somewhat difficult to pinpoint activation sites. More commonly, the activations are superimposed on a rendered three dimensional example of the template brain (see figure 2.5 for an example), which has the advantage of appearing more intuitive, although can provide misleading results, particularly when non-surface activations appear on the surface of the brain due to a “pulling-to-surface” effect of the rendering algorithms.

Figure 2.4 – An example of the "glass brains" default graphical view produced in SPM 99.

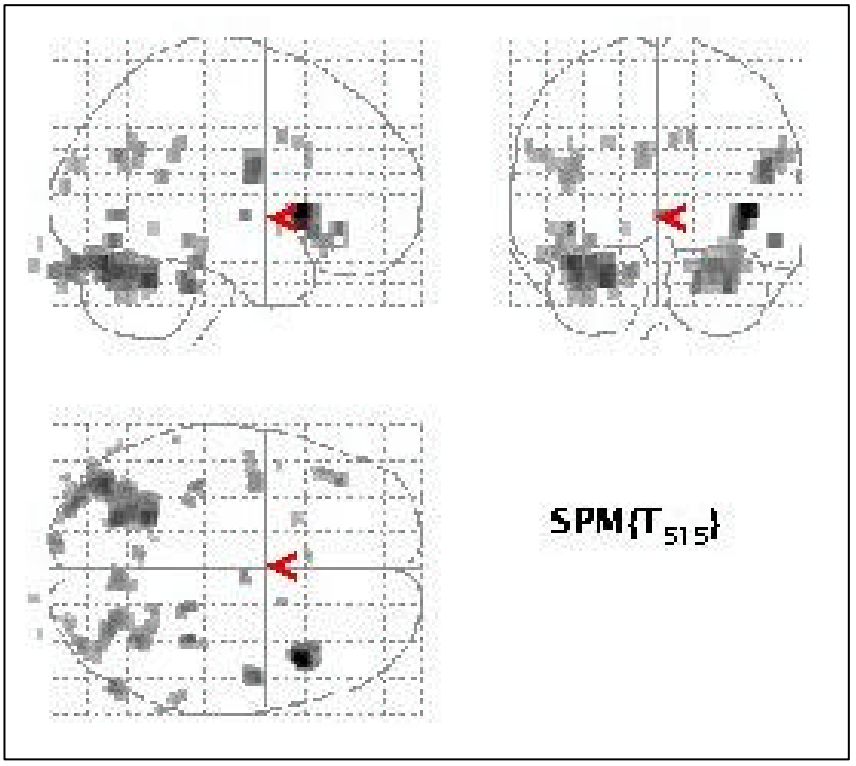
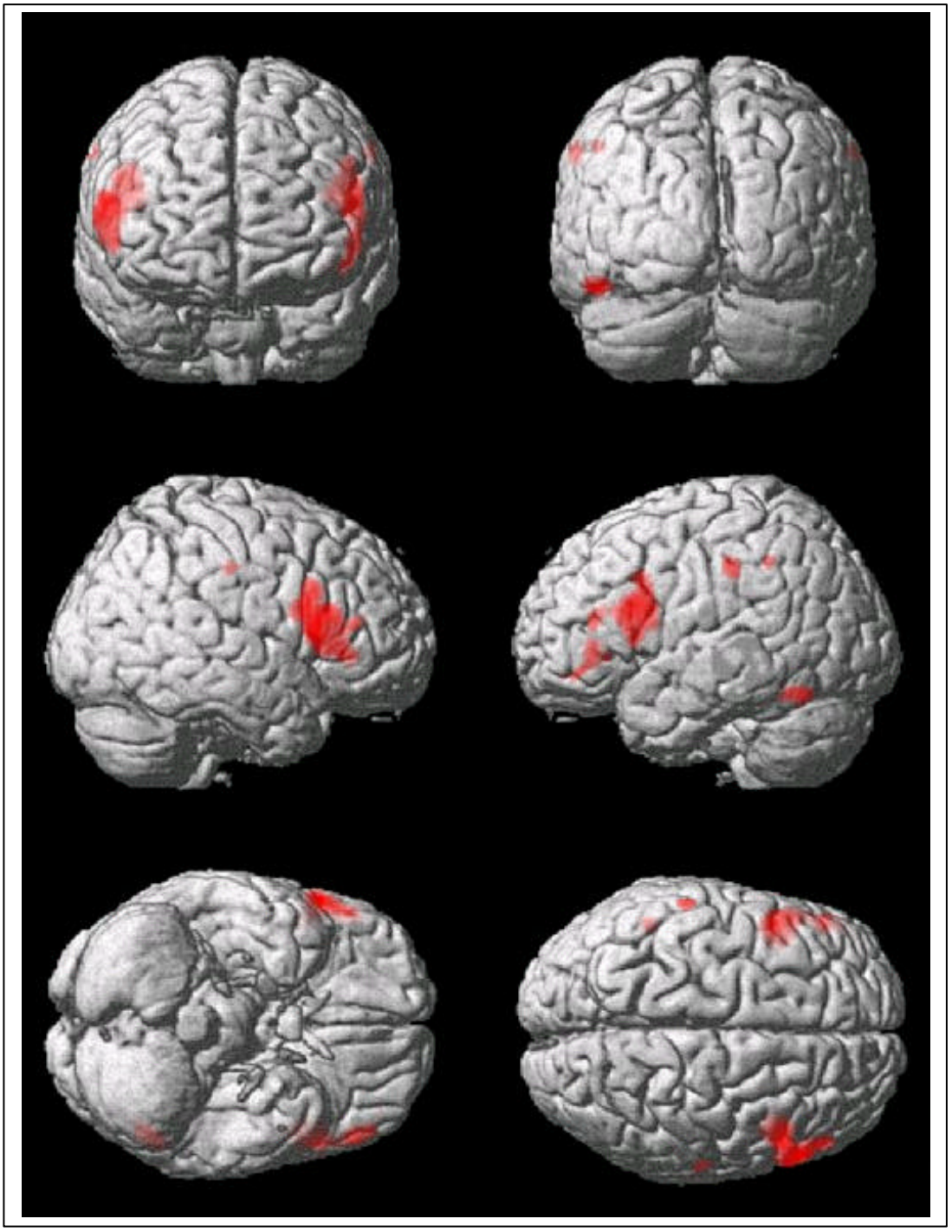


Figure 2.5 – An example of the 3D rendering view produced in SPM 99.



2.2.4 – Neuroimaging and issues relating to experimental chapters

2.2.4.1 – Scanning methodology in PET (for Chapters 3 and 4)

PET scans were obtained with the General Electrics Advance system at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital in Cambridge. This scanner produces 35 image slices at an intrinsic resolution of approximately 4.0 x 5.0 x 4.5 mm. Using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during scans. For each scan, subjects received a 20 second intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 Mbq ml^{-1} and a flow rate of 10 ml min^{-1}. The scan length was 90 seconds from when the tracer first entered the cerebral circulation. For each subject, a 3D MRI volume (whole brain, 256 X 256 X 128 pixels, 3 mm thick at 0.5T) was also acquired.

2.2.4.2 – Scanning methodology in fMRI (for Chapter 7)

Participants were scanned on a 3T Bruker scanner using a head coil, at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital in Cambridge. Functional images were collected using 21 slices covering the whole brain (slice thickness 4 mm, inter-slice distance 1 mm, in-plane resolution 3.91 x 3.91 mm) with an echo planar imaging sequence (TR = 3.02s, TE = 115ms, flip angle = 90 degrees).

2.2.4.3 – Ethical approval for subjects

All studies received approval from the Cambridge Health Authority Local Research Ethics Committee (LREC). For PET studies, only males over 21 and females past the menopause were allowed to be scanned (so that there was no risk of pregnant women being scanned). For the fMRI studies, both males and (non-pregnant) females over the age of 18 were allowed to be scanned.

2.2.4.4 – Details of subject recruitment

Subjects used for all neuroimaging studies were recruited either by local advertisements or via the CBU subject panel. Subjects were carefully screened beforehand to ensure that they were in good physical health, that there was no history of psychiatric intervention, neurological damage, or any form of brain trauma whatsoever. In addition, for fMRI, any metal implants (except for fillings) were grounds for exclusion due to safety concerns for the subject.

All subjects were right handed, under 45 and fully cognisant of the relevant procedure that they would be involved in. All subjects were paid approximately 25 pounds for participation.

There was no reason to exclude any subject from the data due to brain abnormalities, but a small number were excluded due to excessive head movement in the scanner, making accurate normalisation and effective realignment preprocessing untenable.

2.3 – Neuropsychological testing of frontal lobe patients

As mentioned in 2.2, there is still a use for examination of the deficits of patients with focal injuries, since an impairment implies that the damaged region is critical for that function. Although this is generally assumed, there are minor methodological limitations with this approach. If no deficit is discovered, this may mean that cortical plasticity has rectified the impairment, rather than that there is no connection between the damaged brain area and a given psychological process. If there is a deficit, it is

possible that the relevant process is more crucially connected with an intact region, but that a less crucial, or earlier, part of the network has been damaged. Again, confirmatory evidence from other sources is highly useful in making conclusions based on patient data.

Patients for the study reported in chapter 5 were recruited from the Cambridge Cognitive Neuroscience Research Panel (CCNRP). This is a database of patients with focal neurological damage, who are willing to participate in neuropsychological studies. Almost all such patients have been through Addenbrooke's Hospital in Cambridge, and most live in the East Anglia region. Patients were paid approximately 5 pounds for their participation, and were all tested in their own homes.

For as many patients as was practically possible, a structural MRI scan was collected in order to ascertain more accurately the site and extent of lesion. This scan had approximately a 1mm x 1mm x 1mm spatial resolution. The lesions were assessed and subsequently described by a visiting neurologist at the MRC CBU, Dr Facundo Manes. Descriptions of aetiology can be found in chapter 5.

The CCNRP has the approval from the Cambridge Health Authority Local Research Ethics Committee for the testing of patients on the panel.

2.4 – Presentation of Stimuli

Stimuli for all experiments in this thesis were presented on the operating system Microsoft Windows 98, and were written in the programming language Visual Basic 6. The fMRI study had scanner and timing triggers added to the program in the form of an application programming interface (API) written by Rhodri Cusack of the MRC

CBU. The video presentation for the experiment in chapter 7 utilised Microsoft Direct X Media scripts.

2.5 – Analysis of behavioural data

All analyses were either carried out using Excel or SPSS software. Exploratory analyses were first carried out on all behavioural data collected (for instance, reaction times). For data that satisfied assumptions for parametric analysis, either a Student's t-test or an analysis of variance (ANOVA) were carried out. These analyses were able to ascertain whether differences between factors were significant and in the case of an ANOVA, whether any interactions existed between factors.

Chapter 3: The Role of Spatial Configuration in Tests of Working Memory Explored with PET

3.1 - INTRODUCTION

In recent years, the concept of working memory has been described and discussed in various ways although, most commonly, as a cognitive system for both the temporary storage and manipulation of information (Baddeley 1986; Baddeley 1992). Evidence from the study of patients with excisions of frontal cortex (Petrides and Milner 1982; Owen, Downes et al. 1990; Shallice and Burgess 1991; Owen, Morris et al. 1996; Morris, Rowe et al. 1999), from lesion and electrophysiological recording work in non-human primates (Petrides and Milner 1982; Wilson, Scalaidhe et al. 1993; Petrides 1994; Rao, Rainer et al. 1997; Rainer, Asaad et al. 1998; Rainer, Asaad et al. 1998; Asaad, Rainer et al. 2000; Fuster, Bodner et al. 2000; Petrides 2000; Wallis, Anderson et al. 2001), and from functional neuroimaging studies in humans (Paulesu, Frith et al. 1993; Petrides, Alivisatos et al. 1993; D'Esposito, Detre et al. 1995; Coull, Frith et al. 1996; Owen, Doyon et al. 1996; Owen, Evans et al. 1996; Smith, Jonides et al. 1996; Barch, Braver et al. 1997; Braver, Cohen et al. 1997; Cabeza and Nyberg 1997; Cohen, Perlstein et al. 1997; Courtney, Ungerleider et al. 1997; Jonides, Schumacher et al. 1997; Owen 1997; Bechara, Damasio et al. 1998; Carlson, Martinkauppi et al. 1998; Courtney, Petit et al. 1998; Owen, Stern et al. 1998; Grady 1999; LaBar, Gitelman et al. 1999; Owen, Herrod et al. 1999; Postle, Berger et al. 1999; Smith and Jonides 1999; Cabeza and Nyberg 2000; Duncan and Owen 2000; Owen 2000; Prabhakaran, Narayanan et al. 2000; Rowe, Toni et al. 2000; Pochon, Levy et al. 2001), suggests that

the lateral frontal cortex plays a critical role in certain aspects of working memory, although no consensus has been reached regarding the fractionation of function within this region. Until recently, one prevalent view has been that working memory processes are organised according to the type (e.g. domain) of information being processed, with dorsolateral frontal regions being concerned principally with memory for spatial material, whilst the anatomically and cytoarchitectonically distinct ventrolateral frontal regions subserve memory for non-spatial material (Wilson, Scalaidhe et al. 1993; Goldman-Rakic 1998). In general, however, neither functional neuroimaging studies in humans (Owen 1997; Owen, Stern et al. 1998; Owen 2000) nor electrophysiological recording studies in the monkey (Rao, Rainer et al. 1997; Rainer, Asaad et al. 1998; Fuster, Bodner et al. 2000), have provided convincing support for this 'domain-specific' model of lateral frontal-lobe function.

An alternative model for understanding the prefrontal cortex and its role in working memory has been proposed by Petrides (Petrides 1994; Petrides 1998). According to that model, basic memory functions, including storage and immediate processing of incoming and recalled information, are carried out, not within the frontal lobes, but rather within sensory specific and multimodal posterior association areas in the parietal and temporal cortices. The frontal lobes receive and act upon this information i) via bi-directional connections between posterior cortical association areas and ventral frontal regions, which, in turn, are closely connected to the mid-DLPFC and ii) via connections between dorsal regions of the frontal cortex and the medial temporal lobe. Thus, according to this view, the VPFC constitutes a critical point of contact between posterior cortical regions and the entire lateral frontal cortex. In this capacity, it is assumed to be essentially involved in various low level 'executive' processes, such as comparisons between, or judgements about the

occurrence or non-occurrence of remembered stimuli and the initiation of explicit (i.e. intentional), retrieval of information from posterior association cortex. In contrast, the mid-DLPFC is assumed to be recruited only when active manipulation or 'monitoring' of information is required within memory (Petrides 1994; Petrides 1998).

The VPFC and its role in aspects of working memory has been investigated recently in a series of studies using PET and fMRI (Owen, Evans et al. 1996; Owen, Herrod et al. 1999; Owen 2000). For example, Owen et al. (Owen, Evans et al. 1996; Owen, Herrod et al. 1999) used a variant of the Corsi Block Tapping ('spatial span') task (Milner 1971), which required subjects to hold sequences of five previously presented spatial locations in memory, and then to respond directly by touching those same locations following a delay. In the two studies, a significant rCBF increase was observed at almost identical co-ordinates within the right VPFC (area 47). In a second task that required the subjects to retrieve and execute a previously learned fixed sequence of responses the same ventrolateral frontal region was significantly activated (Owen, Evans et al. 1996).

A direct analogue of the spatial span task has recently been used to examine whether a similar role could be identified for this region of the right VPFC in the verbal domain (Owen, Lee et al. 2000). During one experimental task, subjects were required to hold a sequence of auditorily presented numbers in memory (e.g. 7, 3, 8, 2, 9), and then to respond by (verbally) producing those numbers, in order, following a short delay (e.g. 7, 3, 8, 2, 9). Again, a significant increase in rCBF was observed in the right mid-VPFC (area 47).

A visual analogue of these span tasks, which uses simple line drawings as stimuli, has recently been developed to investigate whether the VPFC plays a similar role in the visual domain (Lee, Manes et al. 2000). Subjects were PET scanned while

reproducing previously learned (i.e. prior to scanning) '6-stroke' Chinese characters on a touch sensitive computer screen. Again, activation was observed in the mid-VPFC (area 47).

While the results described above suggest a common polymodal role for the VPFC in working memory, recent findings from the episodic memory literature suggest that this role may generalise to other memory domains. For example, Fletcher et al.(Fletcher, Shallice et al. 1998) have reported activation in a very similar region of the right mid-VPFC during a paired-associates task that required subjects to retrieve previously learned category exemplars, in response to a series of category names. Such similarities strongly suggest that the various processes that are necessary for performing particular working memory tasks or declarative ('long-term') memory tasks may be drawn from a single set of underlying components.

One possible general role for the VPFC in memory may be to trigger active low-level encoding strategies such as rehearsal and to initiate explicit (i.e. intentional) retrieval (Owen 2000). In the case of working memory tasks, this would correspond to the relatively straightforward mapping of stimuli to responses such as that which is assumed to occur in spatial and digit span tasks (Owen, Evans et al. 1996; Owen, Herrod et al. 1999; Owen, Lee et al. 2000), or even simple delayed matching to sample paradigms (Elliott and Dolan 1999). In the case of long-term episodic memory (e.g. verbal paired associate learning), these 'active' encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g. a category exemplar) to a specific stimulus (e.g. a category name) (Fletcher, Shallice et al. 1998; Fletcher, Shallice et al. 1998).

The DLPFC, on the other hand, is generally activated in memory tasks when more complex executive processes are required, including the generation and

execution of mnemonic strategies which may supplement the more basic memory processes that facilitate encoding and retrieval (Petrides 1994; Owen, Morris et al. 1996; Petrides 1998). For example, in one recent study (Owen, Evans et al. 1996), a self-ordered spatial working memory task was employed which required that subjects generate an encoding strategy for determining the optimal sequence of choices; activation was observed in both dorsal and ventral frontal-lobe areas.

Although the spatial span task has been repeatedly associated with activation in the VPFC(Owen, Evans et al. 1996; Owen, Herrod et al. 1999), as a general paradigm it is relatively unconstrained. That is to say, in its usual imaging format with stimuli randomly distributed around a computer screen the overall influence of mnemonic, strategic and spatial processes on performance is unclear. In this preliminary study, therefore, a new version of the spatial span task was developed which would allow for such processes to be systematically manipulated during later follow-up studies. In this version of the task a regular 2 X 4 array of stimuli was used instead of the more usual randomly configured array. In the first instance, and given the strong association between tasks of this type and activation in the VPFC, the task was validated using PET with the strong expectation that this area would be significantly activated.

3.2 - METHODS

3.2.1 - Image Acquisition and Data Analysis

See chapter 2 (section 2.2.4.1) for scanning methods. Three separate scans for each of the two conditions were collected. Five additional scans were also conducted using a further task not relevant here. Using SPM 96 (provided by the Wellcome Department

of Cognitive Neurology, London, UK), the 11 PET scans for each subject were realigned by bilinear interpolation, using the first scan as a reference, to create a mean image. The 11 PET scans were then realigned a second time by bilinear interpolation, using the mean image as a reference, to create a second mean image. The MRI volume for each subject was re-sliced and co-registered with the second mean image. The co-registered PET data were normalised using bilinear interpolation, based on the T1 image (the MNI standard brain, based on 310 MRI images). The normalised images were then smoothed using an isotropic Gaussian kernel with full width half maximum (FWHM) set at 16mm.

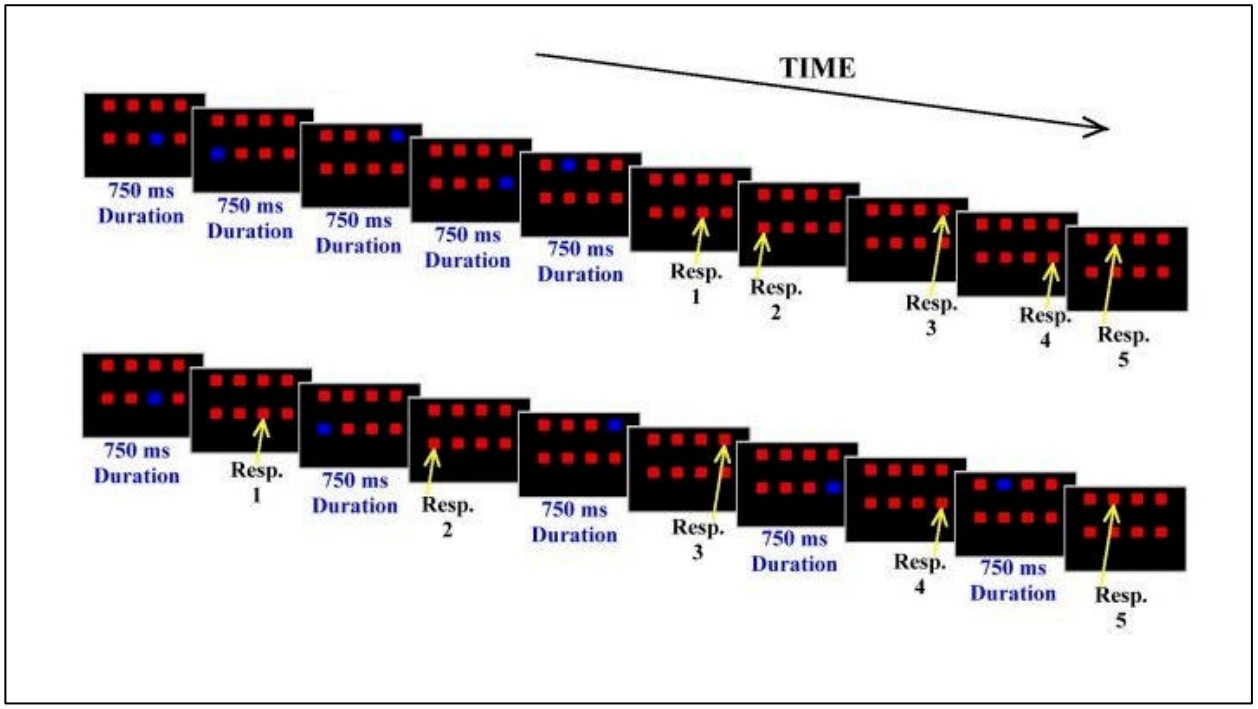
For the condition analysis, a subject specific ANCOVA (analysis of covariance) model was fitted to the data at each voxel, using SPM96. All images were scaled to a grand mean value of 50. The grey matter threshold for each voxel over the whole brain was set at 0.8. Given recent evidence suggesting that head movement across scans is a confounding factor in many PET studies (Brett, Bloomfield et al. 1999), both time (scan order) and head movement data in the three planes of rotation and three dimensions of translation were set as confounding factors. This procedure is believed significantly to improve sensitivity and reduce noise in the data.

For the whole of the brain, an exploratory search involving all peaks within the grey matter (volume 600$cm^{3)}$ was conducted and the threshold for reporting a peak as significant was set at $p<0.05$, corrected for multiple comparisons (Worsley, Evans et al. 1992; Worsley, Marrett et al. 1996). This equates to a threshold Z score of >4.41.

3.2.2 - Subjects

Ten normal right-handed volunteers, all males, participated in the study (age range=21 to 41, mean age 26.5). Each subject underwent the eleven PET scans and one MRI scan within a single session. All subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research and Ethics Committee.

Figure 3.1. Examples of trials from the two conditions in the PET experiment. Top Row: For the span task subjects were shown a sequence of five spatial stimuli, which they were then required to copy by touching the locations of the stimuli in the order that they had appeared. Bottom Row: For the visuomotor control task, subjects were required to touch each stimulus as it appeared.



3.2.3 - Stimuli and Testing Conditions

The stimuli used in both conditions were eight red squares (3.5cm x 3.5cm) presented on a black background, on a high-resolution, touch-sensitive monitor. The stimuli were arranged in two rows of four, one above the other (see figure 3.1), with 3.5 cm between squares horizontally and 7cm between squares vertically. This was done so

as to simplify the task used previously. The monitor was suspended approximately 50cm in front of the subject's eyes and was comfortably within reach.

Span Condition

In this condition (see figure 3.1, top row) one of the eight red squares would turn blue for 750 milliseconds (ms) before turning red again. As soon as the first square turned back to red a second square would turn blue for 750 ms and so on, until five of the eight red squares had turned blue. At this point, the subjects were required to respond by touching the five squares on the touch-sensitive monitor in the order that they had just appeared. They were instructed to respond as fast as they could, but not so fast that they started making mistakes. Subjects were given an interval of 3750 ms within which to make their responses, after which another sequence was presented and so on until the end of the scan. This procedure was very similar to that used in previous PET studies of spatial span (Owen, Evans et al. 1996; Owen, Herrod et al. 1999), except for the ordered spatial arrangement of the array.

Visuomotor Control Condition

For this task (see figure 3.1, bottom row), one of the eight red squares would turn blue for 750 ms, and then turn red again. Once the square had returned to red, the subject was required to respond by touching it as fast as they could, but without making any mistakes. They were given 750 ms within which to make their choice, after which another square would turn blue for 750 ms, and so on until the end of the scan.

The choice of which red squares would turn blue and in which order was pseudo-randomly set in both conditions, so that particular span sequences (or

particular squares in the case of the visuomotor control condition), did not repeat contiguously. The task period for each PET scan lasted 100 seconds, with an onset of 10 seconds prior to the 90 second scan itself. In addition, a 100 second practice task was given to each subject approximately four minutes before each scanned task. This ensured that the subject understood the task, and was performing proficiently. The scans were separated by eight minutes. The two tasks required an identical number of responses (60 per scanned condition). The scan order was designed in three blocks, with each block comprising the two conditions performed in random order. Scan order was pseudo-randomly varied between subjects.

3.3 - RESULTS

3.3.1 - Behavioural Results

To score the span task, each trial was given a maximum of five marks (since five responses were required) and a correct mark was given for each square touched in the right spatial location and in the right temporal position. The average number of marks achieved for the span task was 4.3 per trial.

3.3.2 - Blood Flow

When the visuomotor control task was subtracted from the span task (see Table 3.1 and Figure 3.2a), a significant increase in activity was observed in the right DLPFC, both in mid (BA 9/46) and more anterior portions (BA 46). In the left hemisphere, no significant PFC increases in activation were observed. Significant increases in activity

were also observed in the anterior cingulate cortex (BA 24/32), in the right mid-parietal region (bordering BA 40 and BA 7), in the right medial superior parietal lobule (BA 7), and in the right extrastriate cortex (BA 18). The cerebellum, on the left, was the only non-cortical area to show a significant increase in activation.

In contrast, when the span task was subtracted from the visuomotor control task (see Table 3.1 and Figure 3.2b), significant increases in rCBF were observed in the left medial frontopolar region (BA 10), in left premotor cortex (BA 6) and medially in the left supplementary motor area (BA 6). Outside of the frontal lobe, significant increases in rCBF were observed in the left inferior temporal cortex laterally (BA 20), the right anterior temporal cortex (BA 21), and the left inferior parietal lobule (BA 39).

Figure 3.2. PET subtraction images rendered onto the surface of a standard (MNI) 3D MRI. a) Span task minus visuomotor control task. b) Visuomotor control task minus Span task. For each image, all activation foci above significance ($p<0.05$, corrected) are shown.

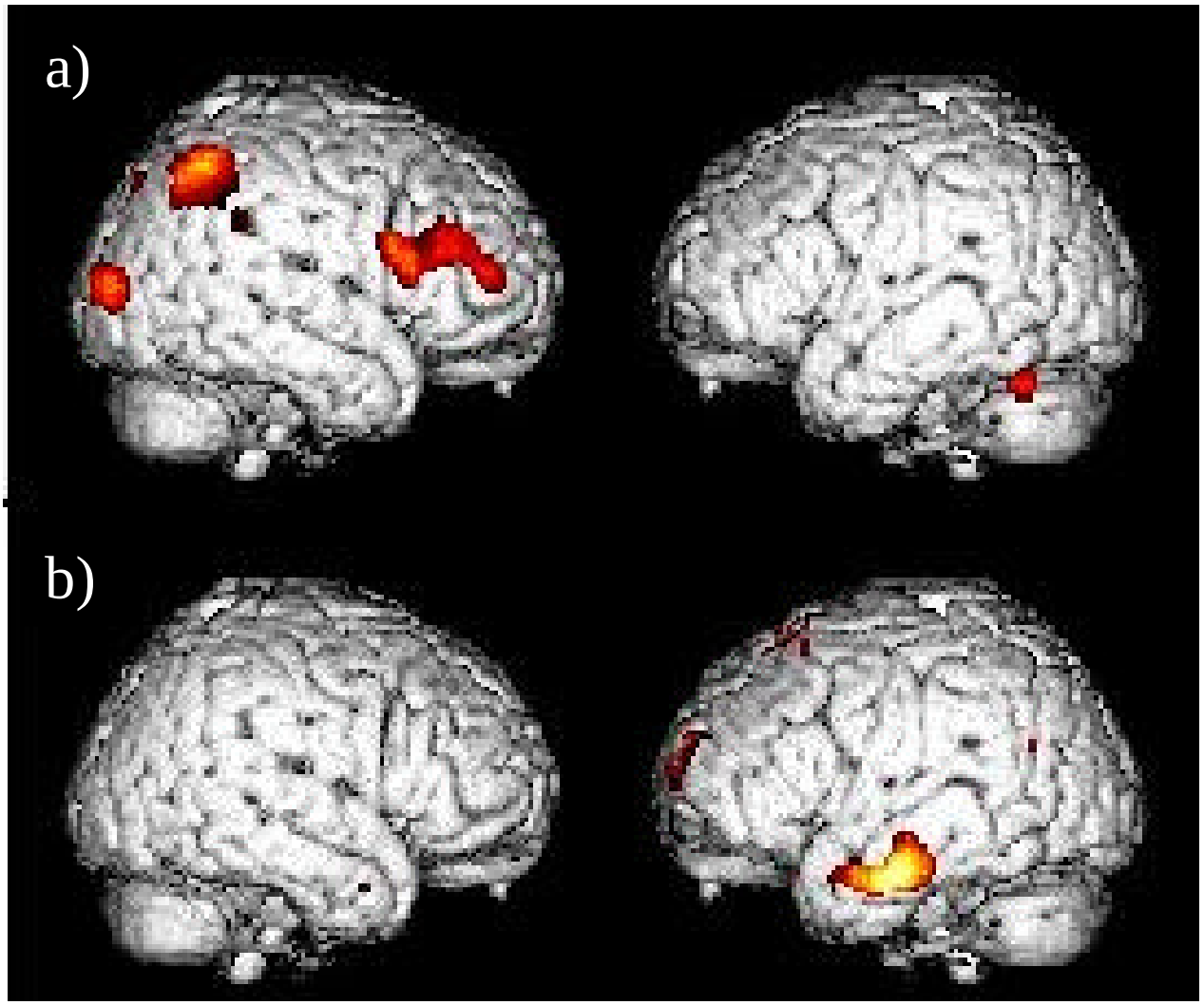


Table 3.1. Foci of peak activation for each subtraction.

Regions of interest	Brodmann area/s	Stereotaxic co-ordinates			Z-statistic
		x	y	z	
Span minus Visuomotor Control					
LEFT					
Cerebellum		-32	-60	-28	4.73
RIGHT					
Anterior DLPFC	46	44	48	12	4.83
mid DLPFC	9/46	38	30	24	5.33
Anterior Cingulate Cortex	24/32	6	8	42	5.16
Mid Parietal Cortex	40/7	36	-50	46	5.97
Medial Superior Parietal Cortex	7	8	-58	44	5.20
Extrastriate Cortex	18	34	-88	6	5.30
Visuomotor Control minus Span					
LEFT					
Medial Frontal Pole	10	-10	60	20	5.92
Supplementary Motor Area	6	-6	24	64	5.06
Premotor Cortex	6	-22	20	58	4.52

Inferior Mid-temporal Cortex	20	-44	-4	-24	5.50
Inferior Mid-temporal Cortex	20	-54	-18	-22	5.69
Inferior parietal lobule	39	-48	-64	24	4.47
RIGHT					
Anterior Temporal Cortex	21	52	6	-26	4.50

3.4 - DISCUSSION

This study set out to replicate the results of previous studies, using a simplified version of the spatial span task, which has consistently been shown to activate the VPFC (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). However, compared to the visuomotor control task, the present spatial span task yielded significant increases in rCBF in the right DLPFC, but not the VPFC. This is a truly surprising finding given that the equivalent comparisons of two previous PET studies activated only the VPFC (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). In both of these previous studies a formally identical control to the current study, of the form of a 1-span task, was subtracted from alternative versions of the spatial 5 span task. Parallel investigations have reported similar findings using verbal (Owen, Lee et al. 2000) and visual (Lee, Manes et al. 2000) analogues of the same general procedure.

It is important to emphasise that the two anatomical regions under consideration here, the mid-ventrolateral and mid-dorsolateral frontal cortices, are quite distinct, both anatomically and cytoarchitectonically, and are easily resolved, even with the relatively limited spatial resolution of PET. In the human brain, the mid-DLPFC comprises the mid-part of the superior and middle frontal gyri above the

inferior prefrontal sulcus, a considerable proportion of this cortex lying within the depths of the middle frontal sulcus (Petrides and Pandya 1994; Pandya and Yeterian 1998). The mid-VPFC, on the other hand, comprises the tissue which lies on the lateral surface below the inferior frontal sulcus.

Aside from trivial differences in stimulus onset and offset times, the main difference between the current form of the spatial span task and that used in previous studies is the spatial layout of the stimuli. In previous studies (Owen, Evans et al. 1996; Owen, Herrod et al. 1999), a random spatial arrangement was used, while in the present study, the arrangement was more orderly in nature, forming a 2 x 4 matrix. It therefore seems possible that simply changing the configuration of the stimulus array from a random (Owen, Evans et al. 1996; Owen, Herrod et al. 1999) to an ordered spatial design, may shift the focus of activation from the mid-VPFC to the mid-DLPFC.

An alternative explanation is simply that, due to the inherently noisy nature of PET imaging, this result is a chance anomaly. In order to investigate whether differences in the level of structure of the array in the spatial span task truly leads to differences in activation patterns within the lateral PFC, a second PET experiment was therefore carried out so that the two spatial span variants could be directly compared within subjects.

Chapter 4: PET study comparing two types of a spatial span task

4.1 - INTRODUCTION

The PET study of the previous chapter provided preliminary evidence to suggest that, under certain circumstances, the DLPFC and VPFC regions may be differentially activated by tasks which neither vary with respect to stimulus modality nor place greater demands on overall cognitive demand (Bor, Duncan et al. 2001). In that study, a variant of the classic spatial span task (Milner 1971) was shown to produce significant activation in the DLPFC. Previous studies, using versions of the same task, have reported ventrolateral, but not dorsolateral, frontal activation and have suggested that this reflects the retrieval demands of this simple working memory task (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). The only real difference between the task of chapter 3 and those used previously was in the configuration of the stimulus array, suggesting that simply presenting the information to be remembered within an ordered or 'structured' format may be sufficient to elicit DLPFC involvement. In this study, this hypothesis was investigated directly: two variants of the spatial span task were used to compare the effect on frontal rCBF of structured and non-structured arrays within a single group of healthy volunteers.

It was predicted that while the VPFC would be activated when the non-structured array was employed, the DLPFC would only be activated in the more spatially structured condition.

4.2 - METHODS

4.2.1 - Image Acquisition and Data Analysis

rCBF was measured during two separate scans for each of the three conditions. Six additional scans for each subject were taken during unrelated conditions which will not be discussed here. Using SPM 99 (provided by the Wellcome Department of Cognitive Neurology, London, UK), the 12 PET scans for each subject were realigned by trilinear interpolation, using the first scan as a reference, to create a mean image. The mean PET images for each subject were normalised using bilinear interpolation, based on the PET template. The normalised images were then smoothed using an isotropic Gaussian kernel with FWHM set at 16mm.

For the condition analysis, a subject specific analysis of covariance (ANCOVA) model was fitted to the data at each voxel. All images were scaled to a grand mean value of 50. Proportional threshold masking was set at 0.8. Global calculation was set at mean voxel value.

Given recent evidence suggesting that head movement across scans is a confounding factor in many PET studies (Brett, Bloomfield et al. 1999), *F*-value images were tested to determine whether scan order or any of the six head movement parameters were significantly associated with rCBF values. Those parameters with significant associations (scan order, translation in all directions, rotation in y and z) were set as covariates of no interest. This procedure is believed significantly to improve sensitivity and reduce noise in the data.

For the whole of the brain, an exploratory search involving all peaks within the grey matter (volume 600cm$^{3)}$ was conducted and the threshold for reporting a peak as significant was set at $p<0.05$, corrected for multiple comparisons (Worsley, Evans et al. 1992; Worsley,

Marrett et al. 1996). This relates to a threshold Z score of >4.41 . In addition to this, a Worsley correction (Worsley, Evans et al. 1992) was applied to the frontal lobes (again, $P<0.05$, with a Z threshold above 3.90). This method involves applying a formula to a specified region of interest in the brain (e.g. the frontal lobes) so that a corrected probability of observing a peak of activity in this region can be calculated. Since an a priori prediction that these spatial span tasks would activate areas within the frontal lobes could clearly be made on the basis of previous experiments (Owen, Evans et al. 1996; Bor, Duncan et al. 1999; Owen, Herrod et al. 1999), I felt fully justified in applying this correction.

4.2.2 - Subjects

Twelve normal right-handed volunteers, all males, participated in the study (age range=21 to 38, mean age 25.6). Each subject underwent twelve PET scans (six of which are not reported here) within a single session. All subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research and Ethics Committee.

4.2.3 - Stimuli and Testing Conditions

The stimuli used in all conditions of this study were eight red squares (3.5cm x 3.5cm) presented on a black background, on a touch-sensitive monitor. The stimuli were presented in two types of array (see figure 4.1). For the “structured” array, there were four columns of two rows, with 3.5 cm between squares horizontally and 7cm between squares vertically. For the “non-structured” array, the squares were arranged randomly on the screen, remaining in the same locations for the duration of the condition. The monitor was approximately

50cm away from the subject's head.

Structured Array Span Condition

In this condition (see figure 4.1a), using the "structured" 4x2 array, one of the eight red squares would turn blue for 500 ms before turning red again. 250 ms after this, a second red square would turn blue for 500 ms and so on, until five of the eight red squares had turned blue. Once the last square had turned red again, the subjects were required to respond by touching the squares on the touch-sensitive monitor in the order that they had just changed colour. They were instructed to respond as fast as they could, but not so fast that they started making mistakes. Subjects were given a maximum of 3750 ms with which to respond, after which the next span would start.

Non-structured Array Span Condition

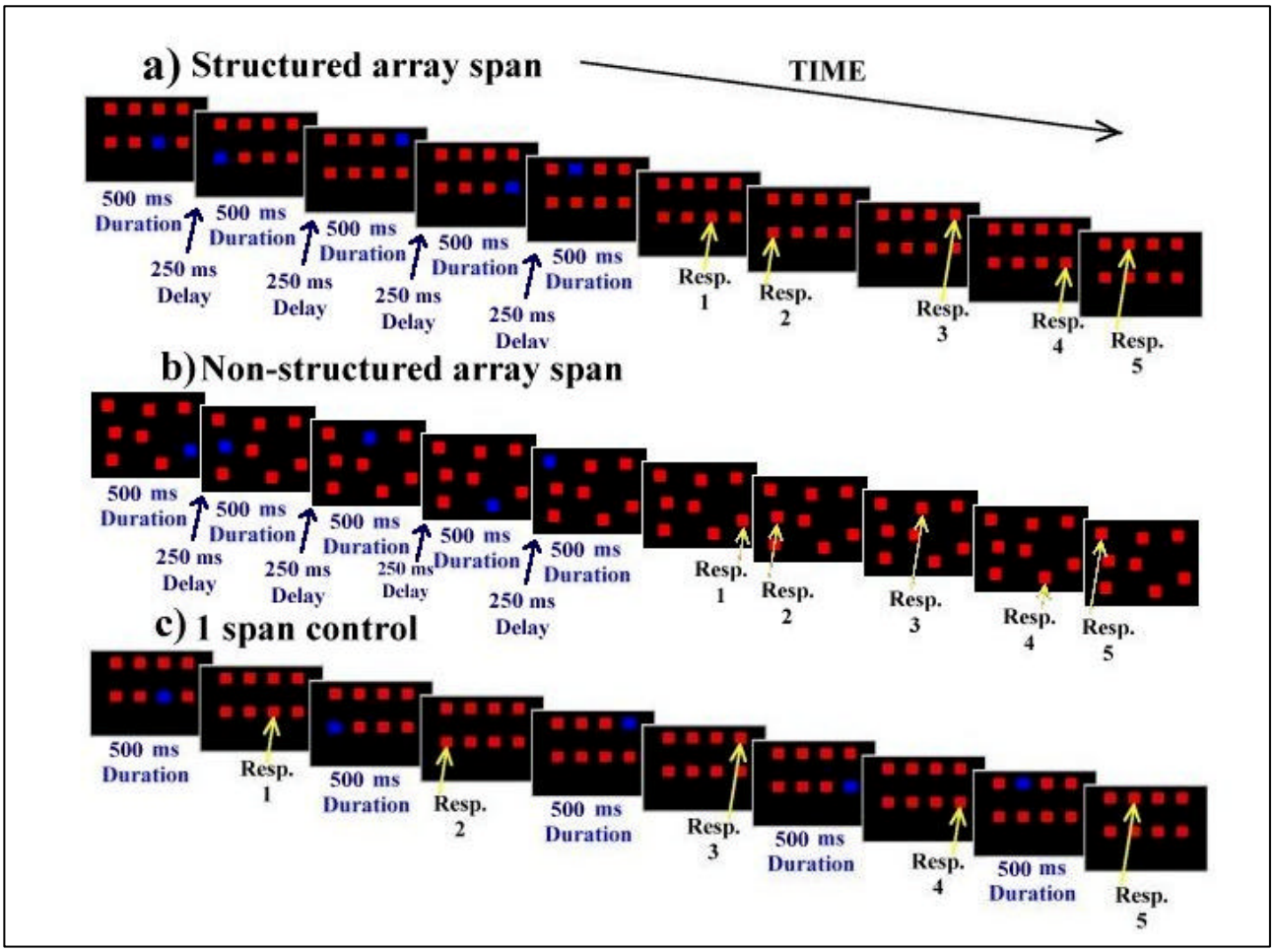
The procedure was identical to that for the structured span condition , except that the "non-structured" array was used (see figure 4.1b). Although the array was the same throughout a scanned condition, the squares were presented in different non-structured locations in each of the 2 scans.

Visuomotor Control Condition

For this task (see figure 4.1c), one of the eight red squares, in a "structured" 4x2 array, would turn blue for 500 ms, and then turn red again. The subjects were required to respond by touching the square that had just turned blue as fast as they could, but without making any mistakes. They were given 1000 ms within which to make their choice, after which a different square would turn blue for 500 ms, and so on.

The choice of which red squares would turn blue and in which order was pseudo-randomly set in all conditions, so that particular span sequences in the span tasks, or particular squares in the control, did not repeat contiguously. Each of the three conditions was performed twice. The testing phase for each PET scan lasted 100 seconds, with an onset of 10 seconds prior to the scan. In addition, a 100 second practice task for the upcoming condition was given to each subject approximately four minutes before each scanned task. This was carried out to ensure that the subject understood the task, and was performing proficiently. The scans were separated by eight minutes. The three different tasks required an identical number of responses (60 per scanned condition). The scan order was designed in two blocks of three, with each block comprising the three different conditions, and both blocks having a different condition order. Scan order was pseudo-randomly varied between subjects.

Figure 4.1 - Examples of trials from each of the three conditions in the PET experiment. A) For the structured array span task subjects were shown a sequence of spatial stimuli, which they were required to copy by touching the locations of the stimuli in the order that they appeared. B) For the non-structured array span task, subjects performed exactly the same task as for the structured span task. C) For the control condition (PET only), subjects were required to touch the last stimulus to turn blue. For each stimulus and response cycle of the 5 span tasks, five stimulus and response cycles were carried out in the control task.



4.3 - RESULTS

4.3.1 - Behavioural Results

For the visuomotor control condition, a trial was marked as correct if the single square touched was the correct square for that trial. For the span conditions, in order to allow for a meaningful comparison, each trial had a maximum of five marks (since five responses were required) and a single correct mark was given for each square touched that was in the right spatial location and in the right temporal order. Performance in all three conditions was above 95%. There was no significant difference between the two span conditions in terms of mean reaction time or mean accuracy. There were also no significant order effects; that is, in terms of accuracy between conditions that were performed first and conditions that were performed second.

Subjects were asked after the experiment which of the span tasks they found the most difficult. Of the 10 subjects who expressed a preference, significantly fewer (only 1 subject) judged the structured array span task to be more difficult than the non-structured array span task ($X^2 = 6.40$, df = 1, p = 0.011).

4.3.2 - Cerebral Blood Flow results

Non-structured array span task vs control

When the control task was subtracted from non-structured array 5 span task (see Table 4.1a and figure 4.2a), significant increases in activation were observed bilaterally in the VPFC (BA 45/47). The co-ordinates of this region were very close to those that have been reported previously in imaging studies using spatial span tasks with similar non-structured arrays

(Owen, Evans et al. 1996; Owen, Herrod et al. 1999). A significant increase in rCBF was also observed more posteriorly, in the right superior parietal cortex (BA 7).

When the non-structured array span task was subtracted from the control task (see Table 4.1b), significant increases in rCBF were observed in the left medial frontal pole (BA 10), the premotor cortex bilaterally (BA 8), the left supplementary motor area (BA 6) and the left primary motor cortex (BA 4). Outside of the frontal lobes, significant increases in activation were only observed in the striate cortex (BA 17).

Structured array span task vs. control

When the control task was subtracted from the structured array span task (see Table 4.1c and Figure 4.2b), a significant increase in activity was observed in the right mid-DLPFC region (Brodmann's area (BA) 9/46), as well as in the right mid VPFC region (BA 45/47). Significant increases in activity were also observed more posteriorly in the right superior parietal cortex (BA 7), and right extrastriate cortex (BA 18).

In contrast, when the structured array span task was subtracted from the control task (see Table 4.1d), significantly increased activation was only observed in the left motor cortex (BA 4).

Figure 4.2 - Schematic illustration of the PET subtraction images rendered onto the surface of a standard (MNI) 3D MRI. a) Non-structured array 5 span task minus control task b) Structured array 5 span task minus control task. For each image, only activations above the Worsley correction (Worsley, Evans et al. 1992) threshold of Z=3.91 are shown. DLPFC = dorsolateral prefrontal cortex; VPFC = ventrolateral prefrontal cortex

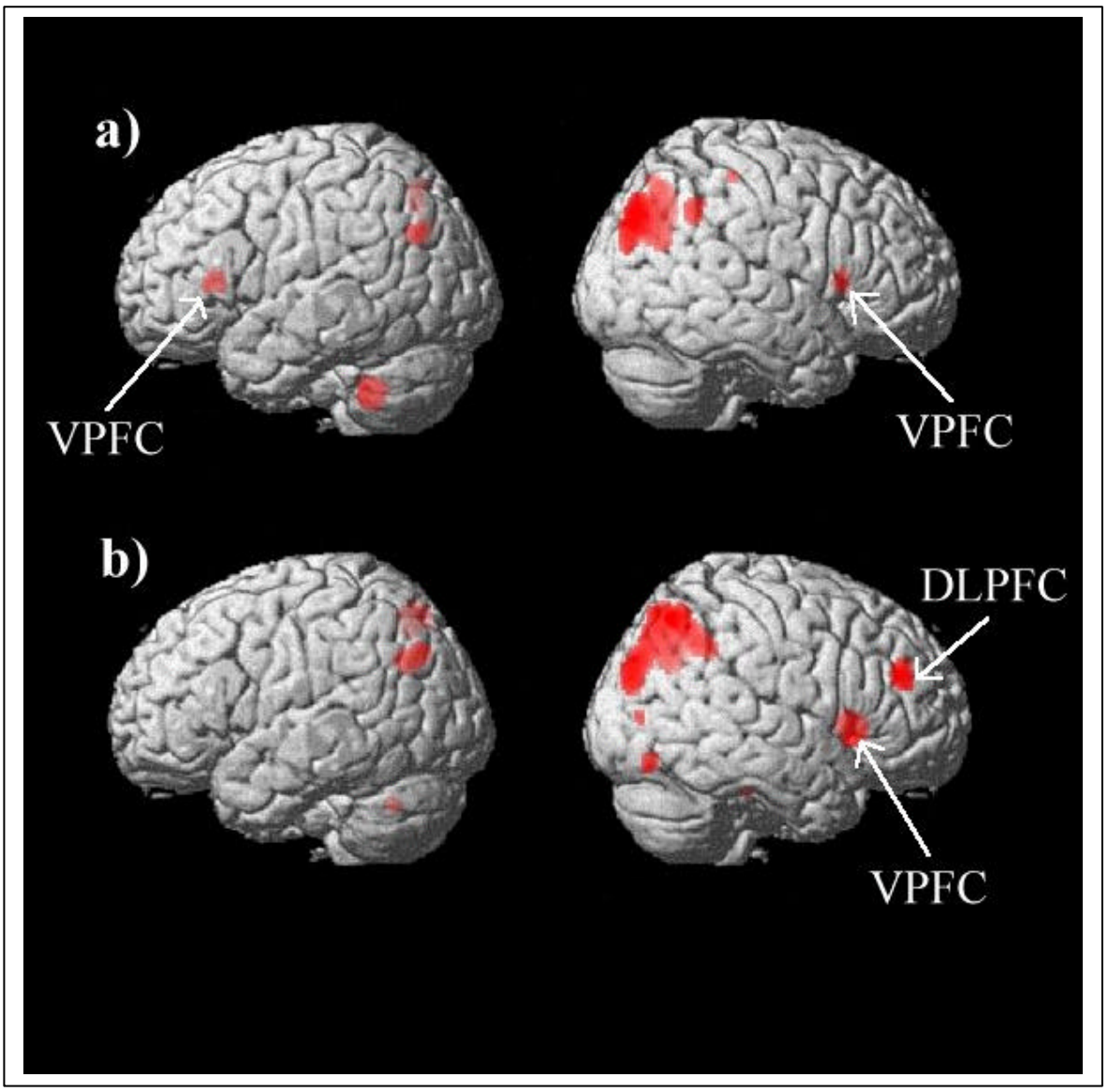


Table 4.1. Activation foci in this table represent peaks of statistically significant changes in normalized rCBF. The p values for non-frontal regions are corrected for multiple comparisons (p=0.05). The p values for frontal regions have a Worsley correction (Worsley, Evans et al. 1992) applied to them (p=0.05).

Regions of interest	Brodman area/s	Stereotaxic co-ordinates			Z-statistic	P-Value (corrected)
		x	y	z		
a) Non-structured array span minus control						
LEFT						
VPFC/White matter		-22	26	10	4.10	0.024*
RIGHT						
VPFC	45/47	32	18	6	3.91	0.047*
Superior parietal cortex	7	20	-70	32	5.58	<0.001
Superior parietal cortex	7	36	-78	38	4.64	0.028
b) Control minus non-structured array span						
LEFT						
Medial Frontal Pole	10	-4	66	-4	3.97	0.038*
Premotor Cortex	8	-44	12	42	4.09	0.025*
Motor Cortex	4	-22	-16	58	5.80	<0.001
Supplementary motor area	6	-12	-16	52	5.15	0.003

RIGHT						
Premotor Cortex	8	0	42	50	3.99	0.036*
Striate Cortex	17	18	-94	4	4.60	0.033
c) Structured array span						
minus control						
LEFT						
(No significant activations)						
RIGHT						
Mid DLPFC	9/46	38	40	26	4.12	0.023*
Mid VPFC	45/47	34	18	0	4.71	0.002*
Superior parietal cortex	7	42	-64	52	4.74	0.019
Superior parietal cortex	7	20	-66	46	5.13	0.003
Extrastriate cortex	18	36	-84	30	4.52	0.046
d) Control minus structured						
array span						
LEFT						
Motor Cortex	4	-22	-16	58	7.30	<0.001
RIGHT						
(No significant activations)						

*Sites within the frontal lobe having probabilities calculated using the Worsley Correction (Worsley, Evans et al. 1992)

4.4 - DISCUSSION

In the current PET study, the non-structured array span task yielded significant activation in the mid VPFC. Similar results have been reported previously in two PET studies using comparable stimuli (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). By contrast, the structured array span task yielded significant increases in the mid VPFC *and* the mid DLPFC, when compared with the visuomotor control. These results confirm that varying the configuration of stimuli in a spatial span task can alone modulate the precise pattern of activity observed in the lateral PFC. Furthermore, virtually all of the subjects reported that the structured array was the easier span task (although all performed at ceiling levels), suggesting that the increase in DLPFC activation does not simply reflect a concomitant increase in cognitive demand.

It should be noted that when the two span conditions were compared directly, no significant activations where found in either the DLPFC or the VPFC. There is ample evidence, however, to suggest that this reflects the power constraints of the PET methodology. Thus, in two recent PET studies, subjects were given a task formally identical to the non-structured array span task of this study (Owen, Doyon et al. 1996; Owen, Herrod et al. 1999). In both cases, significant activation was observed in the VPFC, but not in the DLPFC when the task was compared to a control task similar to that used in the current study. In both the PET study of the current chapter and a separate PET study using an equivalent structured array (chapter 3), significant increases in activation were observed in the DLPFC (Lee, Robbins et al. 2000; Bor, Duncan et al. 2001).

This pattern of activation cannot easily be explained in terms of existing "process-specific" models of lateral frontal cortex organisation (Petrides 1994; Petrides 1998; Owen, Herrod et al. 1999). For example, there is no clear difference in level of manipulation or

"monitoring" (see 1.4.1.2) in memory required by the two span conditions. These results also run counter to the "modality-specific" models (see 1.4.1.1) of lateral frontal organisation (Wilson, Scalaidhe et al. 1993; Goldman-Rakic 1998), since both tasks seem to have a significant and similar spatial component, while only one activates the DLPFC. Finally, these results run counter to the common observation that DLPFC activation is largely responsive to the level of cognitive demand per se (see 1.4.2.1) (Duncan, Burgess et al. 1995; Duncan and Owen 2000; Duncan, Seitz et al. 2000). If anything, the easier task (structured span) produced greater lateral frontal involvement than the more difficult task.

The question arises therefore as to what psychological explanation would best fit the pattern of results observed in this PET study. The 'executive' functions of the lateral prefrontal cortex have been described in a number of ways, although in general these descriptions do not include useful, well-specified components (Baddeley 1992; Petrides 1994; Fuster 1997; Baddeley and Della Sala 1998; Petrides 1998; Owen, Herrod et al. 1999; Fuster, Bodner et al. 2000). Moreover, such concepts have proved difficult to define in a way that differentiates them from simple cognitive demand. For example, although complex working memory tasks such as the widely used n-back tasks generally yield greater dorsolateral prefrontal activity than simpler working memory tasks such as the spatial span tests used in the current study (Owen, Herrod et al. 1999), it is unclear whether this involvement reflects the requirement to manipulate information (Petrides 1994; Petrides 1998; Owen, Herrod et al. 1999), the temporal restructuring of that information (Fuster 1997; Fuster, Bodner et al. 2000), task related central executive processes (Baddeley 1992; Baddeley and Della Sala 1998), or just the increase in cognitive demand (Duncan and Owen 2000). The results of this PET study effectively rule out an increase in task demands per se as the primary explanation for activations in the DLPFC. In this study, an increase in lateral

frontal cortex activity was observed in a condition where cognitive load was either equivalent or even easier to another task that failed to activate the DLPFC.

An alternative suggestion for frontal lobe function has been that this region is involved in processing strategies (see 1.4.2.3). Studies using patients with damage to their frontal lobes have suggested that these patients are critically impaired on tasks where some form of strategic control is necessary for optimal performance (Owen, Downes et al. 1990; Shallice and Burgess 1991; Miotto, Bullock et al. 1996; Owen, Morris et al. 1996; Morris, Rowe et al. 1999; Burgess, Veitch et al. 2000).

Recently, neuroimaging studies have provided some support for this idea. Prabhakaran et al. (Prabhakaran, Narayanan et al. 2000) used fMRI to show that integrated features were both easier to remember than non-integrated features, and were associated with increased lateral prefrontal cortex activation. In addition, Savage et al. (Savage, Deckersbach et al. 2001) found a similar result with semantic encoding. They demonstrated that encoding conditions with high levels of semantic clustering were both significantly easier to remember and yielded greater lateral prefrontal cortex involvement. They concluded that lateral prefrontal cortex is involved in the application of strategies to utilise the semantic connections between items.

One alternative explanation, therefore, for the involvement of the DLPFC when structured spatial sequences are used is that this task elicits more mnemonic strategies than the non-structured condition. Specifically, regular patterns formed by the sequence within the structured array might be recognised as relating to configurations (such as squares, triangles, etc.) previously well specified in memory. The DLPFC may then be involved in updating representations of the means to achieve the goal of the task, by remapping some or all of the sequence to features in long term memory. In this way, the DLPFC may play an essential role in selecting appropriate high-level

organisational ‘chunks’ (Miller 1956) which then serve to facilitate memory by reducing the overall cognitive load, while the VPFC, as the common region of activation for both span conditions, might be involved in more purely mnemonic aspects of working memory tasks.

If this explanation for the current data is correct, then it should be possible to demonstrate a performance benefit in healthy controls for the structured array span task, compared to its non-structured equivalent, with a behavioural study employing greater statistical power than the current study. Such a benefit should underlie the greater strategic involvement relating to the structured array span task. In addition, subject reports describing any differential cognitive approaches to the two types of span may provide hints at the form of possible extra strategic involvement for the structured array span version. These predictions will be tested in the following chapter, where a more sensitive version of the span tasks used in the current study will be given to healthy controls.

In addition, since frontal lobe patients are assumed to have a deficit in strategic processing, these patients should be disproportionately impaired on the structured array spatial span task, if this task does indeed have a greater strategic involvement. This suggestion will be tested in chapter 6, where frontal lobe patients will be compared with healthy, matched controls, on the same span tasks as in the following chapter.

Chapter 5: Behavioural study to compare two types of spatial span in healthy controls

5.1 - INTRODUCTION

Results from the PET studies of the two previous chapters raised the question of why simply altering the spatial configuration of a spatial working memory task from a random array to an ordered design de-emphasises the role of the VPFC in favour of more dorsolateral frontal regions. It was suggested that such a difference may be due to greater strategic involvement for the more structured array, possibly due to some form of spatial chunking. If such an interpretation is correct, then it would follow that there should be some form of performance advantage for the structured array, due to greater strategic involvement. In addition, it may be that subjects are aware of differences in style of behaviour between the two tasks and such reports may show that the structured array version of the spatial span task has a greater potential for strategies.

In order to test these hypotheses, a behavioural study was run using similar tasks to the two spatial span tasks of the previous chapter. The key difference, though, was that while the span length in the two previous chapters was fixed at five, the span length of the current study was variable, such that the subject was usually at the level that would produce 50% fully correct responses. In this way, it was hoped that a more sensitive measure of span score could be reached.

5.2 - METHODS

5.2.1 - Subjects

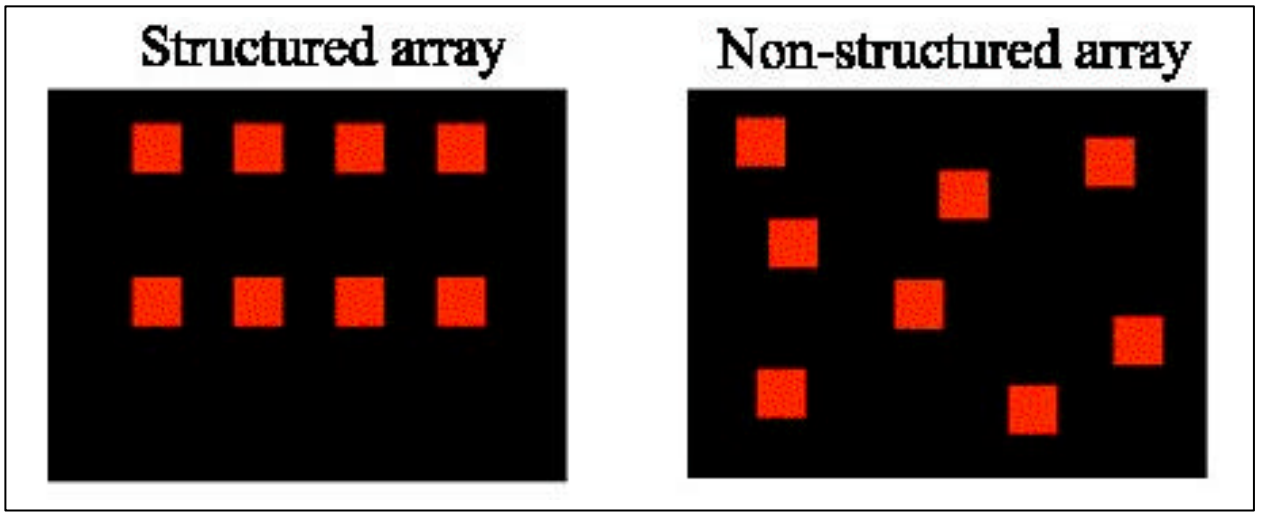
18 healthy subjects, comprising 7 males and 11 females, with a mean age of 30.2, took part in the experiment.

5.2.2 - Stimuli and testing conditions

For each trial, one of eight red squares would turn blue for 750 ms before turning red again. Immediately following this, a second red square would turn blue for 750 ms and so on, until the number of squares that had turned blue equalled the number of the span-length for that trial. Subjects were then required to respond by touching the squares in the order that they had changed colour. If any errors were made in the response, the subsequent trial would begin 4500 ms after that first error. Otherwise, subjects had as much time as they needed to make a fully correct response. The length of the span presented increased by one for the next trial if the subject reproduced the current span without errors, while the subsequent span length decreased by one if the subject made any errors (with a minimum span length of 1 and maximum of 8). Each subject was tested on a randomly distributed spatial array (termed 'non-structured array') of eight red squares and on a more spatially ordered array (termed 'structured array') two by four matrix of squares (see figure 5.1). Both arrays were identical to the two arrays used in the PET study of the previous chapter (see 4.2.3). Half of the subjects were given the non-structured array first and half of the subjects were given the structured array first. For each array, 50 trials were given to the subject and mean span length was computed by averaging the span length for all of the 50 trials in that

condition. Following the tests, all subjects were questioned about how difficult they found the two types of span and whether or not they had employed any strategies to facilitate performance. Specifically, they were asked i) Which of the span tasks did you find the hardest? (structured or non-structured array) ii) Were you aware of using any strategies for each of the tasks? iii) If so, what were they?

Figure 5.1. Comparison of spatially structured (left) and spatially non-structured (right) array span tasks. The structured and non-structured arrays were identical to that used in the PET study of chapter 4.



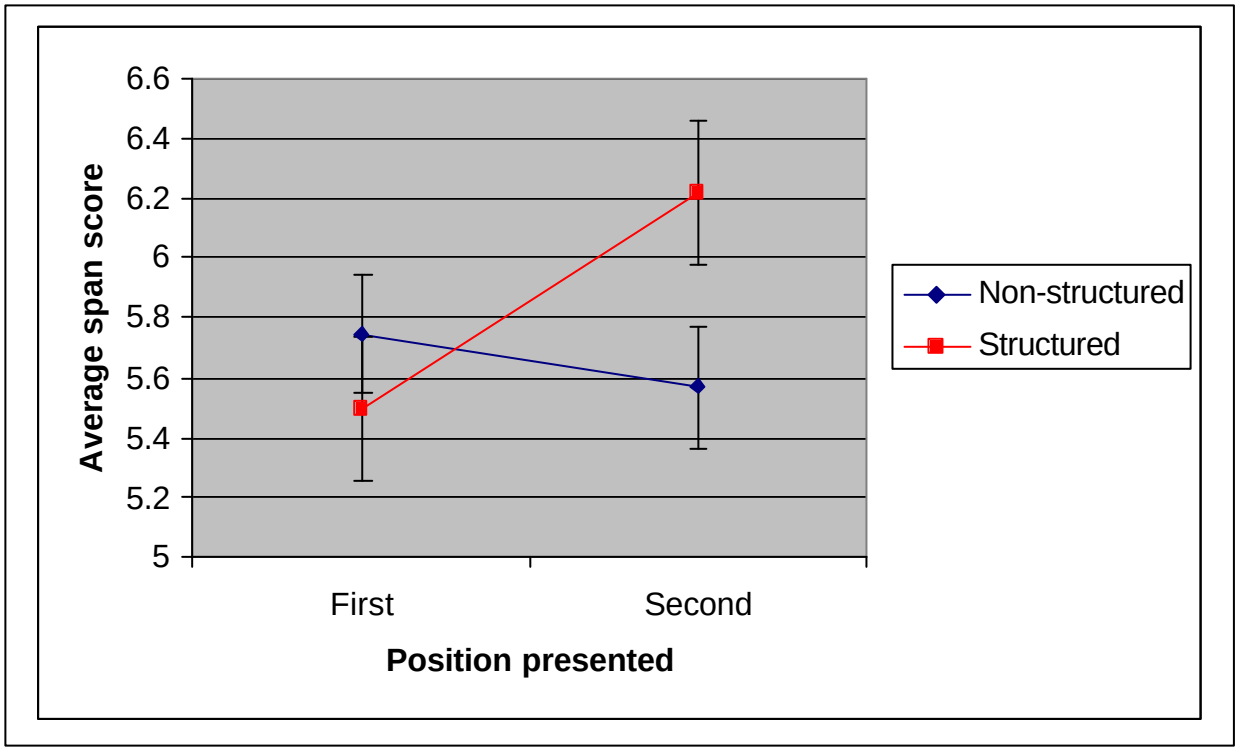
5.3 - RESULTS

See table 5.1 and figure 5.2 for results. There was no significant difference in overall mean span scores between the non-structured array condition (5.66) and the structured array condition (5.86) . There was a significant order effect (t=2.112, df=17 p=0.05), with subjects obtaining higher span scores on the second task given than on the first task. There was a significant interaction between condition and order (F(1, 16)=4.922 p = 0.041). Examination of this interaction revealed that the average span score for the structured array condition when performed second was significantly higher than that for the non-structured array condition when performed second (t=2.06 df = 17 p=0.033). Furthermore, the mean span score for the structured array condition was significantly higher when it was performed second, compared with when it was performed first (t=2.06, df = 17 p=0.028). In contrast, there was no difference between mean scores for the non-structured array condition when it was performed first than when it was performed last.

Table 5.1. Average span scores across order and condition.

Task	1st Condition	2nd Condition	Total over conditions
mean span length for structured array	5.50	6.22	5.86
mean span length for non-structured array	5.74	5.59	5.66
mean span length for both tasks	5.62	5.90	5.76

Figure 5.2 Graph illustrating the interaction between order and condition for average span score.



The examination of subjective reports revealed that, for the non-structured array, subjects usually reported using a very simple strategy involving the use of imaginary lines linking the stimuli (e.g. “I drew a line between the boxes”). In contrast, for the structured array more complex strategies were regularly reported, including using imaginary regular shapes (e.g. “I saw squares and triangles”) to connect the stimuli, chunking sets of stimuli together according to their spatio-temporal relations (e.g. “ I saw the first three stimuli as one set and the last two as a separate set instead of five single stimuli”), using the grid aspect of the ordered array to encode stimuli (e.g. “I remembered that the first three stimuli were in the top row”), and to rule out sections of the ordered array (e.g. “I remembered that none of the first three stimuli were in the top row”). Although such reports are obviously difficult to quantify, careful examination of the responses revealed that for subjects who used more strategies in the structured array condition, 7/9 (77%) reported using strategies more complex than simply drawing imaginary lines between stimuli. In contrast, for subjects who did not use more strategies in the ordered array condition, only 3/9 (33%), reported using strategies more complex than drawing imaginary lines. This difference just failed to reach statistical significance ($Chi^2 = 3.60$, df = 1, p = 0.058).

5.4 - DISCUSSION

Contrary to predictions, there was no performance advantage for the structured array span task, compared with the non-structured array span task. However, there are performance differences that suggest the two tasks were approached in a different way. It appears that there was a practice effect, which only occurred if the structured

array was presented second. It is possible that a strategic set for the structured array task when performed first somehow interfered with performance on the non-structured array task that followed. In addition, perhaps no such strategic set was established for the non-structured array when it was performed first. This could allow for both a strategic set to be established for the second, structured array condition, and possibly a more general practice effect relating to the task to carry over to the second condition.

The subjective reports provide more clear-cut evidence that the two tasks were approached in a different way. Although a low-level strategy of using imaginary lines to join up the stimuli in a sequence was very commonly used for the non-structured array condition, more complex strategies were normally used for the structured array condition. For instance, the use of chunking the stimuli, particularly into regular shapes, was reported almost exclusively for the structured array condition.

It seems likely from this that there is a real difference between the two spans in the cognitive approach taken to each of them. Furthermore, this difference appears crucially to be determined by the extent of strategic involvement for the two tasks.

Evidence from patient studies (Owen, Downes et al. 1990; Shallice and Burgess 1991; Miotto, Bullock et al. 1996; Owen, Morris et al. 1996; Morris, Rowe et al. 1999; Burgess, Veitch et al. 2000), as well as recent, preliminary evidence from neuroimaging (Prabhakaran, Narayanan et al. 2000; Savage, Deckersbach et al. 2001) suggests that the frontal lobes, particularly the lateral PFC, are involved in strategic processing. Consistent with this, the current study suggests that the condition with the greater DLPFC involvement in the PET study of the previous chapter had a greater strategic component to it.

Chapter 6: Frontal lobe patients and the spatial span task

6.1 - INTRODUCTION

In previous chapters, it has been shown that the spatial span task produces widespread lateral prefrontal cortex activation. Depending on the exact nature of the task, such activation may be limited to the VPFC, or it may extend to the DLPFC as well (see 4.3.2). As mentioned in the general introduction (see 2.2), neuroimaging results can only demonstrate an association between a process and pattern of activation. So it would be intriguing to test whether the observed association between lateral PFC and spatial span is due to direct involvement of this region in processes required for the spatial span task. One way of investigating this is via frontal lobe patients. If the lateral PFC is indeed necessary for such tasks, then patients with damage to this region should show a deficit on spatial span.

Although many studies have indicated that patients with frontal lobe damage are impaired on tasks that carry a significant strategic or planning component (Owen, Downes et al. 1990; Shallice and Burgess 1991; Owen, Morris et al. 1996; Morris, Rowe et al. 1999; Burgess, Veitch et al. 2000), there is little evidence that these patients are also impaired on simple working memory tasks, such as the spatial span task (Canavan, Passingham et al. 1989; Owen, Downes et al. 1990; Miotto, Bullock et al. 1996; Greenlee, Koessler et al. 1997). Indeed, in a review of 4 spatial span and 8 verbal span studies involving frontal lobe patients, D'esposito and Postle (D'Esposito and Postle 1999) failed to find a significant impairment for either type of span within

this patient group. They conclude that the PFC may not be involved in standard working memory tasks, such as the span task, which place simple demands on working memory capacity. Instead, they suggest that the PFC will be involved in processing such tasks only when there is a manipulation component,.

However, previous studies testing frontal lobe patients have used relatively crude measures of span performance, that tended to produce span score results for each subject only in the form of integers (Canavan, Passingham et al. 1989; Owen, Downes et al. 1990; Miotto, Bullock et al. 1996; Greenlee, Koessler et al. 1997). For instance, Owen et al. (Owen, Downes et al. 1990) used a spatial span paradigm where the span length would increase by one during the next trial if the current trial was reproduced correctly, but would remain the same length for the next trial if an incorrect response was made for the current trial. The span score for each subject was set as one below the length at which subjects made three successive errors.

Given the robust association between the lateral prefrontal cortex and the spatial span task observed in previous imaging studies (Owen, Evans et al. 1996; Owen, Herrod et al. 1999), as well as in chapters 3 and 4, the lack of impairment on spatial span in frontal lobe patients is surprising, since it seems reasonable to assume that this region is indeed involved in processes necessary for normal performance on this task. However, as previous chapters have indicated, such processes need not necessarily mean working memory *capacity*, which is the central component measured by spatial span tasks.

The study in this chapter sought to devise a more sensitive method for testing whether frontal lobe patients do indeed have an impairment in "standard" working memory tasks such as the spatial span task. The two types of span (the structured array and non-structured array) used in the previous chapter, with the same "ratchet"

paradigm (where the span length constantly varies between trials), was presented either to frontal lobe patients, or closely matched controls. If the paradigm is sensitive enough, it should be the case that frontal lobe patients are generally impaired on these tasks compared to controls. Since the data from the PET study of chapter 4 suggest that there is greater prefrontal involvement for the structured array version of the spatial span task, it should also be the case that there is a larger impairment for the structured compared to the non-structured spatial span.

6.2 - METHODS

6.2.1 - Subjects

Table 6.1 provides a summary of the mean characteristics of the subject groups included in this study. The National Adult Reading Test (Nelson 1982) was administered to all subjects in order to obtain an estimate of premorbid verbal IQ.

Table 6.1 - Summary of characteristics of the unilateral left frontal patients, the unilateral right frontal patients and the healthy controls. M/F = male/female numbers; NART = National Adult Reading Test; Duration = average time between surgery and testing.

Group	N	M:F	Age/yr.	NART IQ	Duration/months
Left frontal	9	5:4	53.20	118	34.22
Right frontal	11	3:8	57.45	116	30.67
Control	20	8:12	55.65	117	-

Frontal lesion patients. Twenty unilateral frontal lobe lesion patients from the Cambridge Cognitive Neuroscience Research Panel (CCRNP) were included in this study and were tested in their homes. The CCNRP has the approval for such studies from the Cambridge Health Authority Local Research Ethics Committee. Of the patients tested, 11 had sustained a right frontal lesion, including one haemorrhage, one aneurysm of the anterior communicating artery, four infarcts, three meningioma resections and two frontal lobectomies. The average period between surgery and time of testing was 30.67 months (range: 18 to 68 months). 9 left unilateral frontal patients were tested, including three aneurysms of the anterior communicating artery, three subarachnoid haemorrhages, two meningioma resections and one case of encephalmalacia due to an haemorrhage. The average period of time between surgery and testing was 34.22 months (range: 8 to 73 months). Figures 6.1 and 6.2 illustrate the location and size of the lesions for all of the frontal lesion patients that were tested and for whom structural MRI scans were available (N=14). In Table 6.2 descriptions are provided of the lesions in those patients who were tested but for whom structural MRI scans were not available (as assessed from clinical computed tomography {CT} scans). Two of the right frontal lesion patients were found to have additional damage to regions outside of the frontal lobe. Apart from one left frontal patient, all the patients were right hand dominant.

Control subjects. The frontal lesion patients were compared with right-handed healthy volunteers from the MRC-Cognition Brain Sciences Unit volunteer panel (20 in total). This panel is an accumulating database of volunteers who have been screened for past and present mental illnesses and brain injury. The subjects were matched for sex, age

and IQ with the frontal lesion patients (Table 6.1). All of the control subjects were tested at the MRC-Cognition and Brain Sciences Unit, Cambridge, UK.

Table 6.2 – Official hospital Computer Tomography lesion descriptions of those unilateral frontal patients without structural MRI scans.

	Hemisphere	**Lesion description**
1.	Left	Small lateral frontal cortex lesion
2.	Left	Inferior frontal cortex lesion
3.	Left	Frontal cortex lesion
4.	Left	Frontal cortex/subinsula lesion
5.	Left	Frontal cortex lesion
6.	Right	Ventromedial frontal cortex lesion

Figure 6.1a-d - Structural MRI scans of unilateral left frontal lobe patients (where available). The MRI scans have been normalised in SPM and are in MNI space. Red shading highlights lesion.

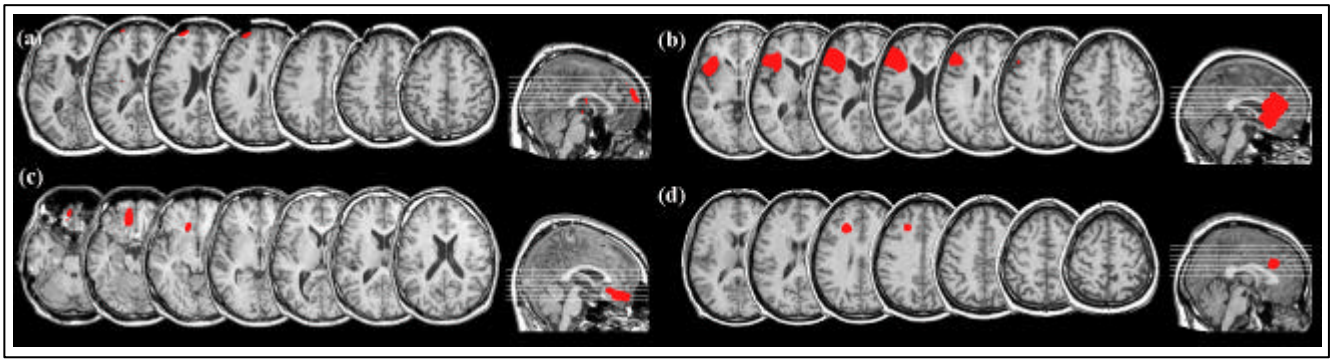
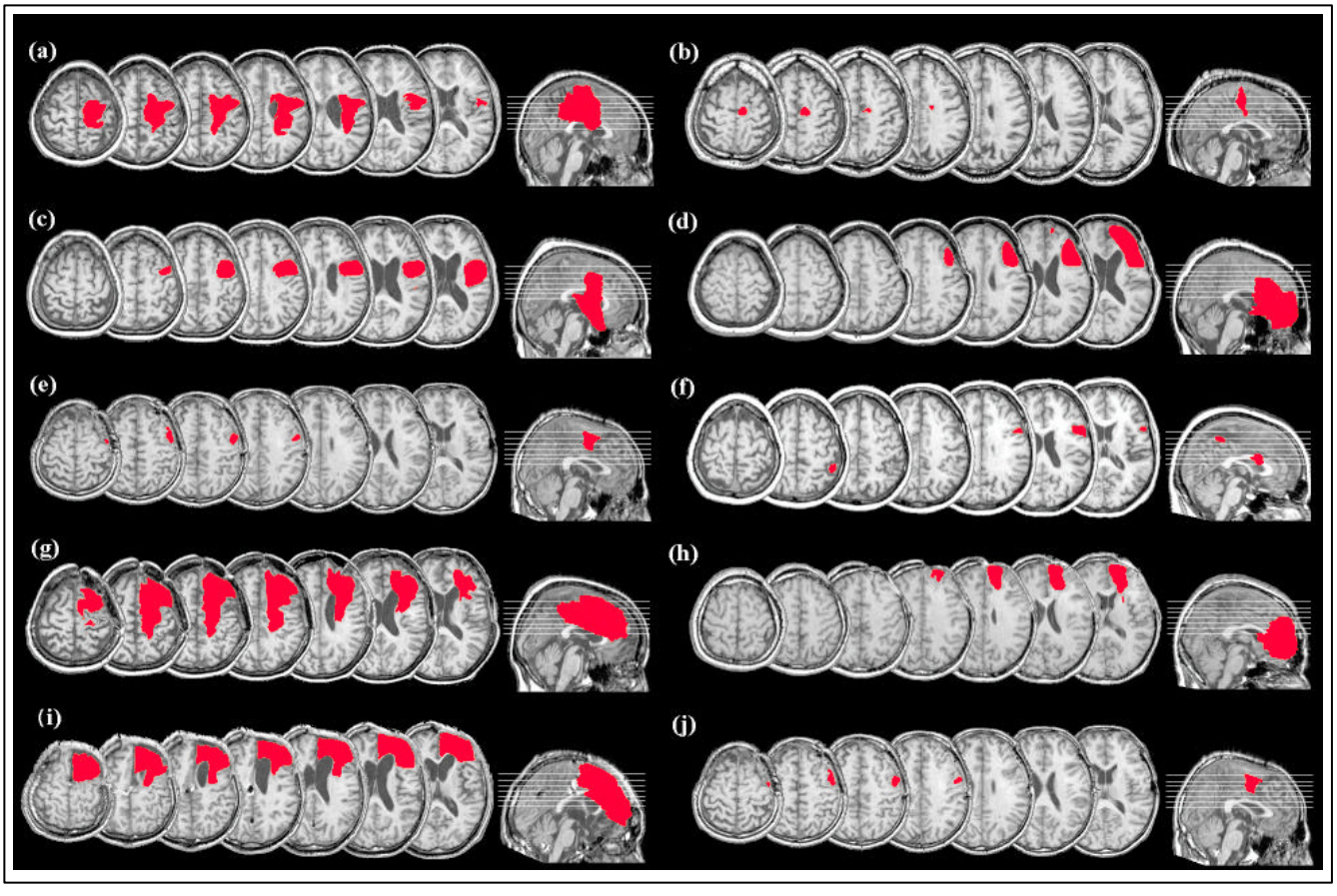


Figure 6.2a-j – Structural MRI scans of unilateral right frontal lobe patients (where available). The MRI scans have been normalised in SPM and are in MNI space Red shading highlights lesion.



6.2.2 - Stimuli and Testing Conditions

In order to avoid the categorical, integer based scoring method of a person's span score, so that a more sensitive measure was used, a method was devised that would potentially provide a continuum of possible span scores. This was carried out by the same "ratchet" setting of span level as the previous chapter, whereby span length would vary from trial to trial, always close to the threshold of the subject.

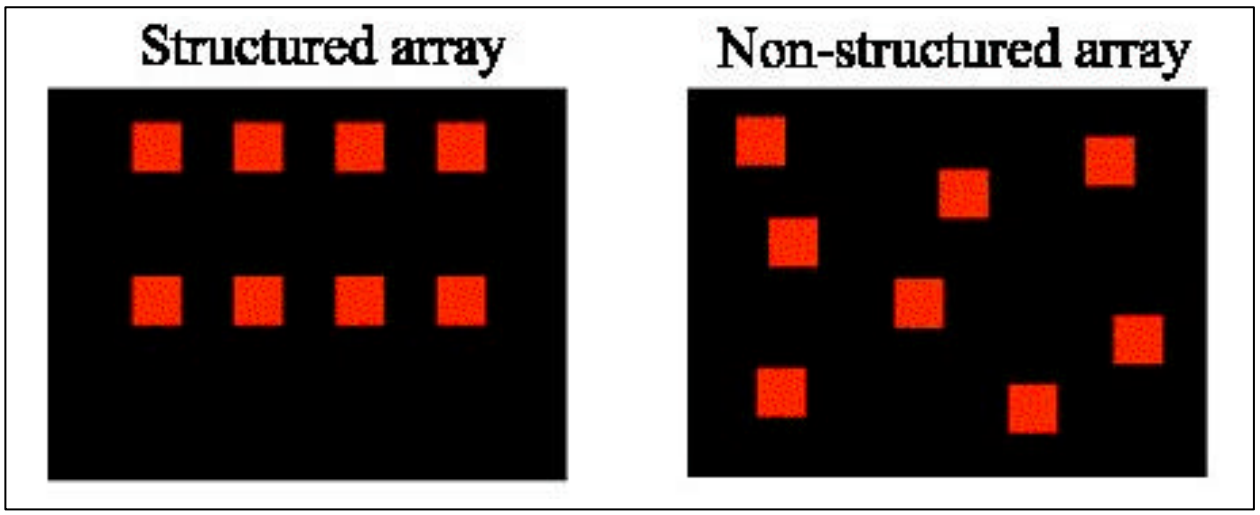
For each trial, one of eight red squares would turn blue for 500 ms before turning red again. 250 ms following this, a second red square would turn blue for 500 ms and so on, until the number of squares that had turned blue equalled the number of the span-length for that trial. Subjects were then required to respond by touching the squares in the order that they had changed colour. If any errors were made in the response, the subsequent trial would begin 4500 ms after that first error. Otherwise, subjects had 2000 ms multiplied by the current span length in order to make their response. The length of the span presented increased by one for the next trial if the subject reproduced the current span without errors, while the subsequent span length decreased by one if the subject made any errors or was unable to provide the full response within the allotted time frame for that trial. There was therefore a possible minimum span length of 1 and maximum of 8. Each subject was tested on a non-structured array of eight red squares and on a structured array two by four matrix of squares (see figure 6.3). Both arrays were identical to the two arrays used in the PET study of chapter 4 (see 4.2.3) and of the behavioural study of the previous chapter. The choice of which red squares would turn blue and in which order was pseudo-randomly

set in all conditions, so that particular span sequences in the span tasks did not repeat contiguously.

Each subject first carried out a practice until they were familiar with the task. The subjects then performed two conditions of each task, with each condition lasting 15 trials. Only the last ten trials were analysed, since in the first five trials subjects would invariably be climbing or descending towards their optimum span. Conditions were administered in the following order: structured span, non-structured span, non-structured span, structured span (for half the subjects) and non-structured span, structured span, structured span, non-structured span (for the other half). This approach was used to counterbalance any possible practice effects. To determine a subject's span score for a given condition, an average of the lengths of the last ten trials in both blocks was computed.

As an example of one condition for one subject, after the first five trials, the last ten trials might have been of the length: 5,6,7,6,7,6,5,4,5,6. In this case, the average would be: ({5+6+7+6+7+6+5+4+5+6} / 10) = 5.7.

Figure 6.3. Comparison of spatially structured (left) and spatially non-structured (right) array span tasks. The structured and non-structured arrays were identical to that used in the PET study of chapter 4 and the behavioural study of chapter 5.



6.3 - RESULTS

In figures 6.4 and 6.5 the behavioural results are illustrated graphically. The mean span for the patient group collapsed across conditions (4.98) was significantly lower than the mean span for the control group (5.52) ($t=1.86$, $df = 36$, $p = 0.036$, 1-tailed).

The frontal lobe group were split to examine separately those with left-sided and those with right-sided lesions. The left frontal lobe group were not significantly different from controls. The right frontal lobe group, however, were significantly different from controls ($t = 2.12$, $df = 16$, $p = 0.025$, 1 tailed). Although the right frontal lobe group were worse than the left frontal lobe group on average, this difference did not reach significance ($t=1.02$, $df = 18$, $p = 0.16$, 1-tailed).

The effect of condition was also examined. There was a trend for the frontal lobe patients to perform worse on the structured span condition compared to the non-structured span condition, with the controls showing the opposite effect, but this interaction did not reach significance. When the frontal lobe group were split into those with right lesions and those with left lesions, neither group compared to controls showed an interaction between group and condition.

In order to examine possible relationships between size and type of lesion and extent of deficit on the spatial span task, only those patients with an MRI (13 subjects) could be included since the CT summary was not sufficiently detailed to determine these factors. When this subset of the frontal lobe patient group were roughly graded according to size of lesion (with 1 being the smallest and 5 the largest), no significant correlation between size of lesion and extent of impairment was found. When the frontal lobe patient group were split according to whether the lesion included the DLPFC or not (as defined by the DLPFC search volume used in Owen et al. (Owen,

Herrod et al. 1999)) , no significant differences were found between these two groups in level of impairment (examples of patients with lesions including the DLPFC are shown on figures 6.1b and 6.2d, while examples of those not included in the groups are shown on figures 6.1d and 6.2h).

Figure 6.4. Histogram to indicate the average scores for the frontal lobe patient and control groups on the two versions of spatial span, with standard error bars.

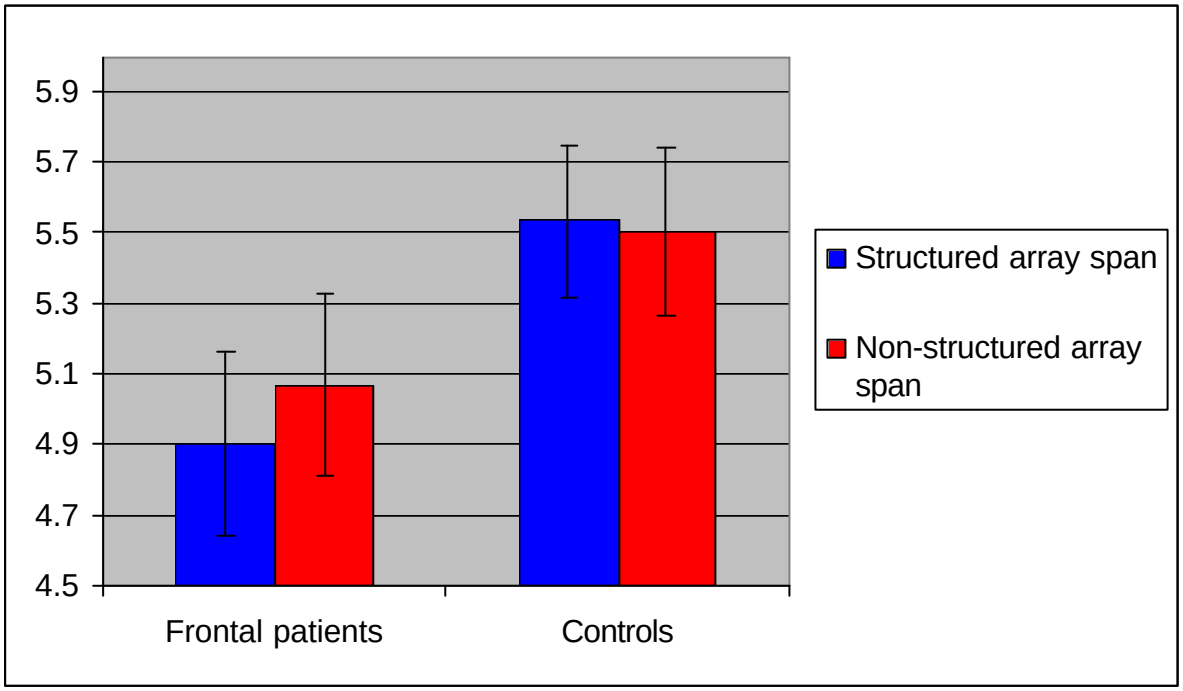
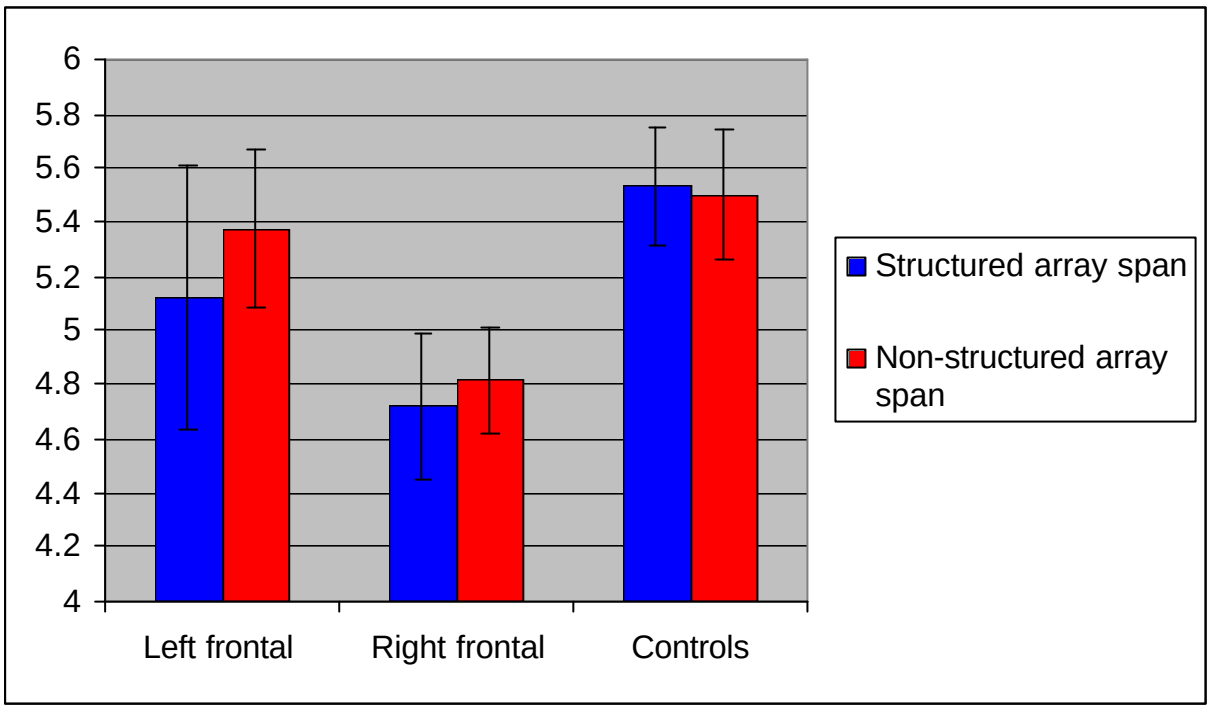


Figure 6.5. Histogram to indicate the average scores separately for the left and right frontal lobe patient and control groups on the two versions of spatial span, with standard error bars.



6.4 - DISCUSSION

In accord with the PET studies of the two previous chapters indicating that there is considerable lateral prefrontal involvement in spatial span tasks, the results from the patient study confirm that frontal lobe patients are significantly impaired on spatial span tasks. This is a surprising result, given that no reports in the literature appear to show a significant impairment in spatial span within frontal lobe patients (Canavan, Passingham et al. 1989; Owen, Downes et al. 1990; Miotto, Bullock et al. 1996; Greenlee, Koessler et al. 1997). In fact, it is widely assumed that frontal lobe patients don't have a span deficit (D'Esposito and Postle 1999). D'esposito and Postle, in a review of all available frontal lobe patient span studies, found no report of significant impairment in spatial or digit span amongst 11 studies (D'Esposito and Postle 1999). The increased sensitivity of the measure used here, however, most likely accounts for the apparent discrepancy. Indeed, most relevant frontal lobe patient studies do report lower scores on spatial span compared to controls, although less sensitive measures are used to estimate span (Canavan, Passingham et al. 1989; Owen, Downes et al. 1990; Greenlee, Koessler et al. 1997). Presumably, with higher numbers of patients, these studies also would have reported a significant impairment, despite the insensitivity of the measures used.

It would be interesting if in other fields, such as the study of those with early Alzheimer's Disease, that the widespread assumption that such patients aren't impaired on standard working memory tasks, such as spatial span, is also attributable to insensitive measures.

When the frontal lobe group was split up, it was shown that while the right frontal lobe patients were impaired on spatial span, compared to controls, this was not

the case for left frontal lobe patients. Although direct comparison between the groups showed no significant difference, this may have been due to the low numbers in the comparison (9 versus 11). The preliminary evidence of greater impairment for right frontal lobe patients on the spatial span task is consistent with evidence from previous chapters. The PET studies of chapters 3 and 4 indicated that spatial span tasks mainly activate the prefrontal cortex in the right hemisphere. Previously published spatial span tasks have shown a similar bias to the right prefrontal cortex (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). Indeed, there is a strong suggestion in the literature that while the left prefrontal cortex is involved in verbal working memory, the right prefrontal cortex is involved in spatial working memory (Smith, Jonides et al. 1996).

When the size of lesion was related to deficit, this possible correlation failed to reach significance. However this isn't surprising for two reasons. First, the number of patients with useful information about size of lesion (i.e. those who had had an MRI scan) was only 13, so there were small numbers to work with. Second, the PET studies of previous chapters indicate that only a small region of the frontal lobes, the lateral PFC, show a possible relationship with processes involved in spatial span performance. The site of lesion, as shown by figures 6.1 and 6.2 varied considerably across the frontal lobes and in some cases was entirely medial.

There was also no significant difference in performance between those patients that had damage to the critical lateral prefrontal cortex region (DLPFC) and those that didn't. Again this may be due to the small sample size of the subset of patients who had an MRI scan (only seven of the patients were shown to have damage that included the DLPFC).

It is unclear from the current study whether frontal lobe patients demonstrated a greater deficit for the structured array span compared to the non-structured array

span, in relation to the controls, although the data tentatively indicate that this is the case. This again would be in accord with the results of the PET study of Chapter 4, which indicated greater lateral prefrontal involvement for the structured array spatial span task.

The working memory impairment found in this study may well be the first such case where a significant deficit in span performance for frontal lobe patients has been demonstrated. The general assumption that there is no basic working memory deficit for patients with frontal lobe lesions may well have to be revised. However, it is highly unclear what precisely the term "working memory" means in the context of such studies, which have deviated somewhat from the original definition of Baddeley (Baddeley 1992; Baddeley and Della Sala 1998). Undoubtedly, though, part of any working memory process would be the holding online of the goal of the task. As discussed in the general introduction (see 1.4.2.2), one current theory for PFC function is that it manages goal states. The current results are more in line with this suggestion, since relatively small deficits on a straightforward task are more likely to be the result of "goal neglect" rather than a significant impairment in mnemonic storage.

As discussed in previous chapters, as well as in the general introduction (see 1.4.2.3), it has been suggested that the PFC is involved in processing strategies (Shallice and Burgess 1991; Owen, Morris et al. 1996; Morris, Rowe et al. 1999). For example, one study (Owen, Morris et al. 1996) demonstrated an impairment in these patients in forming or applying a searching strategy in a spatial working memory task, compared to temporal lobe patients. The observed general impairment in the current patient study might in turn be attributable to deficits in applying low-level strategies (e.g. keeping key aspects of the task "online" at appropriate points, developing habits for preparatory responses, etc.).

Whether the explanation is one of goal-neglect or a strategy deficit, these results should lead to the prediction that frontal lobe patients would be at least slightly impaired on *any* demanding or significantly novel task, since normal subjects may automatically optimise their performance by finding various effective low-level strategies far more easily.

It is entirely possible that the prefrontal cortex can initiate distinct plasticity when there is damage to some region within it. This may mean that damage to the left PFC would take on a more spatial role in working memory tasks following right PFC damage, or even that more anterior regions would take on more executive functioning following DLPFC damage. In this way, any possible impairment maybe lessened or abolished soon after recovery from surgery. In order to circumvent this problem of plasticity, it would be necessary to study those with large bilateral lesions to the lateral PFC. However such patients willing and able to take part in behavioural experiments are extremely rare. An alternative, equally problematic route, would be to study patients weeks, instead of years, after surgery, so that frontal lobe plasticity is not yet an issue.

Further work would also need to include a second patient lesion group (such as temporal lobe patients) as a control, which is a shortcoming of the current study. However, the widespread assumption that there is no impairment in frontal lobe patients in standard working memory tasks means that the current results raise important questions about the relationship between the frontal lobes and working memory processes.

Chapter 7: fMRI study on comparison of spatial span with high and low structural order

7.1 - INTRODUCTION

Several studies in patients with frontal lobe damage have suggested that in terms of working memory performance, such patients are specifically impaired on the strategic component of the task (Petrides and Milner 1982; Owen, Morris et al. 1996). Two recent neuroimaging studies have attempted to refine the association between strategic processing and the frontal lobes, suggesting that the critical region is the lateral prefrontal cortex (Prabhakaran, Narayanan et al. 2000; Savage, Deckersbach et al. 2001). However, in each case, such claims have been problematic. For instance, Prabhakaran et al. (Prabhakaran, Narayanan et al. 2000) found using fMRI that when working memory items comprising both verbal and spatial components were bound or integrated together, there was greater activation in the anterior lateral PFC and frontal-polar regions during the delay compared to an un-integrated equivalent. However, they were not able to show a clear behavioural difference between the integrated and un-integrated trials, since blocks comprised both versions and the analysis was only block related. Savage et al. (Savage, Deckersbach et al. 2001), in a PET study on semantic memory, compared recall on items that were either semantically related or unrelated. There was both an increase in accuracy at retrieval and an increase in lateral PFC at encoding for the related condition compared to the unrelated condition. This led the authors to conclude that the DLPFC is involved in creating an organisational structure during encoding. However, the lateral prefrontal cortex has

also been heavily implicated in semantic memory encoding (Gabrieli, Poldrack et al. 1998; Buckner, Kelley et al. 1999), and so the prefrontal activation observed could be due to more effective encoding per se, rather than any strategic processing.

In addition, the evidence from chapters 3,4 and 5 together suggest that the lateral PFC is involved in strategic processing. Again, though, these studies comprise significant limitations, making such an interpretation merely suggestive until firmer evidence can be found. Chapter 3 provided evidence that a version of the spatial span task involving a more structured array would yield DLPFC activation, while previous studies have shown that a non-structured version of the task consistently activates the VPFC. Chapter 4 extended these results by comparing a structured with a non-structured array spatial span task within subjects in the PET scanner. While the structured array version yielded both VPFC and DLPFC activation compared to a control task, the non-structured array version yielded only VPFC activation. It was suggested that the different pattern of activation was due to greater strategic processing for the structured array. This was explored in the behavioural study of chapter 5. That study found provisional evidence that the subjects were devoting more strategic processing to the structured array version of the spatial span task. Subjects commonly reported chunking the sequences for the structured array into regular shapes, while such a report was considerably rare for the non-structured array. This suggests that it wasn't necessarily the structured array itself that provided the means by which subjects could perform the task in a more strategic way. Instead, it seemed that certain sequences in this task could appear as regular shapes, via the utilisation of the orderly matrix of the array, and it was the regularity of the sequences that initiated greater strategic processing.

This observation provided the main idea for the design of the current study, which attempts to maximise the difference between two span tasks in terms of strategic processing, while at the same time control for differences in the array. Using a structured 4 x 4 array throughout, subjects were presented in the fMRI scanner either with spatial span trials that maximised the orderly nature of the array, thus providing ample opportunity to recode the sequence into regular figures, or highly unstructured span trials that minimised such a chunking process. If chunking stimuli is a relevant strategic process for these kinds of spatial span, then two clear predictions should follow. First, there should be a clear performance advantage for the structured trials, compared with the non-structured trials, on account of the greater strategic processing for the structured version. Second, there should be greater activation in the lateral PFC for the structured trials, since these trials will have greater strategic processing associated with them.

If these predictions are born out, then this will provide clear improvements on the work of previous chapters. First, as mentioned above, the results of chapter 4 indicated that there should have been a behavioural advantage for the structured arrays span task, if this task did indeed involve greater strategic processing. However, neither the behavioural results of chapter 4, nor the behavioural study of chapter 5 demonstrated this. It was suggested at the time that this may have been due to lack of statistical power. With an improved design to differentiate between the two span variants, due to maximising the difference in potential for chunking the stimuli, it is hoped that in the case of the current study there will be a significant behavioural difference.

The second improvement will be in directly demonstrating a difference in activation patterns associated with the two kinds of span trials, whereas in chapter 4 a

difference was only shown when the two span tasks were compared with a control rather than each other. It is hoped that the greater signal to noise ratio of fMRI, compared to PET, as well as the psychological design now providing a greater potential for behavioural difference between the spans, will yield a significant direct difference between the two types of trial.

The third improvement relates to the suggestion in the literature concerning the relationship between lateral PFC activity and task difficulty (see the general introduction, 1.4.2.1). It has been proposed that increases in cognitive demand go hand-in-hand with increases in lateral PFC activation (Cohen, Perlstein et al. 1997; Jonides, Schumacher et al. 1997; Duncan and Owen 2000). There was provisional evidence from chapter 4 that this need not be the case, since in that study, the task that activated a greater portion of the lateral PFC compared to controls was almost universally reported by subjects as easier than a task that activated a smaller part of the lateral PFC. However, as mentioned above, this comparison suffers from being two experimental conditions compared to controls, rather than a direct contrast. In addition, the behavioural results were almost identical and at ceiling, making it unclear whether one task was in fact easier than another. If the current study can indeed demonstrate an easier task (i.e. the structured spans trials) yielding greater lateral PFC activation compared to a more difficult task, then that would raise serious questions for the proposal that PFC activity is related to task difficulty per se.

7.2 - METHODS

7.2.1 - Subjects

16 healthy right handed volunteers (ages 21-34, 6 male and 10 female) participated. All subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research and Ethics Committee. Each subject was given a five minute training session on the task prior to scanning. If proficiency wasn't reached, a further five minute session was given.

7.2.2 - Cognitive task

Stimuli were back projected onto a translucent screen positioned within the bore of the magnet and behind the head of the participant, visible via an angled mirror placed above the participant's head. Sixteen red squares, arranged as an equidistant 4 X 4 matrix, were presented on the screen against a black background (see figure 7.1 and 7.2). On each trial, four of the red squares flashed blue, changing colour for 500 ms with a 250 ms interval between each. The participant was required to remember the sequence and to maintain that information across a delay randomly varying between six and ten seconds. At the end of this period, the participants were required to make a series of responses, prompted by the appearance of a yellow dot placed randomly on the left or right side of each of the sixteen squares. By pressing a button under the first or second finger of the dominant hand, corresponding to a dot on the left or a dot on the right, participants were asked to indicate dot positions for each of the four

locations in memory, in the order originally presented. This rather unconventional method of response was necessary because only a four button box was available in the fMRI scanner, as opposed to the touch-screen used in the PET studies of chapters 3 and 4. Though some such responses would be correct by chance, high performance overall shows that participants complied well with memory instructions.

In half of the trials, the sequence followed a 'structured' rule such that every location was either in the same column, the same row, or on the same diagonal as the location preceding it. In the remaining trials, an alternative 'non-structured' rule was applied such that two successive locations were never in the same column, in the same row, or on the same diagonal. The result of this manipulation was subtle, such that the structured sequences tended to produce more 'shapely' configurations, involving symmetry and parallel sides, and were thus more easily organized into higher-level patterns (Fig. 7.1 and 7.2). Participants were not told that sequences differed in this way. Trials were presented in blocks of 20, pseudo-randomly ordered such that ten structured and ten non-structured sequences were presented in each block. For each participant there were three blocks, each comprising one separate scanning run.

Figure 7.1. Example trials from the spatial span task. In structured trials (a) the sequence of 4 locations presented at encoding followed a predetermined rule which tended to produce orderly visuospatial configurations. In non-structured trials (b) such configurations were avoided. In the actual task, locations in the encoding sequence were indicated by a 500 ms switch from red to blue (see Methods).

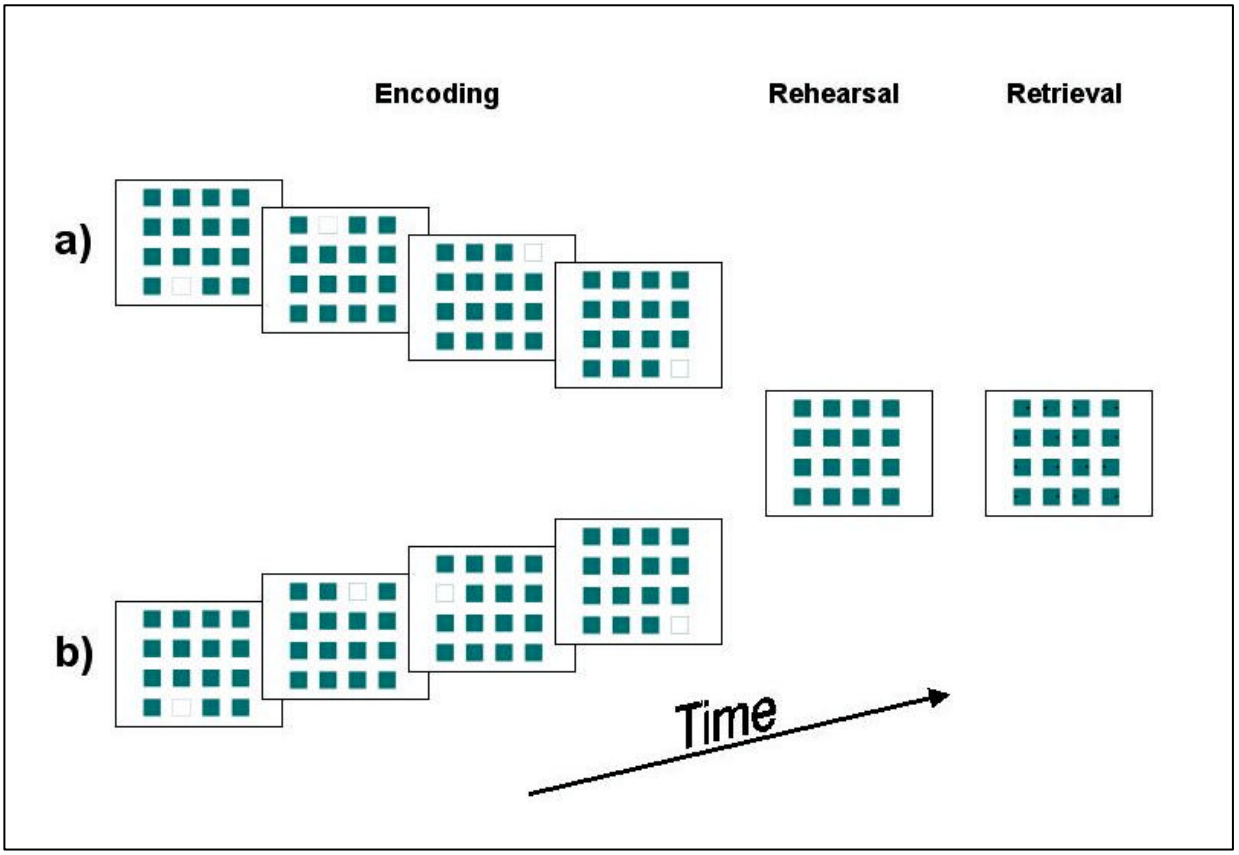
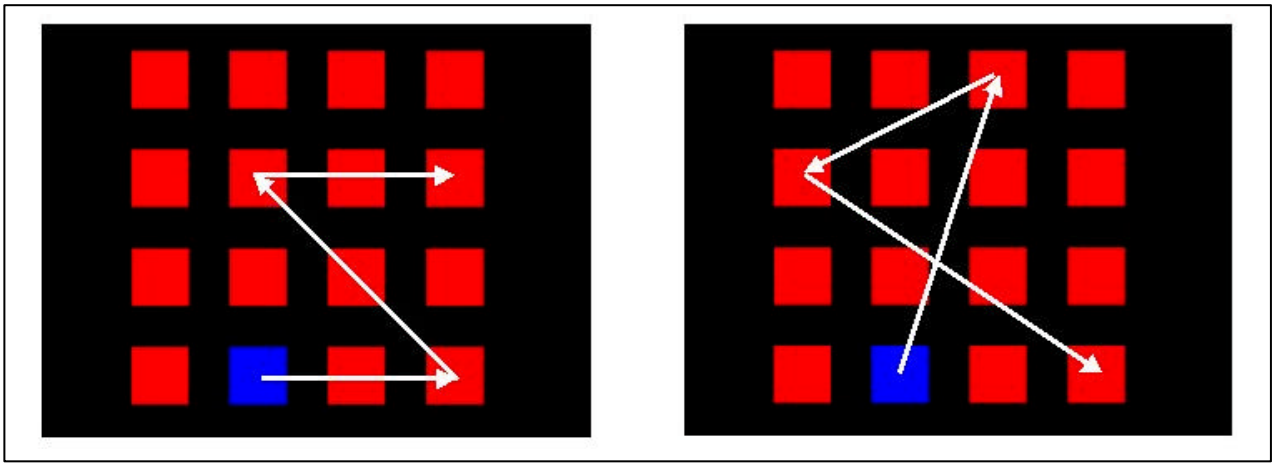


Figure 7.2. Example of trials, presented as a sequence path, to indicate the differential potential to recode the sequences into shapes for the structured (left) and non-structured (right) trials.



7.2.3 - Image acquisition

See chapter 2 (section 2.2.4.2) for the scanning details. The beginning of each trial (encoding phase) was tightly coupled to the timing of the scanning sequence and jittered in 0.5 sec increments around the start of the TR (from 1.5 secs prior to the TR to 1 sec past the TR). The length of the rehearsal phase, which immediately followed the encoding phase, was pseudo-randomly varied in 0.5 second increments from six to ten seconds. The inter-trial interval (ITI), which commenced immediately after the 4th

response (or after 7 seconds if fewer than four responses were made), was pseudo-randomly varied in 0.5 second intervals between eight and twelve secs in order to allow the blood oxygen-level dependent (BOLD) response to return to baseline between trials.

7.2.4 - Image analysis

All fMRI data were processed and analysed using SPM 99 software (Wellcome Department of Cognitive Neurology, London). Prior to analysis, all images were corrected for slice timing, with the first slice in each scan used as a reference. Images were realigned with respect to the first image using sinc interpolation, creating a mean realigned image. Using the mean realigned image, all images were normalised using affine and smoothly non-linear transformations to an EPI template in Montreal Neurological Institute (MNI) space. Finally, all normalised images were spatially smoothed with a 10mm full width half maximum Gaussian kernel. Single subject statistical contrasts were set up by using the general linear model to fit each voxel with a combination of functions derived by convolving the standard hemodynamic response with the time series of the stimuli and removing low-frequency noise with a high-pass filter. Group data were analysed with a random effects analysis. All reported peaks for the group analysis passed a whole-brain false detection rate (Benjamini and Hochberg 1995) threshold of $p<0.01$. Due to lack of power for the single subject data, and a clear a priori hypothesis based on the two PET studies of chapters 3 and 4, a less conservative threshold of $p=0.001$ uncorrected was applied to the frontal lobes for the single subject analysis.

7.3 RESULTS

7.3.1 - Behavioural Results

Subjects were significantly more accurate in performing the structured spans (95.8% of trials without error) compared to the non-structured spans (89.6% of trials without error) ($t = 6.54$, $df = 15$, $p < 0.001$). In addition, subjects were significantly faster at making a complete response for the structured spans (2.54 seconds for all four responses on average) compared to the non-structured spans (2.78 seconds) ($t = 6.27$, $df = 15$, $p < 0.001$). All subjects were asked whether they noticed any difference between the spans. The majority of subjects separated the span types into at least two kinds: the first kind, which they found harder (presumably the non-structured trials), and either one or a set of other kinds, which they classed as easier precisely because they were able to perceive regular shapes within the sequences (presumably the structured trials).

7.3.2 - Neuroimaging Results

7.3.2.1 - Group Analysis

Event-related, random effects analysis of fMRI data identified statistically significant differences in cortical activity between the two types of trials. For this purpose, each 'event' was considered to be the entire trial, from the presentation of the first stimulus to the execution of the fourth and final response (see Methods, section 7.2). Results of analyses including all trials are reported, though essentially identical results were obtained following exclusion of trials with erroneous responses. Structured trials

yielded significantly greater activity than non-structured trials in the lateral prefrontal cortex, the inferior parietal lobe and the fusiform gyrus of both hemispheres (Fig 7.3 and Table 7.1). There were additional small clusters of activation in medial frontal and right sensorimotor cortex (Table 7.1). The reverse comparison between non-structured trials and structured trials revealed no regions of significantly increased neural activity, even when the false detection rate threshold was lowered to $p<0.50$.

A supplementary analysis was conducted to examine separately the encoding (sequence presentation), maintenance/rehearsal (delay period), and retrieval (response generation) stages of structured and non-structured trials. Results from the encoding analysis closely mirrored those of the whole-trial analysis; thus, comparison of structured and non-structured trials again showed significantly increased activity bilaterally in the lateral frontal cortex, the inferior parietal lobule and the fusiform gyrus. In contrast, comparison of the two types of trials during the delay and retrieval phases of the task yielded no consistent changes in signal. Separate estimates of neural response for each task stage showed greatest lateral prefrontal activity at encoding, along with the greatest difference between structured and non-structured trials (Fig 7.4).

Figure 7.3. Regions of increased activation during structured trials as compared to non-structured trials. Whole-brain false detection rate p<.01 applied to activations, rendered onto the canonical T1-weighted brain image of SPM99.

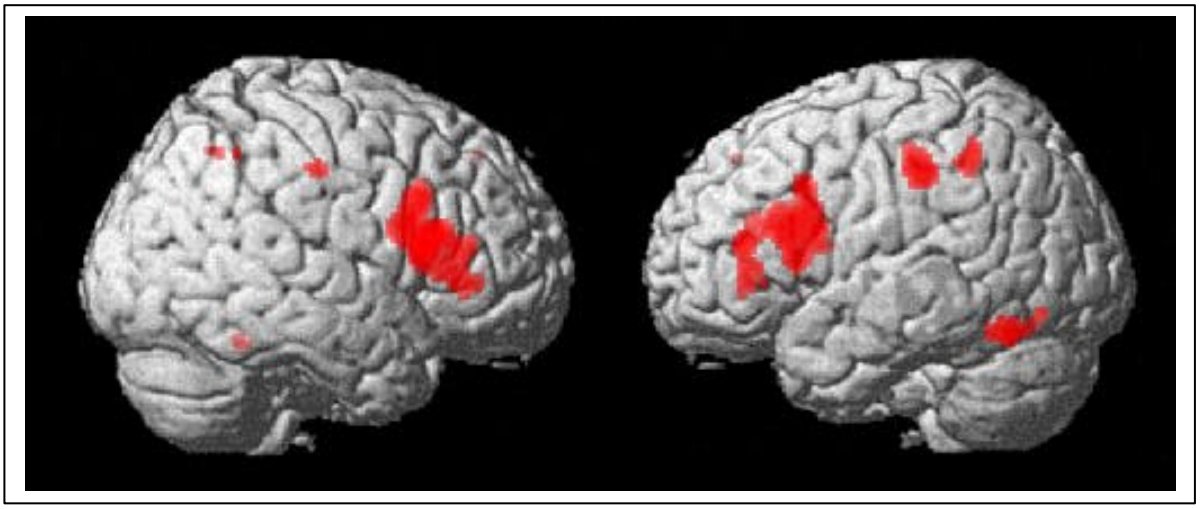
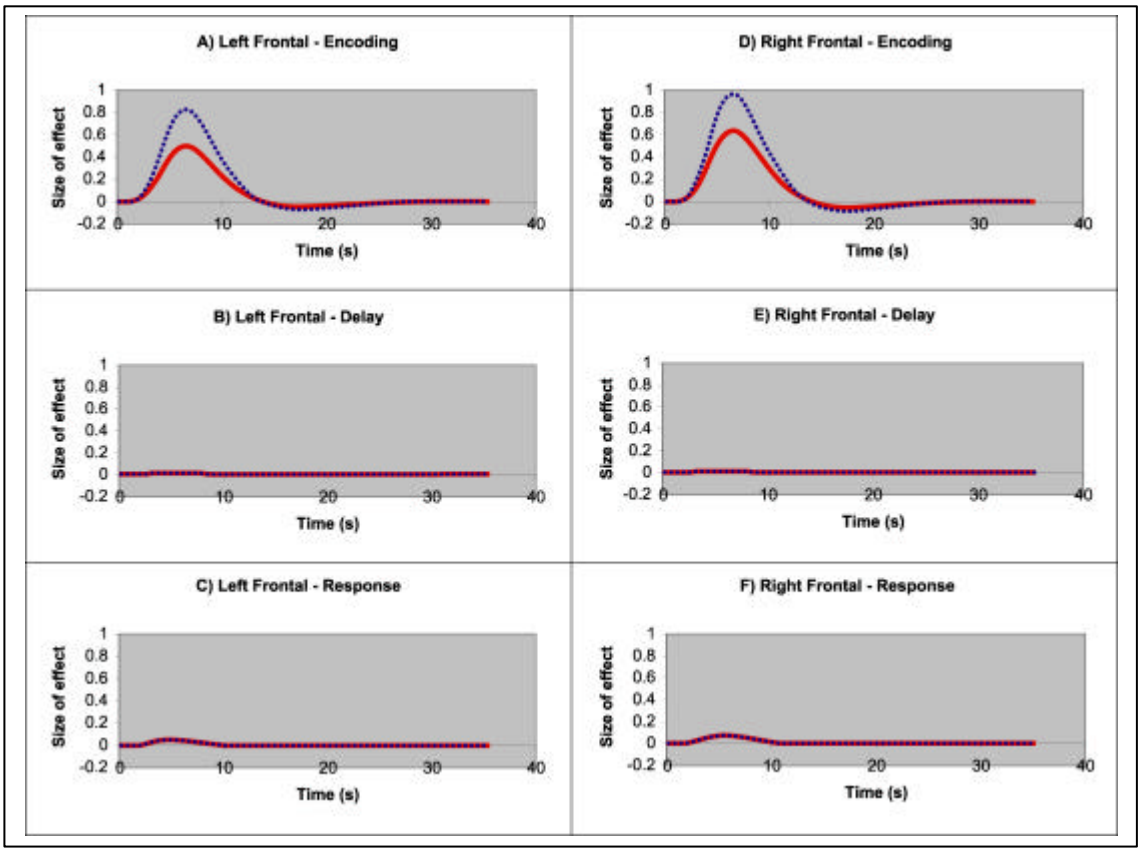


Table 7.1 - Peak activations for the group structured sequences minus unstructured sequences comparison. All regions presented pass the threshold of p=0.01 false detection rate(Benjamini and Hochberg 1995). The location of Brodmann areas have been estimated from the atlas of Talairach and Tournoux(Talairach and Tournoux 1988).

Brain regions and Brodmann areas	Coordinates			t score
	x	y	z	
R lateral prefrontal cortex				
47/45	53	29	0	7.09
45	55	20	16	9.21
9/44	46	13	20	9.50
L lateral prefrontal cortex				
45	-48	20	16	7.06
45	-53	16	7	6.24
9/44	-46	13	21	7.17
Medial frontal cortex				
8	0	39	40	4.92
R sensorimotor cortex				
1/4	61	-18	38	6.00
R inferior parietal lobule				
40	53	-46	47	5.07
40	38	-54	47	5.53
L inferior parietal lobule				
40	-57	-27	38	8.94

40	-48	-43	43	5.66
R fusiform gyrus				
37	36	-48	-16	5.20
L fusiform gyrus				
37	-48	-59	-12	8.47
L occipital cortex				
19	-44	-70	-7	5.18

Figure 7.4. Time course of regional activity relating to encoding, delay and response events. Dotted Blue lines refer to the structured trials, while continuous red lines refer to the non-structured trials. (A) - (C) show neural responses at the maximal activation peak in left lateral prefrontal cortex (co-ordinates -46 13 21 – see table 7.1 above), while (D) - (F) show neural responses at the maximal activation peak in the right lateral prefrontal cortex (co-ordinates 46 13 20 – see table 7.1 above). (A) and (D) relate to the encoding stage, (B) and (E) relate to the delay stage, and (C) and (F) relate to the response stage. Functions show magnitude (arbitrary units) of fitted response to each task event, following deconvolution of event durations.



7.3.2.2 - Single subject analysis

The single subject analysis differed from the group analysis in that the spread of prefrontal activation was more diffuse, usually including both the mid-DLPFC and mid-VPFC. Of the 16 subjects tested, 13 subjects exhibited significant lateral prefrontal activation for the comparison of structured minus non-structured trials, at the threshold of p=0.001 uncorrected (see table 7.2).

Table 7.2 - Peak activations for the single subject structured sequences minus non-structured sequences comparison.

Subject	**Lateral PFC area**	**x co-ord**	**y co-ord**	**z co-ord**	**t score**
S1	*Ventrolateral*				
	L BA 47/11	-20	38	-16	3.16
S2	*Ventrolateral*				
	R BA 45/46	50	36	6	5.08
	L BA 45/47	-54	26	-2	3.33
	Dorsolateral				
	R BA 9	58	16	34	4.07
	L BA 9/8	-44	18	30	3.65
	L BA 9	-54	14	36	3.13
	Anterior				
	L BA 10/47	-50	42	-8	3.37

	L BA 10	-42	52	-4	3.3
S3	*Ventrolateral*				
	R BA 47	44	38	-8	3.17
	R BA 47	60	24	-2	3.82
	R BA 44	62	14	28	3.22
	L BA 47	-46	26	-16	5.1
	L BA 47	-56	22	-6	4.66
	L BA 46	-52	42	2	5.07
	Dorsolateral				
	R BA 45/46	52	36	12	4.86
	R BA 9	48	18	32	3.36
	R BA 9	44	38	36	3.54
	R BA 8	24	36	48	3.61
	Anterior				
	R BA 10	52	44	-10	3.6
S4	*Ventrolateral*				
	R BA 47	40	28	-22	3.42
	R BA 45/47	62	18	-2	3.32
	R BA 45	62	24	16	3.16
	L BA 47	-44	32	-24	3.75
	Dorsolateral				
	L BA 8	-46	18	48	3.23

S5	*Ventrolateral*				
	R BA 47	36	40	-18	3.14
	R BA 47/11	26	42	-16	3.28
	R BA 47	44	34	-8	3.34
	R BA 47/45	50	36	0	3.85
	R BA 45	56	20	16	3.74
	L BA 47	-44	36	-12	3.16
	L BA 45	-52	34	14	3.61
	Dorsolateral				
	R BA 9	60	22	28	3.19
	L BA 9	-48	18	28	4.46
S6	nothing passing threshold				
S7	*Ventrolateral*				
	R BA 47	46	30	-16	3.64
	R BA 47	30	38	-14	3.13
	L BA 47	-50	42	-12	3.28
	L BA 44	-40	12	24	3.73
	Dorsolateral				
	R BA 46	52	36	18	3.18
	R BA 46	56	28	24	3.23
	R BA 8/44	34	10	32	4.83

	Anterior				
	R BA 10	42	54	-16	3.6
S8	nothing passing threshold				
S9	*Ventrolateral*				
	L BA 47	-30	44	-22	3.24
	L BA 44	-42	10	20	3.79
	L BA 45/46	-40	36	10	3.28
	Dorsolateral				
	R BA 46/45	42	32	16	3.77
S10	*Ventrolateral*				
	R BA 45	48	30	4	4.3
	R BA 44	48	16	16	3.52
	L BA 47	-50	18	-2	4.19
	L BA 47	-40	32	2	4.11
	Dorsolateral				
	R BA 9/45	52	24	22	3.3
	R BA 9	-48	12	30	3.15
	L BA 46	-38	28	20	4.6
	Anterior				
	R BA 10	40	50	12	3.15

S11	nothing passing threshold				
S12	*Ventrolateral*				
	R BA 47	38	38	-6	4.08
	L BA 47	-56	30	-6	4.18
	L BA 45	-46	36	8	4.92
	L BA 44/45	-52	14	18	5.13
	Dorsolateral				
	R BA 46	56	38	12	5.59
	R BA 46	52	42	18	4.86
	R BA 46/9	58	28	24	3.98
	L BA 46	-50	38	0	5.07
	L BA 8	-52	14	44	3.44
	Anterior				
	R BA 10/46	48	44	-6	3.98
	R BA 10	28	64	14	4.32
	L BA 11	-26	48	-24	4.26
	L BA 10	-22	64	8	4.84
S13	*Dorsolateral*				
	R BA 46	52	38	14	3.37
	R BA 46	44	42	14	3.44
	R BA 46/45	42	34	18	3.41
	L BA 46/10	-44	50	4	4.32

S14	*Ventrolateral*				
	R BA 47/45	54	36	-4	3.85
S15	*Ventrolateral*				
	L BA 45/46	-50	30	14	3.32
S16	*Ventrolateral*				
	R BA 45/46	58	36	4	6.67
	R BA 44	64	16	24	3.62
	R BA 44	52	12	22	3.62
	L BA 47	-46	38	-22	3.95
	L BA 44/45	-42	14	16	4.29
	Dorsolateral				
	L BA 46	-48	40	14	4.66
	L BA 46/9	-52	34	22	4.31
	L BA 9	-54	24	32	3.82
	Anterior				
	L BA 10	-44	52	-10	3.30

7.4 - DISCUSSION

Neurologically normal participants performed a spatial span task on a 4 x 4 array, while being scanned using fMRI. Two types of span were used - spans that utilised the regular array to produce highly structured sequences (that tended to form regular shapes, such as squares, triangles, etc.), or spans that minimised the structured nature of the sequence. While both accuracy and speed were significantly better for the structured sequences, lateral prefrontal cortex activation was observed when the non-structured sequences were directly subtracted from the structured sequences. This result was observed both at the group level and at the single subject level, with almost all volunteers activating the lateral prefrontal cortex for this comparison. In addition, a further set of analyses indicated that the activation reflected processing demands at encoding, rather than rehearsal or response.

These data provide evidence that the lateral prefrontal cortex is involved in strategy optimisation, without the potential confound of task difficulty. A more specific way of viewing this particular form of strategic control might relate to the concept of "chunking" (Miller 1956). "Chunking" as a strategy for encoding blocks of information within memory has been well studied in cognitive psychology (Miller 1956; Ericcson, Chase et al. 1980). Organisation of materials into familiar or regular structures can increase working memory capacity, sometimes very substantially (Ericcson, Chase et al. 1980), and has been proposed as one major basis for expertise in a variety of domains including sending and receiving Morse code (Bryan and Harter 1899) and chess (Chase and Simon 1973). Chunking in this case could have occurred as the four locations were recoded into regular shapes, such as squares, diamonds, etc.

The results can be interpreted as showing that the implementation of chunking strategies at encoding relies on co-recruitment of specific frontal and posterior systems. The fusiform gyrus has been repeatedly associated with object perception, and object recognition is impaired following damage to this region in patients (Arguin, Bub et al. 1996; Gerlach, Law et al. 1999). It is suggested that patterns or structure in spatial sequences are detected early in the visual processing stream by neurons in the fusiform region, effectively generating candidate structured descriptions of the material to be remembered. The lateral frontal cortex – perhaps acting in concert with the inferior parietal cortex - may act on this information by selecting the most useful descriptions for memory. In this way, the lateral frontal cortex may play an essential role in selecting appropriate high-level organisational 'chunks' which then serve to facilitate memory by reducing overall cognitive load.

Neuroimaging results have often been taken to suggest a role for prefrontal cortex, not just in storage, but in control and organisation of working memory contents (Owen 1997; D'Esposito, Aguirre et al. 1998). Increased activity in dorsolateral prefrontal cortex is associated, for example, with the requirement to reorganize a sequence of digits or letters into reverse (Owen, Lee et al. 2000) or alphabetical (Postle, Berger et al. 1999) order. In such cases, however, increased control demands are generally confounded with large increases in task difficulty, making prefrontal recruitment impossible to associate with specific control operations. Across domains as diverse as working memory, response selection and perceptual recognition, indeed, recruitment of lateral frontal cortex is generally increased with increasing task difficulty (Duncan and Owen 2000). In the case of chunking, this association is reversed, greater prefrontal recruitment being associated with easier sequences. These data show frontal involvement in construction of an optimal working memory strategy.

It should be pointed out that the lateral prefrontal peak of activation in the group analysis is somewhat posterior to what is commonly seen in working memory paradigms (Awh, Jonides et al. 1996; Owen, Doyon et al. 1996; Jonides, Schumacher et al. 1997; Owen, Herrod et al. 1999), where the mid-DLPFC instead is activated. However, if the threshold is lowered, the spread of activation extends to these regions, while in the single subject analyses, the mid-DLPFC and mid-VPFC were commonly activated, suggesting that these results are indeed related to other studies exploring working memory.

Chapter 8: Large-scale study on variations of the spatial span task

8.1 - INTRODUCTION

As part of a public science exhibition (Creating Sparks 2000), an opportunity arose to perform a large-scale behavioural experiment at the London Science Museum. This experiment was designed to test a set of hypotheses about the previous work in this thesis, and relating issues concerning the possible role of strategies in spatial span.

While the results of the PET study described in chapter 4 suggested that the structured array span task may differentially recruit the DLPFC, the reasons for this effect are not at all clear. The result is all the more interesting theoretically since almost all subjects reported that the structured array span task was the easier of the two tasks. For an easier task to be associated with greater lateral PFC demands raises critical questions for the prevailing view that the more difficult a task, the more activation would be observed in lateral PFC (Duncan and Owen 2000). A non-significant trend among the control subjects in the patient study described in chapter 6 also suggested that the structured array span task is the easier task. Although in neither case was the result statistically robust, this may simply reflect the small numbers of subjects included in the imaging and patient studies. An experiment was designed to test whether given a larger sample, performance on the structured array span task would indeed be better than the non-structured array span task.

In the PET experiment in chapter 4, when subjects were asked what strategies they had used during the two span conditions, different answers were given for the two

tasks. For the non-structured array span task, subjects almost exclusively reported joining the individual stimuli using "imaginary lines." However, for the structured array span task, subjects reported a range of more complex strategies, most commonly involving chunking the sequence into regular shapes (e.g. squares, rectangles, triangles) in order to aid memory. This raised the intriguing possibility that the degree of "order" within a stimulus array or within the stimulus sequence itself (as a function of the degree of order within an array) may facilitate specific types of strategies among subjects, and further, that such strategies may underlie the DLPFC involvement in these tasks.

In the fMRI experiment in chapter 7, behavioural differences between the structured and non-structured span tasks provided preliminary evidence that the greater organisational nature of the structured span trials gave rise to more effective encoding strategies. Although a strategy analogous to chunking seems to be the most obvious basis of this improvement, conclusive evidence was lacking.

In order to further investigate the specific nature of mnemonic strategies applied to the structured array span task of chapters 3,4, 5 and 6 and the structured span trials of chapter 7, subtly different versions of the spatial span task were employed, which differed principally in terms of the specific strategies that could be applied to the sequences. For instance, it was suggested in the previous chapter that the structured sequences were spatially chunked into regular shapes to lower mnemonic demands. Two conditions in this experiment were designed to be identical, except for the ease with which the stimuli could be spatially chunked. If such a strategy is indeed relevant to spatial span, then it would follow that the condition where the chunking strategy is more obviously available would have a performance benefit.

In addition, given the large number of subjects that were to take part in the experiment, a number of other factors that could modulate performance on spatial span tasks were simultaneously investigated. For example, it is possible that the differences between the structured and non-structured trials of the fMRI experiment of chapter 7 *could* have been attributed to a greater amount of spatial interference within the non-structured trials, leading to interference. In other words, if subjects utilised the "imaginary lines" strategy for both types of trials, then it may well have been that lines crossed-over more often within a sequence for the non-structured trials. In order to ascertain whether this is an important factor, two conditions that maximised or minimised the numbers of crossovers within each span trial were given to subjects.

The opportunity was also taken to examine spatial analogies of an important working memory result, known as the word-length effect (Baddeley, Thomson et al. 1975). The word length effect relates to the observation that the time it takes to articulate words is inversely proportional to success rates at retrieving such words from short term memory (Baddeley, Thomson et al. 1975). This word length effect has been critical in supporting theories of the underlying mechanism of short term memory; it has been suggested from the word length effect that rehearsal is necessary to refresh items in short term memory that would otherwise decay over time. Shorter words are more likely to be recalled because the rehearsal rate is faster than the decay rate, while this is less likely to be the case for longer words. Smyth and Scholey (Smyth and Scholey 1994) developed a series of tests involving spatial span that they hoped would provide a spatial analog of the word length effect. In that study, the authors varied the distance between squares in a spatial span task, in order to vary the response times. So while the array involving shorter distances was analogous to short words, the array that was more spaced out was analogous to longer words. Although

they failed to find a similar effect for spatial span as the word length effect, this may again be due to lack of sensitivity of their method of applying and scoring the span tasks. By applying the more sensitive paradigm applied in chapters 5 and 6 (i.e. the "ratchet" method of presenting spans) for spaced-out and compressed spatial arrays, it may be possible to discover a clear analogy to the word length effect in the spatial domain.

Finally, Smyth et al. (Smyth and Scholey 1994) varied the number of possible stimuli for each span. Different experiments in this thesis in addition have used different numbers of possible stimuli (chapters 3, 4, 5 and 6 all using 8 possible stimuli, while chapter 6 used 16). While it is not clear what effect this may have, there is some evidence that a critical factor in frontal lobe involvement may be the size of the set from which a given sequence of remembered items is drawn. For example, Petrides has argued that increasing the potential set size within the visual domain increases the "monitoring" demands of the task (Petrides 1995; Petrides 2000). In order to test this suggestion, the number of possible items from which to make a response in the spatial span task was varied, with all other factors held constant.

8.2 - METHODS

Throughout the month of September 2000, coinciding with the Creating Sparks science festival, an unattended machine involving a sealed computer, touch-screen monitor and a small video camera (see figure 8.1) was placed in the London Science Museum. This machine was constantly on, with a video loop encouraging subjects to take part in the experiment.

Figure 8.1 – An illustration of the machine used to test subjects in the Science Museum, with the touch screen monitor towards the top

8.2.1 - Subjects

Subjects were asked three questions before the experiments commenced: whether they had participated in the experiment before, their gender and their age. For age answers, all ages could be entered exactly, except those who were 70 or over, who were all classed together as "69+". To verify the authenticity of these answers, two photographs were obtained of the subject before the beginning of the experiments. In this way, it was possible to check roughly whether subjects were answering all the questions correctly.

After removal of datasets where subjects had not completed the experiment, datasets where subjects had admitted taking part in the experiment before (or where it was obvious from the photographs that this had been the case), or outliers (those subjects with a span average of 3 or less), 1345 volunteers participated. All volunteers were visitors to the London Science Museum during September 2000. 546 volunteers were female, while 799 were male. The average age for volunteers was 27.3.

8.2.2 - Stimuli and Testing Conditions

The task was clearly explained to the subjects via a short instruction video on the touch-screen monitor in front of them. Each subject performed just one block of 10 trials of a spatial span task. Which version the subject performed was randomly assigned out of 13 different types of span condition (for details see below). All conditions except 12 and 13 shared the following details: the stimuli were between 8 and 16 red squares (3 cm x 3 cm) presented on a black background, on a high-resolution, touch sensitive monitor. One of the red squares would turn blue for 500 ms before turning red again. 250 ms after this, a second red square would turn blue for

500 ms and so on, until a specified number of squares (initially five) had turned blue. Once the last square had turned red again, a short auditory signal indicated that the subjects were required to respond by touching the squares on the touch-sensitive monitor in the order that they had just appeared. If the subjects were able to reproduce the span without errors, the span length of the subsequent trial would be increased by one. However, if any errors were made, the span length of the subsequent trial would be decreased by one. Since a given span would never involve the same square twice, the maximum possible span length was equal to the number of squares in that condition, while the minimum span length was always 1. Allowable response time was a function of the current span length (3000 ms + (1250 ms * current span length)).

The possible conditions were:

Variant 1: Standard Structured Array (2 x 4 Squares)

This task was identical to the structured array task of the behavioural study of chapter 5 and the patient study of chapter 6 (see sections 5.2.2, 6.2.2 and figure 8.2). Stimuli were randomly generated.

Variant 2: Standard Non-Structured Array (8 Squares)

This task was identical to the non-structured array span task used for the behavioural study of chapter 5 and the patient study in chapter 6 (see sections 5.2.2, 6.2.2 and figure 8.2). Stimuli were randomly generated.

A comparison between variants 1 and 2 was carried out to test whether, given a large enough group of subjects, the structured spatial array would indeed lead to improved performance, confirming that there is a clear behavioural advantage arising from a structured array.

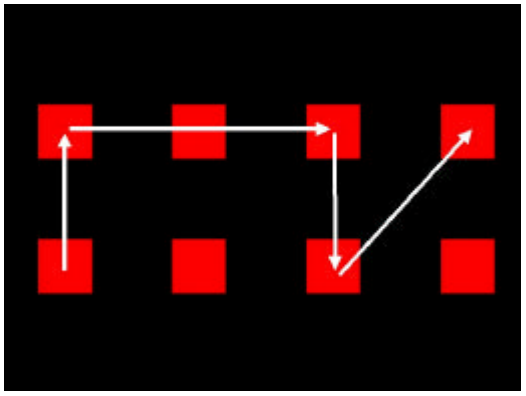


Fig 8.2a – Variant 1

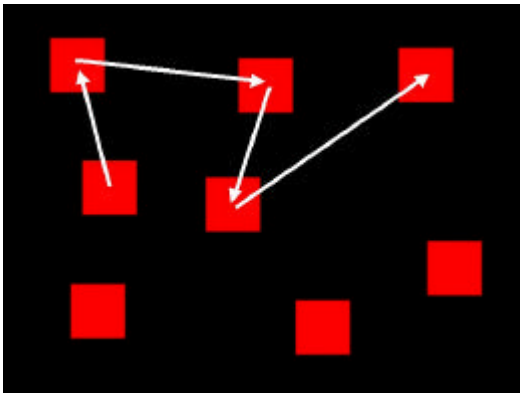


Fig 8.2b – Variant 2

Figure 8.2 - Examples of **a)** the standard structured array (2 x 4 Squares) task and **b)** the standard non-structured array (8 Squares) task.

Variant 3: Standard Structured Array (4 x 4 Squares)

This task was identical to that of variant 1, except that instead of a 2 x 4 matrix, a 4 x 4 orderly matrix of possible stimuli was used (see figure 8.3). Stimuli were randomly generated.

Variant 4: Standard Non-Structured Array (16 Squares)

This task was identical to that of variant 2, except that instead of 8 squares presented in pseudo-random locations, 16 squares in pseudo random locations were used (see figure 8.3). Stimuli were randomly generated.

A comparison between variants 3 and 4 was carried out to make the same test

as the comparison between variants 1 and 2, except with 16 squares instead of 8. In addition, variant 3 was compared with variant 1 and variant 4 was compared with variant 2 so that the effect of number of stimuli (8 versus 16) in the array could be tested.

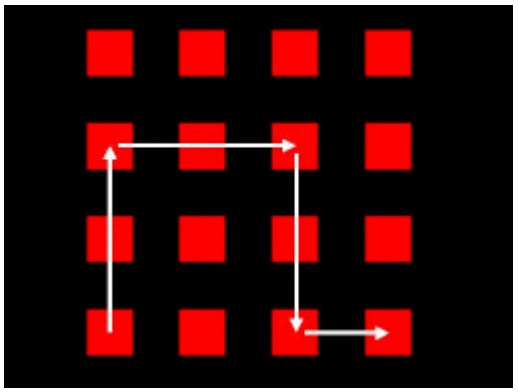


Fig 8.3a – Variant 3

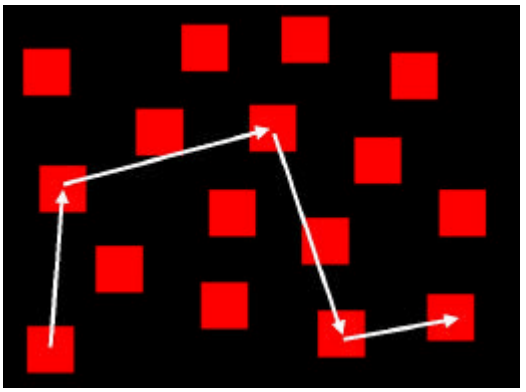


Fig 8.3b – Variant 4

Figure 8.3 - Examples of **a)** the standard structured array (4 x 4 Squares) task and **b)** the standard non-structured array (16 Squares) task

Variant 5: Circle With Crossovers (12 squares)

12 squares were presented on the screen as if marking out the numbers of a circular clock-face (see figure 8.4). If lines were drawn between stimuli in any given span, the number of times these lines would cross was maximised. Stimuli were generated from a pre-arranged list.

Variant 6: Circle Without Crossovers (12 squares) – The layout of the squares was identical to that of variant 5 (see figure 8.4). In contrast, if lines were

drawn between stimuli in any given span, the lines would never cross. Stimuli were generated from a pre-arranged list.

This comparison was made to assess whether the number of "crossovers" was a significant factor in determining span performance. If a difference is found between these two variants, then this would suggest that at least part of the behavioural difference between the two types of span in the fMRI study of chapter 7 was not due to strategies but to a difference in the level of interference between stimuli.

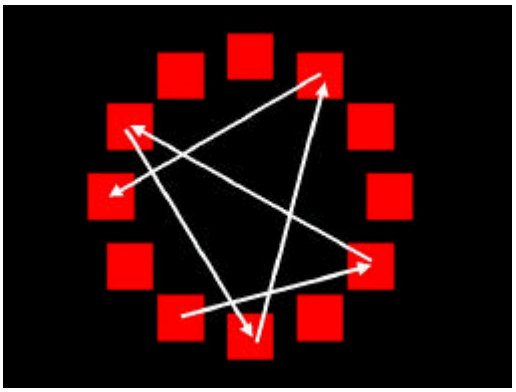


Fig 8.4a – Variant 5

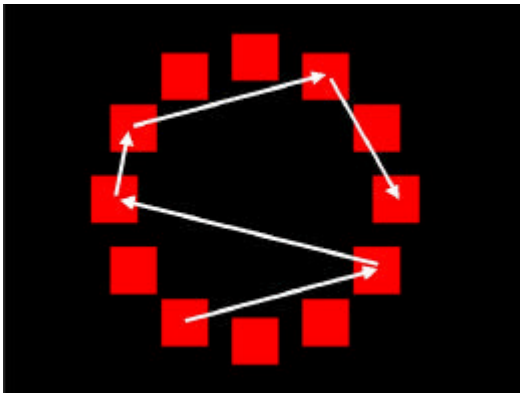


Fig 8.4b – Variant 6

Figure 8.4 - Examples of **a)** the circle with crossovers task and **b)** the circle without crossovers task.

Variant 7: Structured "Squashed" Array (2 x 4 Squares)

This task was identical to that of variant 1, except that the location of each square in the stimulus array was warped towards the centre of the screen (see figure 8.5). Stimuli were randomly generated.

Variant 8: Structured "Stretched" Array (2 x 4 Squares)

This task was identical to that of variant 1, except that the location of each square in the stimulus array was warped towards the edge of the screen (see figure 8.5). Stimuli were randomly generated.

This comparison was designed to test whether the average distance between stimuli in the array is a relevant factor that contributes to span performance. This question relates directly to the possibility of a word length effect in the spatial domain. If there is such an effect, there should be an increase in performance relating to the compressed array of variant 7. In addition, the standard array of variant 1 should have a performance score in between variants 7 and 8.

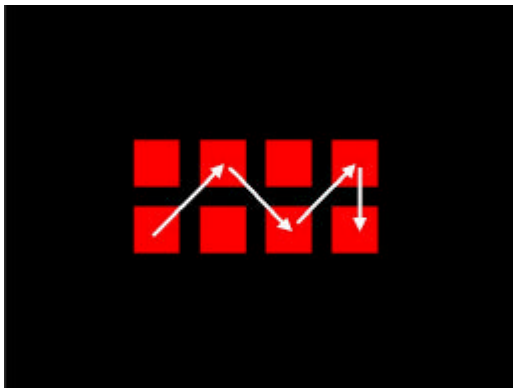


Fig 8.5a – Variant 7

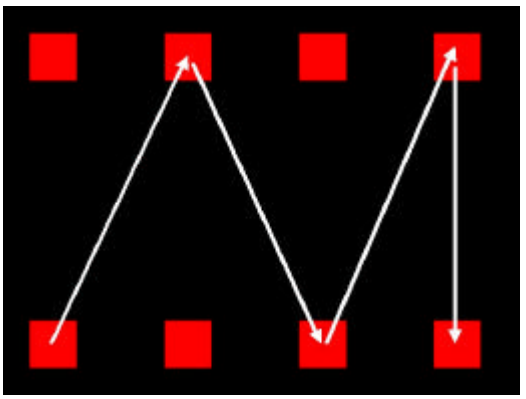


Fig 8.5b – Variant 8

Figure 8.5 - Examples of **a)** the structured squashed array (2 x 4 Squares) task and **b)** the structured stretched array (2 x 4 Squares) task

Variant 9: Non-Structured "Squashed" Array (8 Squares) - This task was identical to variant 2, except that the location of each stimulus in the stimulus array was warped towards the centre of the screen (see figure 8.6). There was no "stretched" equivalent since most squares of the standard non-structured array of variant 2 were already close to the edge of the screen. Stimuli were randomly generated.

This comparison was designed as a non-structured equivalent of the structured squashed versus stretched array comparison (see variants 7 and 8). If there is an equivalent of the word length effect in the spatial domain, then there should be a performance benefit for the squashed array of variant 9, compared with variant 2.

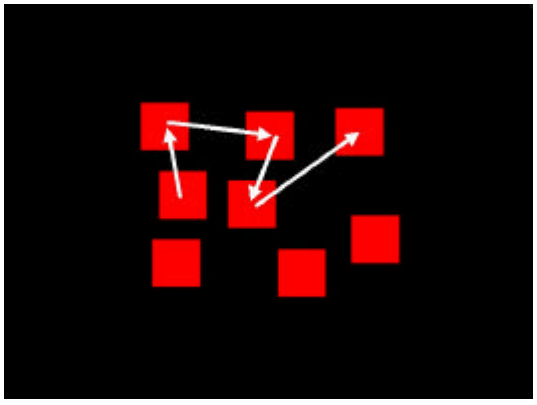


Fig 8.6a – Variant 9

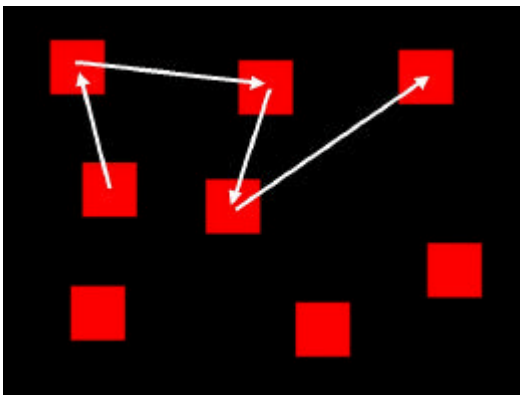


Fig 8.6b – Variant 2

Figure 8.6 - Examples of **a)** the non-structured squashed array task and **b)** the non-structured standard array (8 squares) task, i.e. the task from fig 7.2b. Given the constraints of giving the non-structured standard array a truly random appearance, further stretching of this array was not possible from that of variant 2.

Variant 10: Structured Spans (4 x 4 Squares)

This task was identical to the structured span trials of the fMRI study of chapter 7, except for the "ratchet" nature of the span length over the 10 trials (see figure 8.7). Stimuli were generated from a pre-arranged list.

Variant 11: Non-Structured Spans (4 x 4 Squares)

This task was identical to the non-structured span trials of the fMRI study of chapter 7, except for the "ratchet" nature of the span length over the 10 trials (see figure 8.7). Stimuli were generated from a pre-arranged list.

Spans between variants 10 and 11 were roughly matched for the average distance between contiguous stimuli in a sequence. This comparison was used to replicate the behavioural results of chapter 7, which indicated both an accuracy and reaction time benefit for the structured spans.

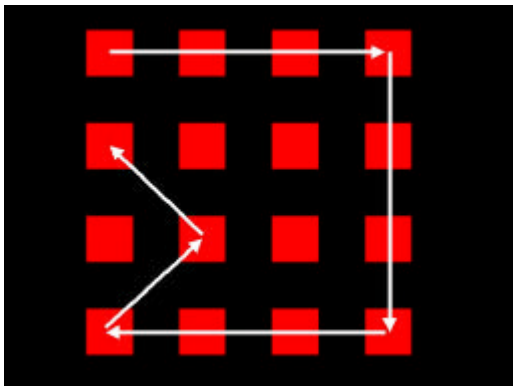


Fig 8.7a – Variant 10

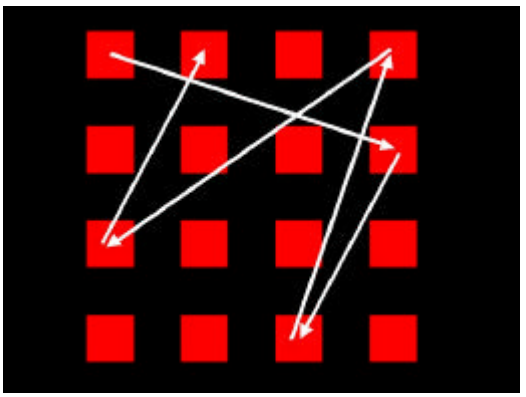


Fig 8.7b – Variant 11

Figure 8.7 - Examples of **a)** the structured spans task and **b)** the non-structured spans task.

Variant 12: Congruent spatio-temporal spans task

This task was similar to that of variant 10, except that during every span trial, two structured sequences (making squares, triangles, etc.) were joined by a single irregular step (see figure 8.8). During the middle of the sequence, an extended inter-stimulus interval (500 ms in addition to the usual inter-stimulus interval) was added immediately before the non-structured "step" to attempt to enhance the appearance of the two structured sections within the span.

Variant 13: Incongruent spatio-temporal spans task

This task was identical to that of variant 12, except that the extended inter-stimulus interval occurred either one stimulus before or after its occurrence in the same span for the congruent condition, thus minimising the appearance of two regular sections (see figure 8.8).

Variants 12 and 13 were matched according to how close to the middle of a span the extra pause would be presented. Exactly the same stimulus set, generated from a pre-arranged list, was used for both variants. This comparison was used to test whether the strategy of spatially chunking the stimuli into regular shapes is indeed a relevant strategy in such spatial span tasks.

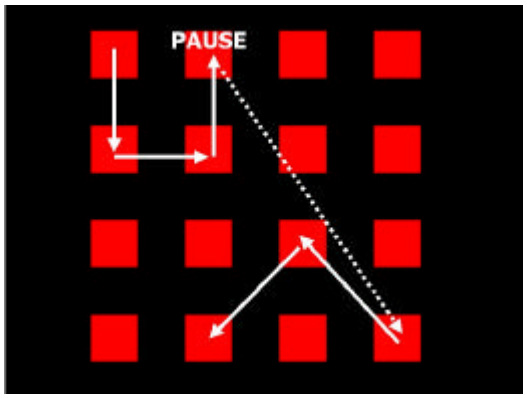


Fig 8.8a – Variant 12

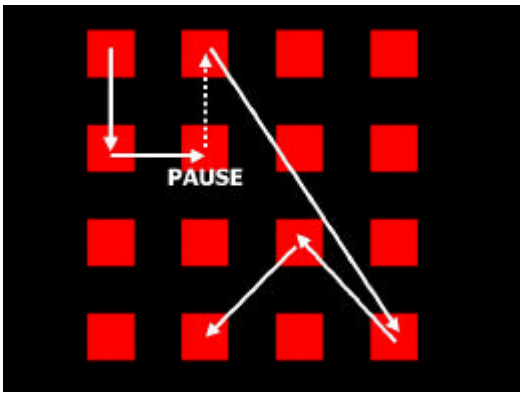


Fig 8.8b – Variant 13

Figure 8.8 - Examples of **a)** the congruent spatio-temporal spans task and **b)** the incongruent spatio-temporal spans task.

8.3 - RESULTS

8.3.1 - Uniformity of groups

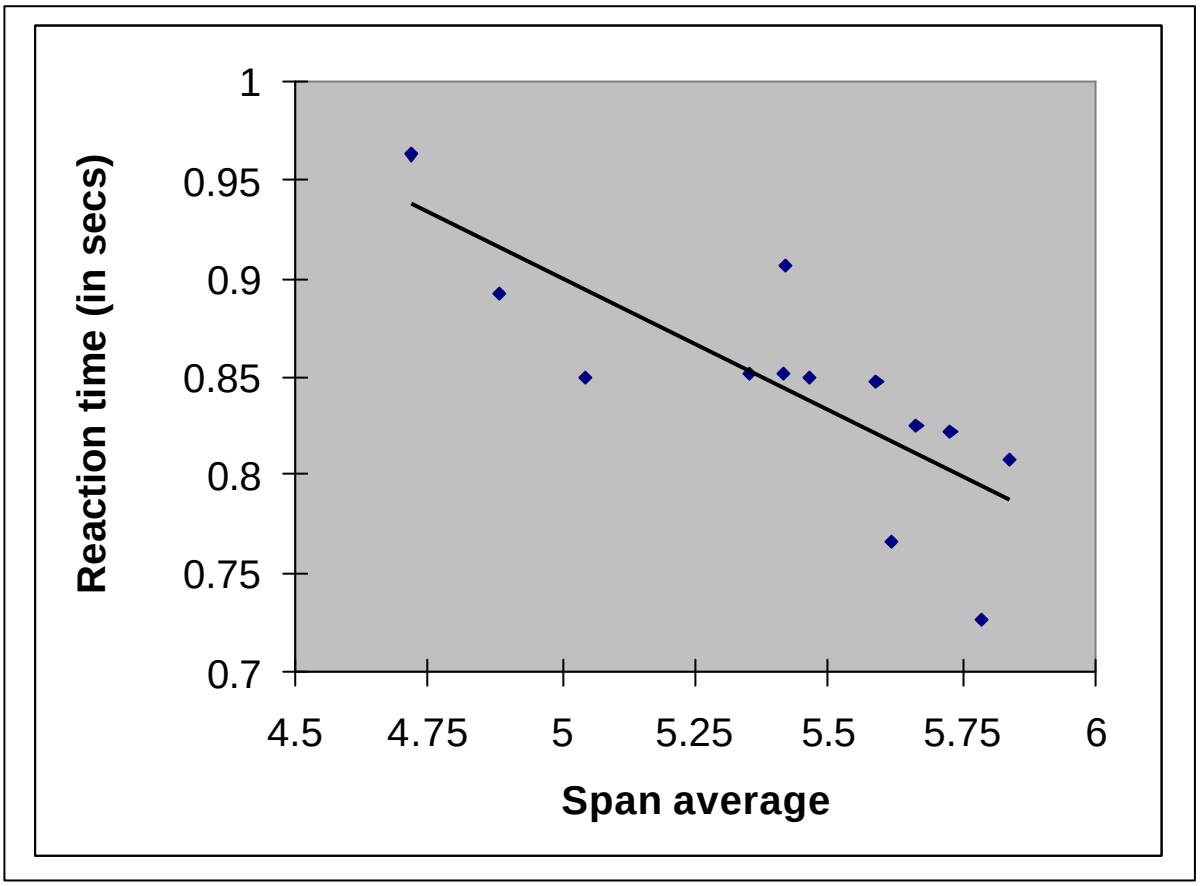
A one-way ANOVA was conducted across the 13 conditions for the factor of age, which revealed that the groups did not differ by age {F (12, 1332) = 0.574, p = 0.864}. Furthermore, a Chi-squared test indicated that there was no difference in the male to female ratio between groups (Chi-Squared = 6.79, df = 12, p = 0.871).

8.3.2 - Overall trends

On a single subject level, there was a significant negative correlation between average reaction time per response for all responses in a condition and average span score across the condition {r = 0.245, F (1,1344) = 85.76, p < 0.001}.

When the subject scores were collapsed across the condition, there was also a significant negative correlation between average reaction time per response for all subjects for a given condition and overall average reaction time for that condition {r = 0.79, F(1,12) = 17.97 p = 0.0001} (see figure 8.9).

Figure 8.9 - Relationship between span score average and reaction time per condition. The y-axis relates to the average reaction time per response for a given condition collapsed across subjects. The x-axis relates to the average reaction time for a given condition collapsed across subjects. Each data-point relates to a single condition.



8.3.3 - Differences between groups

A subject's span score was calculated as the average of the span length presented over the 10 trials. All reaction time figures relate to the average time it took to hit a single target. Figure 8.10 shows the average span score for each condition, while figure 8.11 shows the average reaction time for each condition.

In addition, table 8.1 provides a summary of the results.

Figure 8.10 - Average span scores by condition, with standard error bars.

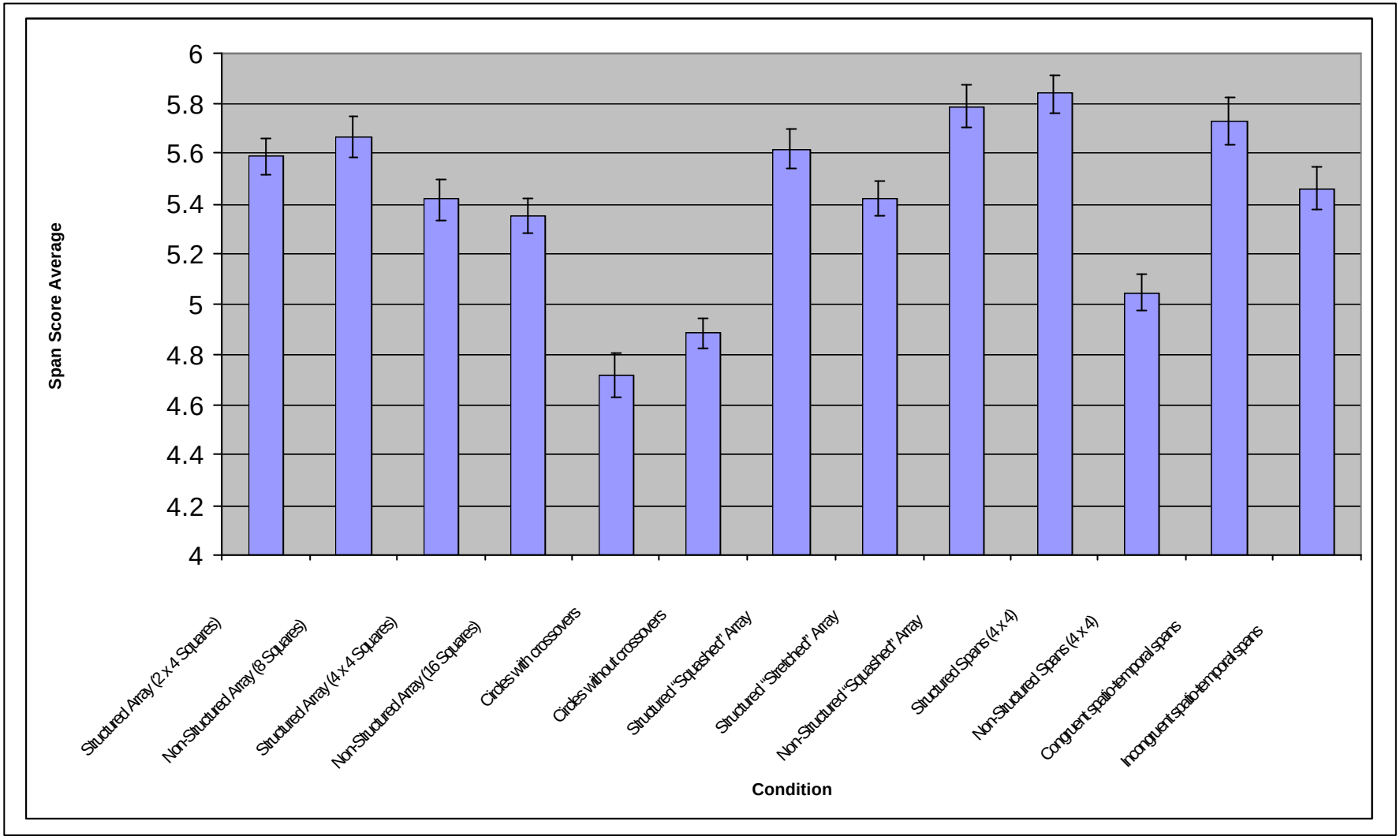
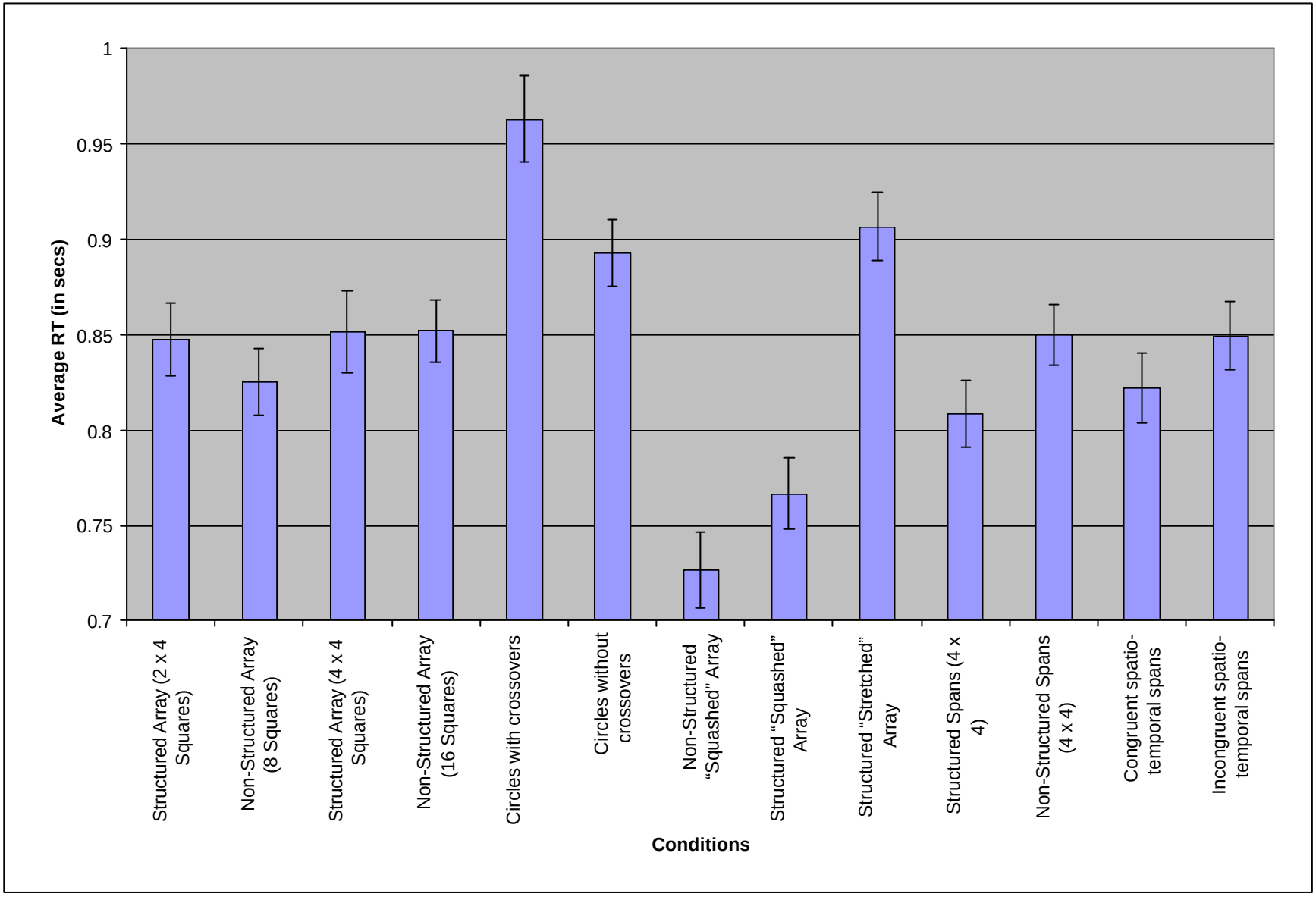


Figure 8.11 - Average reaction times by condition, with standard error bars.



a) Effect on performance of structuring the array and number of stimuli in the array

A 2 x 2 factorial analysis was run for variants 1 to 4 (structured 2 x 4 array, non-structured 8 square array, structured 4 x 4 array and non-structured 16 square array), examining the effect on average span score of whether the array was structured or unstructured, and the number of possible stimuli in the array (8 versus 16). There was a significant effect of number of possible stimuli {$F(1,440) = 10.779$, $p < 0.001$), no significant effect of type of array, and no significant interaction.

When the standard structured array group average span with 8 squares (5.59) was compared with the equivalent 4 x 4 squares condition span (5.42), the difference failed to reach significance {($F(1, 210) = 2.64$, $p = 0.11$}. However, when the equivalent comparison was made between the non-structured array 8 squares average span (5.67) and the 16 squares span (5.35), subjects performed significantly better in the 8 square condition {($F(1, 227) = 9.21$, $p = 0.003$}.

A 2 x 2 factorial analysis was run for variants 1 to 4 (structured 2 x 4 array, non-structured 8 square array, structured 4 x 4 array and non-structured 16 square array), examining the effect on average reaction time per response of whether the array was structured or unstructured, and the number of possible stimuli in the array (8 versus 16). There was no significant effect of number of possible stimuli, no significant effect of type of array, nor was there any significant interaction between the two.

b) Effect on performance of size of the array

A one-way ANOVA was run for variants 2,7,8 and 9 (structured 2 x 4 "squashed" and non-structured 8 square "squashed" versus the non-structured 8 square standard array and the structured "stretched" array), examining the effect on average span score of whether the array was "squashed" or "stretched". There was a significant effect of the size of the array {(F(1, 403) = 4.17, p = 0.042}, with the more "squashed" array being performed with a significantly higher span score.

For the structured array comparison, the difference between the "squashed" array average span (5.62) and the "stretched" array average span (5.42) approached significance {(F(1, 200) = 3.45, p = 0.065}, while the equivalent non-structured "squashed" (5.79) vs. standard array (5.67) had the same trend, though didn't approach significance {(F(1, 200) = 1.13, p = 0.289}.

A one-way ANOVA was also run for variants 2,7,8 and 9 (structured 2 x 4 "squashed" and non-structured 8 square "squashed" versus the non-structured 8 square standard array and the structured "stretched" array), examining the effect on average reaction time per response of whether the array was "squashed" or "stretched". There was a significant effect of the size of the array {(F(1, 403) = 41.77, p < 0.001}, with the shortest reaction times for the "squashed" arrays.

For the structured array comparison, the "squashed" structured array reaction time (0.767) was significantly less than the "stretched" structured array reaction time average (0.906) {(F(1, 200) = 26.40, p < 0.001}, while the same was true of the "squashed" non-structured array (0.727) compared with the standard non-structured array reaction time (0.825) {(F(1, 200) = 15.65, p < 0.001}.

c) Comparisons of structured vs. non-structured spans

When the structured span condition span score (5.84) was compared with the non-structured span condition span score (5.05), the structured span group performed significantly better {(F(1, 210) = 56.79, p < 0.0001}. However, the difference between the structured span (0.808 secs) and the non-structured span (0.850 secs) condition average reaction time just failed to reach significance {(F(1, 210) = 3.11, p = 0.079}.

d) Comparisons of congruent vs. incongruent spatio-temporal spans tasks

When the congruent span group average (5.73) was compared with the incongruent span group average (5.46), the congruent span group performed significantly better {(F(1, 200) = 4.45, p < 0.036}. However there was no significant difference when reaction times between the congruent (0.822 secs) and incongruent spans groups (0.849) were compared {(F(1, 200) = 1.16, p = 0.28}.

e) Circle array with crossovers vs. circle array without crossovers task

Subjects performing the circular array condition involving the maximising of crossovers achieved a marginally worse score (4.72) than those that performed the condition without crossovers (4.88), although this did not reach significance {(F(1, 191) = 2.58, p = 0.11}. The difference in average reaction time, however, between the crossovers condition (0.963) and the condition without crossovers (0.893) did reach significance {(F(1, 191) = 6.14, p = 0.014}.

f) Comparison of types of structured array

Examination of the average span scores in Figure 8.10 revealed a clear tendency for the circles task to be performed more poorly than any of the other tasks. This result seems rather surprising since the results of chapters 3 to 6 would suggest that a structured array should lead to the same or even improved performance. In many ways a clock face configuration is a more structured array (e.g. greater symmetry) than the configuration used in variant 1. Since the circles tasks varied with respect to the number of crossovers (which were randomly manipulated in the other tasks) an average was computed for the two circles tasks together. Since the number of items in the circle tasks (12) did not equate to any of those used in the more quadrilateral structured array tasks, an average was computed between variants 1 (8 items structured array) and 3 (16 items structured array).

The average span score for the circles tasks (4.81) was significantly less than the average span score for the combined 2 x 4 and 4 x 4 structured array spans tasks average span score (5.51) {$F(1,404) = 88.57$, $p < 0.001$}. In addition, the average reaction time for the circles tasks (0.925) was significantly slower than the average reaction time for the 2 x 4 and 4 x 4 structured array spans tasks (0.849) {$F(1,404) = 13.86$, $p < 0.001$}.

Table 8.1 – Summary of results for the group comparisons. "V" stands for "variant", and "NS" stands for "non-significant".

Comparison	More accurate?	Faster responses?
8 vs. 16 stimuli in array (V1,2 vs. 3,4)	**8**	**NS**
Structured vs. non-structured array (V1,3 vs. 2,4)	**NS**	**NS**
Squashed vs. stretched array (V7,9 vs. 2,8)	**Squashed**	**Squashed**
Structured vs. non-structured spans (V10 vs. 11)	**Structured**	**NS**
Congruent vs. incongruent spans (V12 vs. 13)	**Congruent**	**NS**
Circles with vs. without crossover (V5 vs. 6)	**NS**	**Without Crossovers**
Circles vs. quadrilateral structured array (V5,6 vs. 1,3)	**Quadrilateral**	**Quadrilateral**

8.4 - DISCUSSION

In all previous chapters of this thesis, variants of spatial span were used to tap into neurophysiological mechanisms, either via neuroimaging or studies with frontal lobe patients. However, due to the constraints of these paradigms, it was not possible in each case to investigate fully the factors that modulate performance on the spatial span task. The present study sought to provide a behavioural framework for the neuropsychological results of previous chapters, by comparing the performance of groups who had performed different versions of the spatial span task.

In previous chapters there were hints that the 8 square structured array (figure 8.2a) was somewhat easier than the 8 square non-structured array (figure 8.2b). In chapter 4 almost all subjects reported finding the structured array task easier (see 4.3.1), while in the patient study of chapter 6, the normal control group performed slightly better on the structured array task (see 5.3). It was surprising, therefore, to find that when a large sample of volunteers were given the structured array 8 square span task, their performance was no different to another similarly large sample who had performed the non-structured array 8 square span task. There was also no difference for the equivalent comparison involving 16 squares. However, there is one key difference between the spans given in the PET study of chapter 4 and those of the present study, which may help to explain this apparent anomaly. In the PET study, spans were a fixed length (5), while in the present study, span scores were approximately at the maximum span of the volunteer throughout the experiment. Given that the fixed span length of the PET study was considerably lower than the average span of the volunteers in either the structured or non-structured array 8 square equivalents of this study, it is possible that sub-threshold spans increasingly

differentiate in terms of difficulty. For instance, a structured array span 1 less than a subject's threshold might be perceived as significantly easier - possibly due to strategic involvement - than a non-structured array span 1 less than a subject's threshold. It should also be pointed out that all comparisons in this study involved a between subject design while the subjects from the PET study were all given both the structured and non-structured array conditions. It is possible that had the volunteers in this study been given both the structured and non-structured array tasks, they would have reported finding the structured array task easier, despite showing no difference in span score.

In a replication of the behavioural result of the fMRI study reported in Chapter 7 (see 7.3.1), performance on the structured span 16 square array condition was significantly greater than for the equivalent non-structured span task. This indicates that volunteers were preferentially able to utilise the organisational structure of the 4 x 4 array for the structured spans, compared with the non-structured spans. More direct evidence for the cause of this difference in performance comes from the congruent and incongruent spatio-temporal conditions (see figure 8.8). Those that performed the condition that was designed to enhance the perception of regular shapes (the congruent condition) had a significantly higher span average than those that performed the condition that was designed to interfere with the perception of regular shapes (the incongruent condition). This is particularly striking given that the spans presented were identical for each condition, with only the place of the extra pause differing. This clearly indicates that the chunking of parts of a sequence into regular shapes is a relevant organisational strategy in the performance of the types of span task presented in the fMRI study of chapter 7. It therefore provides further evidence that the reason for the activation in lateral PFC when the structured spans were compared with the

non-structured spans in the fMRI study was due to the additional organisational processing, probably in the form of chunking, that occurred during the structured spans.

For the structured versus non-structured span comparison, it is possible that the difference in performance could instead be explained by greater "crossovers" in non-structured spans, which may interfere with span performance. Despite attempts to balance these conditions for crossovers, it was undoubtedly the case that the non-structured spans condition had a greater number of such sequences, due to the algorithm used to produce these spans. However, the explanation of crossovers to explain the difference in performance between these conditions is unlikely for two reasons. First of all, there was no difference in span score between the circles condition, where virtually every subsequent square "crossed-over" the overall sequence path, and the corresponding circles condition where this never happened. Also, there was a significant benefit of the congruent spatio-temporal span average compared to the incongruent spatio-temporal span average, despite both conditions sharing the same stimulus set and therefore identical number of "crossovers", indicating again that this factor is not relevant to the structured versus non-structured span comparison.

One intriguing result relating to the circle array conditions is that average span on these tasks was significantly worse than for equivalent quadrilateral structured array span conditions. This is surprising, given that the circles array is arguably the most structured of all, given the level of symmetry within the array. However, as mentioned in a previous chapter (see section 7.1), subjective reports during structured array tasks indicate that it is not the array itself that leads to the chunking strategies being applied, and therefore any potential performance benefit, but the actual

sequences themselves within the array. Due to the constraint of making both circles conditions obey rules to maximise or minimise the appearance of crossovers, one inadvertent result was that the spans themselves were almost always non-structured in nature (see figure 8.4 for examples). In addition, the array itself was not nearly as amenable to producing patterned shapes by chance as the more quadrilateral structured arrays (e.g. variants 1 and 3). In fact, the most appropriate comparison would be with the non-structured spans condition (variant 11), which in actual fact has the next worst average span score to the circles conditions. This all again confirms the importance of strategies as a factor in determining performance on seemingly straightforward working memory tasks, such as spatial span.

It was also found that the number of stimuli in the array was a significant factor in determining performance, with span conditions with 16 possible stimuli performed with a significantly lower span average than the equivalent conditions with only 8 possible stimuli. There were hints that the difference was greater for the non-structured arrays than the structured arrays, although the interaction was not significant. It is possible, however, that the greater strategic components relating to the structured arrays limited the difference between them. It is worth noting that the condition with the greatest span score, that of the structured spans (variant 10), was one such condition with 16 squares. This indicates that the strategic factor in these spans is a highly important aspect of performance.

In general, though, it may be that the greater number of choices for response in the 16 squares condition makes it more likely that a sequence not perfectly retrieved will be incorrect. These results are consistent with similar findings from a recent study (Fischer 2001). Fischer et al. found a performance benefit of presenting at the

retrieval phase of a spatial span task only the subset of target stimuli from the encoding phase, compared with the presentation of all nine stimuli.

Another factor found to modulate performance was the degree to which the spatial array was "squashed" or "stretched." For both average span score and reaction time, there was a significant benefit of the array being more "squashed" towards the centre. This factor may make the spatial component of the task more difficult when the spatial layout of the stimuli is larger. Instead, it is possible that the increase in reaction time that is probably due to larger motor responses is the cause of the decrement in performance (see later discussion about the spatial analogue of the word length effect). It is unclear whether this factor relates to results found previously in this thesis, since in each case spatial variants given to subjects were roughly matched for the average distance between the squares.

The differences in the average distance between squares of various spatial arrays does relate to an important issue in working memory, mentioned in the introduction to this chapter. Baddeley et al. (Baddeley, Thomson et al. 1975) demonstrated that the level of success of articulation of a sequence of verbal material was in part dependent on the rate of articulation. According to Baddeley (Baddeley 1986), covert rehearsal of a verbal sequence underlies this relationship. Smyth and Scholey (Smyth and Scholey 1994) attempted to extend this result into the spatial domain. They compared spatial span performance on the same array either expanded or contracted in a similar way to the span conditions of figures 8.5 and 8.6. The authors found no difference in performance between these arrays. However, only 36 subjects took part, and the means by which subjects were tested involved giving all subjects the same span lengths (i.e. 6 trials each at lengths from 4 to 7). The "ratchet" methodology of the current study, along with a larger sample size, allowed for a more

sensitive measure. Consequently, in contradiction to the study of Smyth and Scholey (Smyth and Scholey 1994), a significant benefit was found overall for the "squashed" pair of array conditions compared with the "stretched" pair of array conditions, with a corresponding benefit in reaction time for the "squashed" array conditions. This is consistent with a study by R.H. Logie (personal communication), when the difference between the array sizes was extended beyond the confines of a computer screen, and the larger array produced significantly worse performance, and significantly greater reaction time.

In a general sense, this result fits in with Baddeley's suggestion (Baddeley, Thomson et al. 1975; Baddeley 1986) that increased rehearsal time leads to a decrease in performance. However, a number of observations suggest that this might not be as true in the spatial domain as in the verbal domain. For example, in another contrast in this study that produced a significant difference in reaction time (the circle array tasks), there was no corresponding difference in performance. In addition, for the comparison that produced the most significant difference in span score (the structured versus non-structured span conditions), there was a non-significant difference in reaction time (albeit in the right direction). Also, the congruent and incongruent spatio-temporal conditions had an additional 0.5 seconds for every span trial compared with all other conditions, and yet the span average of these conditions doesn't appear worse than the other conditions. In fact, the congruent condition has the third highest span score out of the thirteen conditions. These results indicate that rehearsal time might not play as important a role in spatial short-term memory as it does in verbal short-term memory.

A recent study (Fischer 2001) indicated that in spatial span, increasing encoding and rehearsal times actually improves retrieval performance, lending support

to this proposal. It may be instead that other factors, such as the greater potential for spatial sequences to be chunked, or other strategies (such as drawing imaginary lines) swamp any influence of the gradual decay over time in success of response that Baddeley and others have found in verbal span (Baddeley, Thomson et al. 1975; Cowan, Day et al. 1992).

Another issue addressed in the current study was whether the number of items influences performance on the spatial span task. Only the non-structured array comparison yielded a significant benefit for the 8 squares compared with the 16 squares. It may be that the greater number of choices for response in the 16 squares condition makes it more likely that a sequence not perfectly retrieved will be incorrect. These results are consistent with similar findings from a recent study (Fischer 2001). Fischer et al. found a performance benefit of presenting at the retrieval phase of a spatial span task only the subset of target stimuli from the encoding phase, compared with the presentation of all nine stimuli. The reason why there wasn't a significant difference for the ordered array conditions might again be due to the chunking factor partially compensating for the greater choice of the higher stimulus set.

Chapter 9: General discussion

9.1 – Introduction

This chapter will first summarise the main findings of the thesis. These will then be discussed in relation to how they correspond to current theory outlined in chapter 1. There will follow speculations concerning the general functioning of the PFC. Finally, limitations with current work and future directions will be outlined.

9.2 – Summary of findings

In chapter 3, it was shown using PET that a spatial span task using a structured (2x4) array matrix was associated with increased activation in the DLPFC. This was a surprising result, since previous neuroimaging studies using the spatial span task have demonstrated only increases in the VPFC (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). It appeared that the key difference between the study of chapter 3 and that of previous studies was that previous studies used a non-structured array, where the stimuli were spatially arranged in random locations on the screen. However, given the limitations of comparing activation patterns between studies, it was not clear whether the shift from VPFC to DLPFC was indeed the result of the difference in arrays.

Therefore a second PET study was carried out to address this issue (see chapter 4), where both the structured and non-structured array spatial span tasks were given to subjects in the PET scanner. Activations were observed in only the VPFC for the non-structured array spatial span task, in line with previous studies (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). For the structured array spatial span task, activation

was observed in both the VPFC and DLPFC, replicating the DLPFC activation for the same task in chapter 3. This therefore was firmer evidence for a valid differentiation in activation pattern within the lateral prefrontal cortex for the two types of spatial span. Hints for a psychological difference between the two conditions came from behavioural reports of the relative ease of the structured, compared with the non-structured array span tasks. In combination with evidence from frontal lobe patient studies (Owen, Downes et al. 1990; Shallice and Burgess 1991; Miotto, Bullock et al. 1996; Owen, Morris et al. 1996; Morris, Rowe et al. 1999; Burgess, Veitch et al. 2000), and recent neuroimaging studies (Prabhakaran, Narayanan et al. 2000; Savage, Deckersbach et al. 2001), this led to the suggestion that subjects may have been applying mnemonic strategies to a greater extent for the structured array span task.

This was tested explicitly in chapter 5, where a behavioural study was run on a modified version of the structured and non-structured array span tasks in order to explore the possible strategic involvement of such tasks. Although there was tentative behavioural evidence that subjects were performing the two tasks differently, there was no overall difference in span scores, as there should have been if the structured array span task involved a significant strategic component. However, subjective reports clearly indicated that the two tasks were approached differently. For the non-structured array span task, subjects commonly reported a low-level strategy of forming imaginary lines between the stimuli in the sequence. For the structured array spans, on the other hand, more complex strategies were usually reported – for instance, spatially chunking some of the sequences into regular shapes, such as squares and triangles. This result in turn provided a preliminary explanation for the difference in activation pattern between the structured and non-structured array span tasks of the PET study of chapter 4. It was suggested that while the non-structured array span task involved

little more than basic encoding and retrieval of items in short term memory, which may be one of the roles of the VPFC, the structured array span task in addition involved a chunking strategy, which may well be one of the roles of the DLPFC.

The identical tasks to chapter 5 were given in chapter 6 to frontal lobe patients and carefully matched controls. Contrary to the prevailing opinion that frontal lobe patients are not impaired on simple working memory tasks(D'Esposito and Postle 1999), such as those that require the retention of information over short periods, a significant impairment was demonstrated in these patients for the spatial span task, when a more sensitive measure was applied than has been used before with such patients (Canavan, Passingham et al. 1989; Owen, Downes et al. 1990; Miotto, Bullock et al. 1996; Greenlee, Koessler et al. 1997; D'Esposito and Postle 1999). This result is surprising and may well be the first such example of frontal lobe patients being impaired on simple working memory tasks. However, such a result is consistent with the results of all of the neuroimaging studies of this thesis (see chapters 3,4 and 7), which reported lateral prefrontal activation in association with spatial span tasks. In addition, previous spatial span studies have reported the same association (Owen, Evans et al. 1996; Owen, Herrod et al. 1999). It was suggested that the deficit may be to do with minor mismanagement of the task, by failing efficiently to utilise mini-strategies in order to make the task demands easier.

Although chapter 4 provided preliminary evidence that the lateral PFC is involved in strategic processes, such as chunking, various limitations with that study make this conclusion problematic. For instance, the comparisons were between experimental conditions and the control, rather than directly between the experimental conditions. It is possible that the difference in activation pattern between the structured and non-structured array tasks, therefore, was merely a statistical anomaly.

In addition, if there was indeed a difference in activation pattern between the two tasks, there was no definitive behavioural evidence to demonstrate that this difference is due to greater strategy use in the structured array condition, since greater strategy should lead to a performance benefit and there was no difference in performance between the two tasks. In Chapter 5, an attempt was made to find a performance benefit for the structured array condition, but the results didn't support this. In order to provide firmer evidence that the lateral PFC is indeed involved in strategies, it became clear that both a performance difference between two versions of a spatial span task (one with greater and one with lesser strategic involvement) was required, as well as a difference in activation pattern when the two tasks are compared directly.

An fMRI study was carried out to address both these issues (see chapter 7). This time, the two variants of the spatial span task used the same structured 4 x 4 array. The difference between the versions lay instead in the spans themselves, since it was specifically the spans, rather than the arrays, that were associated with complex strategic processes, according to the subjective reports of chapter 5. Spans were designed either to appear highly structured, automatically forming regular shapes and patterns, or to appear almost completely without structure. When the two types of spans were compared directly, the structured span trials yielded significantly greater activation in the lateral PFC than the non-structured span trials. In addition, subjects were significantly faster and more accurate at recalling the structured spans. In combination with evidence from previous chapters, it appeared that there was greater strategic involvement for the structured spans, which enhanced performance and increased activation in the lateral prefrontal cortex.

Considerable evidence from the literature has suggested that there is a tight coupling between cognitive demand and increases in activation in the lateral PFC

(Cohen, Perlstein et al. 1997; Jonides, Schumacher et al. 1997; Duncan and Owen 2000). Importantly, results of the fMRI study of chapter 7 also demonstrated that this association can be reversed under certain circumstances, since the easier of the two span tasks yielded greater lateral prefrontal activation.

In order to support the hypothesis that the key difference between the two types of span in chapter 7 was due to differences in strategic processing, a large behavioural study was run with multiple variations of the spatial span task (see chapter 8). In particular, two span conditions with identical stimuli sets, very closely resembling the span tasks of the fMRI study from chapter 7, were varied according to the ease with which the stimuli could be chunked. Subjects that performed the condition with the more obviously chunked stimuli had a significantly higher span score, indicating that the chunking process is occurring during at least some kinds of spatial span, most notably the structured spans of chapter 7.

Taken together, these results suggest that the lateral prefrontal cortex, particularly the DLPFC, may play a role in strategically chunking aspects of a task in order to optimise performance and lower cognitive demand.

9.3 – Relation of findings to recent theories of prefrontal cortex function

9.3.1 - Goldman-Rakic's domain-specific model of the lateral prefrontal cortex

This model (see 1.4.1.1) states that while the VPFC is involved in object-based working memory processes, the DLPFC is involved in spatial-based working memory processes (Wilson, Scalaidhe et al. 1993; Goldman-Rakic 1998). Some evidence in support of this model was found in chapter 3, with the first PET study reported, where a working memory task with a clearly spatial component did indeed preferentially activate the DLPFC. However, it was also argued that there may have been a distinct object-based component to this task, due to the strategic recoding of the sequences into regular, familiar shapes. According to the model, this should lead to additional VPFC activation, but no such activation was observed. In chapter 4, the non-structured array span task was a more purely spatial working memory task (object based strategies appeared not to be a significant factor in performance), and yet this task only activated the VPFC, completely opposite to the predictions of the model. However, it should be mentioned that the structured array span task in this instance did indeed activate both the DLPFC and VPFC, in accord with the model (since it appeared this task had both spatial and object-based aspects to it). In the frontal lobe patient study of chapter 6, the prediction from the model would be that those patients with damage that included the DLPFC should be impaired to a greater extent on the spatial span task. However, this was not the case. If there was any dissociation between the patients, it was that

the patients with damage to their right frontal lobe were more impaired on the spatial span task, which is in keeping with suggestions in the literature that the right PFC is preferentially involved in spatial working memory, while the left PFC is preferentially involved in verbal working memory (Smith, Jonides et al. 1996). However, it is not consistent with the domain specific model.

Finally, in the fMRI study of chapter 7, the domain specific model would predict that the more purely spatial trials, i.e. the non-structured spans, would activate the DLPFC when compared with the structured spans. At the same time the model would predict that the structured span task should activate the VPFC when compared with the non-structured trials, since object-based chunking seems to be a critical factor in performance on the structured trials. The results supported neither of these predictions, since the lateral PFC increased in activation (in a region spanning both DLPFC and VPFC) in association with the more object-based span task (the structured span task), while no increase in activation in the lateral PFC was observed at all during the more purely spatially-based span task (the non-structured span task). In general, these results fail to support the domain-specific model, and in combination with the behavioural data, which implicate the lateral PFC in strategic demands, suggest that an alternative model of lateral prefrontal organisation is required.

9.3.2 - Petrides' 2-stage model of the lateral prefrontal cortex

This model (see 1.4.1.2) posits that the VPFC is involved in first order working memory processes, such as active retrieval of items from short term memory, while the DLPFC is involved in second order functions, such as the "manipulation" or "monitoring" of information (Petrides and Pandya 1994; Petrides 1998). If

strategically recoding information into useful chunks can be considered to fall under the rubric of "manipulation" then the experiments within this thesis are highly consistent with Petrides' 2-stage model. In all three neuroimaging experiments (see chapters 3, 4 and 7), only when there appeared a significant chunking component did activation occur in the DLPFC. Otherwise (such as in the non-structured array spatial span task of chapter 4) where there was little opportunity to spatially chunk the stimuli, only the VPFC was activated. However, the data do not shed any light on one question outlined in the general introduction concerning how the two regions might interact – does activity in the DLPFC "take-over" the activity in the VPFC, or does the VPFC still need to be involved for the DLPFC to be active? In some contrasts in the neuroimaging experiments of this thesis both were active and in some experiments only the DLPFC was active, and on this basis very little can be concluded about the relationship between these two regions. In addition, as mentioned in the general introduction, the model lacks specificity in its definition of processes, such as "manipulation" and "monitoring". Until a more robust, specific definition of such processes is found, it is difficult to reach definitive conclusions about the overall relevance of the findings of this thesis to that model.

9.3.3 - The prefrontal cortex and cognitive demand

According to this theory (see 1.4.2.1), the PFC will increase in activity as the difficulty of a cognitive task increases. This thesis provided some evidence against such an idea. First of all, in chapter 4, the structured array span task activated a larger portion of the lateral PFC (including the DLPFC and VPFC) than the non-structured span task, despite the structured array version seeming easier to almost all subjects. Stronger

evidence comes from the fMRI study of chapter 7, where a task that was performed with a greater degree of accuracy and shorter reaction times yielded greater lateral PFC activation compared with a "harder" equivalent of the same task. It appears, therefore, that there are at least some circumstances where a more difficult task will not lead to higher PFC activation. It is important to emphasise that it still may be that the PFC does increase in activation in association with a more difficult task in the vast majority of cases. However, evidence from this thesis suggests that the processes that are involved when the PFC is usually recruited in association with a difficult task are the kinds of processes that *can in fact* make a task easier.

9.3.4 - The prefrontal cortex and processing details of the tasks or current goals

Various authors have suggested (see 1.4.2.2) that a major role of the lateral PFC is in managing current goals, when such goals are non-automatic and complex. Such a view may be taken as the process whereby task details are kept online, while the most appropriate goal details and response commands at a given time are given an increased weighting (Duncan 1990). Assuming this view, one possible implication should be that there will be a close association between number of task details kept online and PFC involvement. The current thesis provides partial support for this idea. In the PET study of chapter 4 and the fMRI study of chapter 7, the tasks that had additional goal-based components due to strategic chunking also demonstrated greater PFC involvement. In addition, the patient study of chapter 6 indicated that even on standard working memory tasks, frontal lobe patients are significantly impaired. One

interpretation of this result is that the patients were impaired at appropriately keeping all of the aspects of the task online.

However, where the evidence from this thesis diverges from such a suggestion is in the type of increase in task details that led to lateral PFC increases in chapters 4 and 7. It seems likely that these increases were in relation to greater strategic demands, with greater task details occurring as an epiphenomenon. There is no mention in the theory above, however, for strategic processing being associated with increases in PFC activation. Instead, a more active process is suggested by the current thesis, whereby current goals are streamlined by the PFC in order to optimise performance.

9.3.5 - The prefrontal cortex and strategic processing

Based largely on evidence from frontal lobe patient studies, it has been suggested that one key role of the frontal lobes is in strategic processing. The results of this thesis both confirm and extend this idea. The three neuroimaging studies, in combination with the two behavioural studies in healthy controls, suggest that under certain circumstances, the lateral PFC is involved in forming or maintaining strategies in order to lower cognitive demand. The results of this thesis extend the suggestion that the frontal lobes are involved in strategic processing in two ways. First, previous patient studies have only been able to localise strategic processing to the frontal lobes as a whole, while this thesis has associated such processing with the lateral PFC. Second, evidence from the neuroimaging studies has provided a more specific definition of strategic processing, that is, chunking information into meaningful sub-groups. It is as yet unclear whether all forms of strategic processing that are mediated

by the lateral PFC involve chunking, or whether activity in this region would also be observed during other types of strategies.

9.4 – Speculations concerning the role of the lateral prefrontal cortex

This thesis has provided evidence to show that carrying out non-automatic goals (e.g. spatial span) is associated with the lateral PFC. Within this context, optimising performance by strategically chunking useful aspects of the task has been shown to be associated with additional activation in the lateral PFC, particularly the DLPFC. This section will attempt to elaborate on the chunking mechanism, particularly in terms of its relation to the general processing of non-automatic goals.

As was mentioned in the introduction, in all animal species (with the possible exception of humans) there are only two basic goals of both automatic and more adaptable behaviour: maximising the animal's chances of survival (encompassing food, fighting, and fleeing) and of reproduction. Natural and sexual selection dictates that this must be the case. All non-human behaviour can be placed into one or the other of these two bins.

Utilising fully automatic responses to stimuli is an economical approach in terms of metabolic demands, and may be crucial for the basic goals of survival and reproduction. However, the cost comes in the form of inflexibility, which in turn increases the probability that the animal will not survive. If the animal is capable of being more adaptable, the metabolic costs may be outweighed by the greater ease with which the animal can find food, avoid dangers, etc. At the same time, adaptability can occur hand-in-hand with more automatic behaviour. Indeed, in order to respond

swiftly in dangerous situations, and to make significant savings on metabolic costs, the ability to shift from novel, complex behaviour, to automatic behaviour via laying out the behavioural "rules" permanently in memory, is obviously essential.

Adaptability in this context involves being able to generate and carry out sub-goals that maximise the animal's chance of achieving the more global goals. For instance, many species of whale travel thousands of miles at specific times of the year to specific locations, as a sub-goal to the main goal of mating.

There are various features of generating and carrying out non-automatic sub-goals:

1) **Motivation**: current motivational states dictate both the type of goal (for instance, mating, or food, or shelter) and the degree of urgency of that goal. For instance, if an animal is both cold and hungry, but is only a little cold, while requiring food to the point of exhaustion, then hunger should dictate the immediate goal state.

   Such motivations would normally be "driven" by sub-cortical structures, such as the amygdala or the hypothalamus, which I would suggest activate the PFC in order to generate new sub-goals for addressing the more global goal, if there are no obvious, simple ways of satisfying that global goal. In "higher" animals, though, it may be that other areas, probably in posterior cortex, could compete for the current goal-state. This could occur as a result of more basic needs, where the result would be taken over by the PFC, in order to make the complex goal occur. For instance, the basic goal state of hunger generated sub-cortically may trigger in a chimpanzee the memory in posterior cortex of the experience of eating termites, which in turn might lead to the PFC holding online the goal of eating termites. Alternatively, particularly in humans, goal states may be dictated largely independently of sub-cortical structures. For instance, every day I come to work,

and my memory triggers the goal state of completing my thesis. This is a complex task, which my PFC may well devote most of its resources to achieving, despite no apparent engagement of subcortical structures to motivate me towards food, procreation, or away from life-threatening events.

2) **The generation of sub-goals**: once the non-automatic goal has been specified, one main role of the human lateral PFC may well be to generate the details of achieving that goal. For instance the goal, win at chess, would require protecting your king, developing a good pawn structure, creating forks, attacking the enemy king, etc. In other words, effective achievement of a non-automatic goal requires the specification of a set of sub-goals, as well as information about how the sub-goals interact. The generation of an interactive set of sub-goals can in turn be broken down into at least two processes:

    a) **Generating a set of possible solutions**: in order to find a workable solution, the creation of possible answers is essential. Consider a chess game at a critical stage. There are over 50 possible moves that can be made. If a person can only choose between three moves, all of which she's played before, and each time she's lost soon afterwards, then she is not effectively achieving the goal (winning the game). On the other hand, if she continues to search until she finds a move that will give her a distinct advantage, then the effective search is essential for achieving the goal. Searching for the best sub-goal can not be performed in a vacuum, however. What is needed is both the current context (the rules of the chess game, and the position as it stands, for instance), as well as connections between the possible solutions and memory (for instance, doubling up

rooks in the past was always very successful; this move here will create doubled up rooks, therefore this will be a successful move).

b) **Checking whether a possible solution will fit the designated goal**: for this to occur effectively, obviously a comparison is required. For instance, in the Tower of London puzzle (Owen, Downes et al. 1990; Owen, Doyon et al. 1996), where subjects have to mentally rearrange sets of stimuli from one configuration to another, there needs to be a comparison between the goal-state (the end configuration) and the set of transformations suggested to achieve that goal-state. At other times, the comparison might be entirely between a possible solution and an item from memory (for instance, answering the question "right is to wrong, as good is to _____"), or between a possible solution, and a transformation of an item from working memory (either retrieved from long term memory, or from the environment).

It is important to emphasise that both outlined aspects of the generation of sub-goals are likely to be PFC functions. One useful illustration of this comes from the link between random number generation and DLPFC activity. Jahanshahi et al. demonstrated that transcranial magnetic stimulation (TMS) to the DLPFC interferes with both random number and letter generation (where each letter or number choice could be considered a sub-goal), by making responses more habitual and less random (Jahanshahi, Profice et al. 1998; Jahanshahi and Dirnberger 1999). Presumably such a task for each number or letter requires the generation of a candidate number or letter, and a comparison between the

candidate and recent choices to ascertain whether it would appear truly random or not (Jahanshahi, Profice et al. 1998; Jahanshahi and Dirnberger 1999).

In addition, the Tower of London puzzle, which appears to depend on the integrity of the PFC (Owen, Downes et al. 1990; Owen, Doyon et al. 1996), probably involves both the generation of possible solutions, and the comparison of those candidate answers with the template solution presented.

It is also an intriguing possibility that similar mechanisms may be called upon to deal with the specific, though highly frequent case where it is unclear which goal amongst a set of competing alternatives should be carried out at the present. For instance, it may be that I'm very hungry while in the middle of a train of thought about my thesis. Both goals appear to have equal weighting. After some thought, I remember that putting off eating for half an hour has had little effect on me in the past, while cutting off my train of thought has been more disruptive. I therefore opt for the strategy of delaying food until this current train of thought is completed.

3) **Holding goals online**: once the appropriate goal has been specified to be acted upon, if such a goal is complex and non-automatic, then it seems likely that the PFC would be required to organise the details of that goal. For instance, with the example above of the chimpanzee deciding to eat termites, this would require retrieving from memory a set of items – all relevant to the task. The chimp would need to remember appropriate locations, or know how to search for new ones. He would also need to search for an appropriate stick, remember how to use the stick to get the termites, retrieve the motor skill relating to the stick use, carry out the motor tasks appropriate for this, etc. Many of these sub-goals would require a high

degree of management in order to be carried out in the appropriate order, particularly if novel aspects are introduced into the task – such as other chimps are already feeding off the same targetted food source, the stick is rotten, etc.

As highlighted in the general introduction (see 1.4.2.2), there is ample evidence, particularly from the monkey literature, to suggest that the lateral PFC, is involved in holding online the details of the task (Rao, Rainer et al. 1997; Rainer, Asaad et al. 1998; Rainer, Asaad et al. 1998; Asaad, Rainer et al. 2000; Fuster, Bodner et al. 2000; Freedman, Riesenhuber et al. 2001; Miller and Cohen 2001; Wallis, Anderson et al. 2001). In addition, it should be noted that the task of holding goals online overlaps somewhat with that of generating goals. For instance, if a possible sub-goal is to be successful, it has to be compared with the current goal at the time to see if it will achieve that goal.

4) **Chunking successful goals**: as mentioned towards the start of section 9.4, one essential feature of adaptable processing is the ability to transform complex, novel behaviour and goal-states into an automatic form. This is highly advantageous both for speed and efficiency of processing and response, as well as in order to lower metabolic demands. But how can complex goal-states *become* simple? Consider one example used in chapter 7 – that of Morse code (Bryan and Harter 1899). Say a set of dots and dashes are given as a span task. One complete novice may code each dot and dash separately – perhaps being able to memorise around 7 such items. Another complete novice might group any repetitions, or patterns together – for instance first as two dots, then three dashes, then an alternation between dots and dashes for four items. In this way, perhaps twice as much can be memorised. However, someone else who is experienced at Morse code might be

able to remember a whole sentence, or say 30 items, with ease. This illustrates the two key forms of chunking. The more proficient novice was able to extract a pattern, or structure from the sequence – just as subjects did with the structured spans of the fMRI study (see chapter 7). The complex sequence becomes somewhat more simple as a result of the recognition of patterns (Newell 1990). Another way of putting this is that the more proficient novice was able to compress the data based on the redundancy in that information – a redundancy that required little knowledge to detect, since it was mathematical, or logical in nature. Now turning to the expert at Morse Code. His form of chunking was dependent entirely on memory, and was the most automatic of the three people. The chunking has largely already occurred in the prior learning of Morse Code and now all he has to do is retrieve those chunks. However, it may also be the case that there is more chunking that can occur to optimise performance even for the Morse code expert (Newell 1990). If that expert is proficient at recognising letters, then a benefit would be gained by recognising whole words amidst the recognition of dots and dashes as letters. Furthermore, whole phrases might eventually be recognised via the recognition of dots and dashes as words. The chunking process can in many cases, therefore, be aided by prior chunking (Newell 1990).

Perhaps one role of the lateral PFC is, wherever possible, to perform one very general example of 2 above (the generation of sub-goals), i.e. to search for useful redundancies in task-related information. Such redundancies would either be in the form of logical or mathematical patterns within the information, or in the form of relationships between such information and chunks already established in memory. The result would be a significant increase in proficiency, as less cognitive resources are required for a given task, and the PFC can be “freed up” to

perform similar processes on other tasks if need be. Evidence to support this notion comes from this thesis, which indicated that the lateral PFC was associated with recoding task-related information into regular shapes, presumably by recognising the relationships between information in short-term memory with shapes from long-term memory. In this way, both reaction time and accuracy were enhanced, while the cognitive load was presumably lessened.

One very intriguing question arising from this is what differentiates the two novices in the Morse code example. Could it be that the novice that scored better was searching more actively for ways to chunk the data? Or perhaps the search was merely more effective, with the more proficient novice able to search in a more wide semantic space than the less proficient novice. Whatever the mechanism, it is possible that differences in ability to chunk information relates directly to intelligence levels. As mentioned in the introduction (see section 1.4.2.2), it has been shown that those with frontal lobe damage are significantly impaired on fluid intelligence tests, such as Cattell's culture fair IQ test (Duncan, Burgess et al. 1995). It has also been shown that those at the low end of the IQ scale can closely resemble frontal lobe patients in their performance of relatively simple tasks (Duncan, Emslie et al. 1996). In addition, a recent PET study has indicated that when tasks with a high IQ correlation are compared with similar tasks correlating far less with IQ on a range of modalities, the lateral PFC is significantly activated (Duncan, Seitz et al. 2000). All these studies suggest that there is a clear association between the lateral PFC and IQ. It may be that such an association is most dependent on the ability to chunk information effectively.

In sum, I have suggested that a principle role of the lateral PFC, is as the initiator of effective adaptable behaviour. I have argued that this involves generating and carrying out a hierarchy of non-automatic sub-goals, as specified by more basic goals sourced either directly from sub-cortical structures involved in motivation, or posterior cortical regions comprising stored information about previously successful goals. Specifically, the PFC needs to search through possible solutions to complex, or initially insoluble tasks. The generation and testing of possible solutions occurs as a result of comparing potential solutions with the desired goal. One very general and important form of this generation of sub-goals is the chunking of task-related information so as to store successful sub-goals in memory, to be retrieved later in a more automatic form. At the same time, such a process can further feed the chunking process, by relating new items at a later date to existing chunks. Finally, the PFC needs to hold the non-automatic goal "online" in order to organise and carry out the various aspects of that goal, and the connected sub-goals, while also maintaining an easily comparable image of the desired state for the generation of possible solutions to occur more easily.

It is unclear whether these separate functions are represented in different regions of the PFC, or within the same network of PFC areas, as Duncan and Owen suggest (Duncan and Owen 2000). Due to the overlapping nature of these processes, or at the very least the requirement for the processes to work together to achieve the chosen goal, it may well be that one large region in PFC is devoted to all of them in concert. Further testing is needed to ascertain whether these functions can be divided according to PFC region.

9.5 – Limitations with current work and future directions.

This thesis has focused on one general paradigm, that of spatial span. It is possible, therefore, that the results discussed throughout the experimental chapters relate to some aspect of spatial processing, rather than chunking processes generally. In order to confirm that such results are independent of modality, it would be beneficial to replicate the fMRI experiment of chapter 7 with structured and non-structured variants of a verbal, rather than spatial span (for example, by manipulating phonological similarity). A further extension could even use musical notes given to proficient musicians, either randomly distributed, or as part of a standard key. If both of these further fMRI studies associate the lateral PFC with the chunking of the more structured sequences, then this would demonstrate a general cognitive process, independent of modality.

In addition, current work has centred on a task with a heavy mnemonic component. This has made it unclear whether the chunking aspect relates purely to the stimuli or to the task itself. It would be interesting to test whether the lateral PFC would also be activated in a neuroimaging experiment when the demands of the task are less mnemonic and more manipulative in nature, so that chunking would have to relate only to the task itself.

Although the patient study of chapter 6 did find a significant deficit for frontal lobe patients, this deficit may not have been strategic in nature. It was also unclear whether the deficit would not occur with almost any significant brain lesion, since a patient control group (i.e. with non-frontal lesions) was not tested. It would be useful to carry out a further patient study, this time with both a frontal lobe group and control patient group (for instance temporal lobe patients), while using the structured and non-structured span trials of the fMRI study of chapter 7. In this way, it would be more likely

for any differences in strategy use to be discovered between patients and controls, since there is a robust, replicable difference in performance between the two types of span in healthy controls, which appears to be due to chunking strategies applied to a greater extent to the structured spans. It would also be essential in such a study to increase the number of patients as much as possible, to make it easier to split the frontal lobe patient group up into sub-groups, who have lesions to specific areas of the frontal lobes. With a larger group, it may also be possible to ascertain how the size of lesion relates to the deficit. For both location and size of lesion, lack of significant differences between patients in the study of chapter 6 may well be due to lack of statistical power due to too small a sample size used.

Although some useful results were found from the behavioural study of chapter 8, this study relied on a between-subjects design, weakening the conclusions about differences between various span sets. In addition, the study was carried out unsupervised in a non-experimental setting undoubtedly involving regular distractions. Such an approach probably increased the noise of the data considerably. For the more interesting results, it would be beneficial to carry out a within-subjects design in a more controlled setting with a subset of the conditions. This would provide an opportunity to replicate the results of that chapter, while also showing that single subjects can demonstrate differential approaches to the congruent and incongruent spatio-temporal span tasks, for instance.

It would be very interesting to test some of the implications of my speculative suggestions of this chapter. For instance, if one of the roles of the lateral PFC is to seek patterns within task-related information, would there be increases in PFC activation in the fMRI scanner associated with one condition when the subject is forewarned that certain patterns will help her perform the task, compared with another condition with identical stimuli, when the subject is told there are no such patterns? If the lateral PFC is generally involved in searching for patterns to chunk within stimuli, would simply viewing large,

seemingly random, textured arrays of squares increase PFC activation when the set has a slightly less random, greater mathematical pattern to it? Would such activation occur, regardless of whether the subject were conscious of the greater regularity of the textured array, or would awareness of this regularity be a pre-requisite for prefrontal activation?

One large limitation of this thesis has been that it has only discussed the lateral PFC in detail. However, other regions are commonly implicated in higher cognitive functions. The anterior cingulate has also been found to be activated when almost any task is demanding (Duncan and Owen 2000). In addition, the parietal cortex is almost universally activated in working memory tasks (Cabeza and Nyberg 1997; Jonides, Schumacher et al. 1998; Cabeza and Nyberg 2000). In all neuroimaging tasks in this thesis, the parietal cortex was also activated in relation to the structured version of the span task. Is the role of this region largely attentional, as many authors have suggested (Corbetta, Miezin et al. 1993; Corbetta, Shulman et al. 1995; Cabeza and Nyberg 1997; Tzourio, Massioui et al. 1997; Corbetta and Shulman 1998; Duncan 1998; LaBar, Gitelman et al. 1999; Cabeza and Nyberg 2000; Corbetta, Kincade et al. 2000; Duncan 2000; Hopfinger, Buonocore et al. 2000), or are more complex, task-based processes being mediated by this region? In addition to attempting to dissociate parts of the PFC according to specific goal based processes discussed in this chapter, it would be highly beneficial to attempt to dissociate activation between parietal cortex and PFC with the same experiments, as well as potentially segregating regions within parietal cortex according to such functions.

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