Functional neuroimaging studies of long-term memory in humans.

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Abstract

This thesis explores contributions of prefrontal cortex (PFC) to memory using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

I begin by considering the cognitive neuroscience of memory processes and the impact that functional neuroimaging may have upon this. I then describe a series of PET and fMRI experiments concerned, primarily, with dissociating frontal contributions to encoding and retrieval processes. These initial studies show that left PFC activation predominates at encoding and right PFC activation at retrieval. Four further studies of left prefrontal activation at encoding are presented. Together, they show that left PFC is sensitive to tasks that require the organisation of encoded material according to its semantic attributes and that a more dorsal region of lateral PFC may specifically reflect the requirement to select from amongst semantic attributes in order to meet specific demands of the tasks. This region, and the behavioural performance associated with it, is shown to be sensitive to interference produced both by competing semantic attributes and by a simultaneously performed, distracting motor task.

The two experiments on memory retrieval that are presented here provide evidence for distinctive roles of right dorsolateral and ventrolateral PFC during retrieval of verbal material. The ventrolateral region appears to reflect the changing specification of search parameters that occurs at the outset of a memory search and the dorsolateral PFC activation pattern is consistent with a role in monitoring and verification processes optimising the retrieval process.

In conclusion, I review the broader literature on neuroimaging of memory-related frontal cortical function. While there are a number of inconsistencies, I suggest that the results presented here fit into an emerging pattern indicating the importance of PFC in memory encoding and retrieval and the distinctive roles of dorsolateral and ventrolateral regions within and between these memory stages.

Contents

This work is dedicated to my parents.

They were selfless in offering my sisters and me an upbringing that was secure, stimulating, happy and full of laughter.

Considered against their labour, the work described here seems especially paltry. I would contentedly set a match to it in exchange for the hope that my own children may come to think of me as I do of my parents.

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Finally, none of this would mean anything without my wife Nicky.

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Chapter 1

Episodic Memory and Prefrontal Cortex: introductory discussion.

Introduction

In this chapter, I shall consider some areas relevant to the application of functional neuroimaging techniques in the study of episodic memory encoding and retrieval. While the next chapter is concerned more explicitly with the neuroimaging techniques, their strengths and limitations, the aim of the current one is to explore a number of behavioural, neuroanatomical and neuropsychological aspects of frontal lobe function with reference to how these inform and shape our interpretation of findings from functional neuroimaging studies. The following themes will be considered:

1.1 A taxonomy of human memory function.

1.2 A consideration of prefrontal cortical structure.

1.3 A consideration of prefrontal cortical function with emphasis on possible roles in episodic memory encoding and retrieval.

1.1 A taxonomy of human memory function.

The aim of most functional neuroimaging studies has been to map psychological function onto brain structure as precisely as possible. The success of this enterprise depends, to a great extent, on the validity of the psychological models and classifications that are used. Since these models govern the analysis and interpretation of imaging data, flaws in psychological models will ultimately produce inconsistencies in neuroimaging observations. The results of PET and fMRI studies are only interpretable insofar as they are based upon a thorough understanding of the experimentally defined context in which imaging measurements are made. This point will be reiterated and considered more fully in the next chapter.

Crucial to an understanding of the relationship between brain structure and memory function, is the capacity to observe correlations between estimated brain activity and manipulations in precisely defined and described memory sub-processes. Limitations in our understanding of these sub-processes cautions against over-confident interpretation of any functional neuroimaging study. Conversely, however, it would be over-cautious to withold a search for the neuronal implementation of a functional architecture even though that functional architecture is incomplete (Shallice, 1988). With this in mind, an existing taxonomy guides the experiments that follow. This taxonomy is based upon evidence that memory can be fractionated into several distinct systems (Squire, 1987; Schacter and Tulving, 1994). It will not be described in great detail but is represented diagrammatically in figure 1.

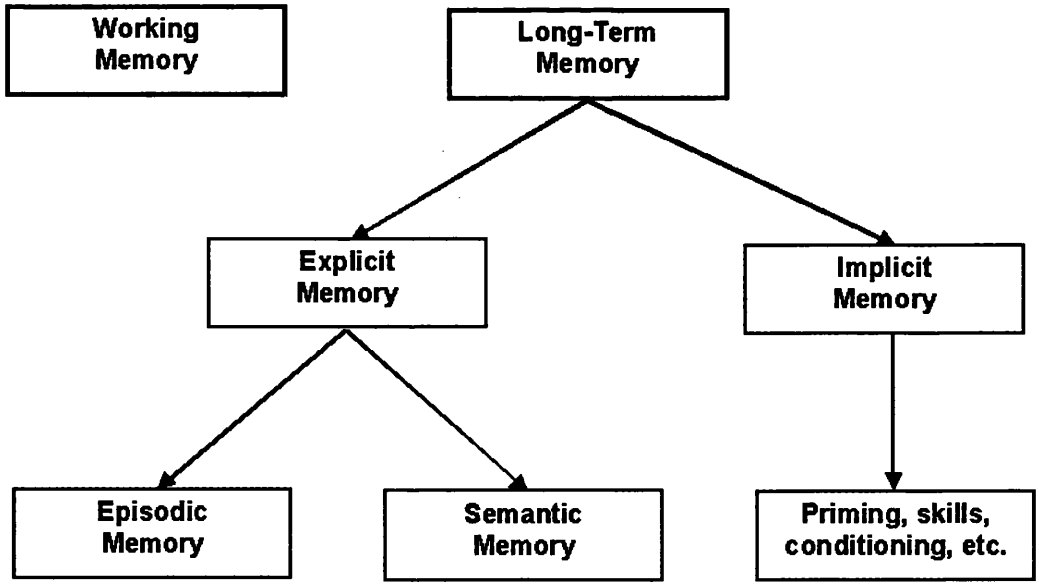

Figure 1 – A taxonomy of memory, taken from (Squire, 1987).

These sub-divisions will now be considered.

1.1.1 Long term versus working memory

Initially, memory can be divided into working memory (WM) and long term memory (LTM) components. The former refers to a limited capacity store (traditionally, somewhere in the region of 7 items or chunks of information) that is maintained by rehearsal and fades quickly when unattended. LTM does not require continuous attention or rehearsal, may endure over a lifetime and is apparently unlimited in capacity. The validity of this first distinction within memory is established on the basis of a number of strands of evidence. For example, WM, but not LTM, is vulnerable to the detrimental effects of phonological similarities in study material (a subject will have increased difficulty in repeating a list of words if they sound similar to each other) (Conrad and Hull, 1964; Baddeley, 1966). LTM, on the other hand, but not WM, will show a decrement when studied items have similar meanings to each other (Baddeley, 1966). These phenomena might suggest that the 2 forms of memory rely on differing brain systems (with WM favouring phonologically based processing and LTM favouring semantically based processing) and neuropsychological work has backed this up (Milner, 1966; Baddeley and Warrington, 1970; Shallice and Warrington, 1970; Shallice, 1988; Mccarthy and Warrington, 1990). However, the notion of two separately functioning sets of regions seems a simplistic one. Mayes makes the important point that dissociations between long-term and working memory systems probably only arise when the long-term memory task taps different information to that identified by the working memory disorder (Mayes, 2000). Furthermore, while it is interesting to define these systems according to their differences, it is equally important, when considering the healthy brain, for example when interpretating functional neuroimaging data, to envisage the ways in which they might overlap. Though the double dissociation between WM and LTM is highly suggestive of different brain

systems subserving these two functions, it is plausible that memory tasks employed in the laboratory engage both systems. Even the use of carefully designed control conditions may not fully disentangle them. This thesis is not explicitly concerned with working memory systems, but in the concluding chapter (chapter 7) the reported patterns episodic memory-related frontal activations will be considered in terms of general cognitive processes that may be observed in association with episodic memory but are unlikely to be unique to it. The experiments that follow are framed in terms of episodic memory but, while there is clearly a distinction between episodic and working memory systems, it seems highly likely that they share certain cognitive processes and that many of these may be reliant upon frontal lobe function. The results I believe may therefore be applciable to working memory function too.

1.1.2 Implicit versus explicit memory

A number of sub-divisions have been suggested within long-term memory. Primarily, it can be divided into explicit and implicit components. Explicit memory refers to those memories that are accessible to consciousness, a property also alluded to in an alternative nomenclature: *Declarative memory.* Implicit memory refers to memories that are inaccessible to consciousness. Such memory may also be termed *procedural* insofar as it is manifest in carrying out physical or mental procedures or operations without the substrate for such procedures being directly accessible to consciousness. It has been suggested that a crucial difference between these two types of memory lies in the fact that the former is *propositional* (has content that can be adjudged as true or false) whereas the latter cannot be expressed propositionally (Wheeler et al, 1997).

Behavioral tests of explicit memory function generally rely upon the subjective ability to recognise or recall, during a "test" phase, material that was previously presented in a "study" phase. Interestingly, with respect to functional neuroimaging explorations of the study phase (generally referred to as "encoding" experiments), it is not necessarily the case that subjects need to encode information intentionally in order for them to have a good level of subsequent explicit recall and to engender patterns of brain activation that are comparable with when they are trying to encode the material. Behavioural tests of implicit memory rely on indirect measures of memory-related changes, usually an enhanced performance of a task as a result of a preceding study phase (a study phase whose intended nature is often hidden from the subject). Crucially, for the task to be a truly implicit one, such enhanced performance must not be associated with a conscious retrieval of information encountered during the study phase. In such experimental set-ups, of course, especially when the paradigm is applied to functional neuroimaging, it is important to be aware that some of the material may be explicitly and automatically recalled even when the subject is not required to remember the items. Thus, this functional distinction is a difficult one to make.

In a recent review of the literature, Kopelman suggests that, while the conventional wisdom is that implicit memory is spared in amnesic patients with medial temporal lesions, and that damage further afield must be present for, say, a priming deficit, this is not entirely consistent when priming is tested with certain experimental designs (Kopelman, 2002). Thus, while the explicit-implicit dichotomy is descriptively compelling, and notwithstanding that there is neuropsychological evidence for its validity (Verfaellie et al, 1991), it may be over-simplistic and it has been argued (Green and Shanks, 1993) that the evidence is open to alternative interpretations.

1.1.3 Episodic versus semantic memory

A further, and highly influential, sub-division within long-term memory is that between episodic and semantic memory (Tulving, 1983). Episodic memory refers to memory that has spatio-temporal attributes and is accompanied by a subjective recollection of the encoding or learning episode. Semantic memory on the other hand, has no such autobiographical reference and refers to memory for meaning: a knowledge of objects, words, symbols, etc. For example, an episodic memory of Paris might comprise the recall of a trip to the city, the places one had stayed, the meals that one had eaten, etc. Such a memory would be located within a certain time frame and may be accompanied by the memory of one's thoughts and feelings whilst there. A semantic memory of Paris, on the other hand, might comprise the knowledge that it is the capital city of France, that it is situated on the banks of the Seine, etc. None of these aspects of the memory need include the essential personal element that appears to be the hallmark of episodic memories. The distinction between episodic and semantic memories has been couched in terms of the sort of conscious experience that they represent, with episodic memories holding *autonoetic* (self-knowing) consciousness or awareness and semantic memories *noetic* (knowing) awareness (Wheeler et al, 1997).

There is good evidence for the distinction between episodic and semantic memory from neuropsychological observations (thus, episodic memory may be impaired in the face of preserved semantic memory (Vargha Khadem et al, 1997; Verfaellie et al, 2000; Baddeley et al, 2001) although the systems underlying event- and fact-memory may lie in close proximity (Mishkin et al, 1997)). It seems unlikely, nevertheless, despite evidence for a double dissociation (Patterson and Hodges, 1995) that epsiodic and semantic memory systems operate entirely independently of each other. Important work by Graham and Hodges (Graham and Hodges, 1997) indicates

that, in semantic dementia, autobiographical memory may show a specific impairment: a greater deficit in remote autobiographical memories than in recent ones. This is a reverse of the normal temporal gradient. The conclusion from this and from another study (showing that famous current faces better recognised than famous faces from the past (Hodges and Graham, 1998)) is that semantic dementia may be a misnomer in that subjects are able to learn new facts but the neocortical structures necessary for long term storage (of facts and episodes) are damaged. Mayes points out (Mayes, 2000) that this is compatible with the view of Squire and Alvarez (Squire and Alvarez, 1995) that the medial temporal lobe (MTL) acts initially to store memory but that there is gradual reorganisation leading to its transfer to neocortex (perhaps, anterolateral temporal lobe). He further suggests that, with respect to the question of whether there is truly a dissociation between episodic and semantic systems, a dissociation "...seems likely to the extent that episodic information differs from semantic information provided one assumes that memories are stored where they are represented, and that different information is represented in different neural structures". The same may hold for the question of whether different brain systems are associated with accessing these different types of memories. The extent to which there is dissociation in these systems may be a question that is well addressed by functional neuroimaging. In experiment 2, I report an attempt to represent the episodic-semantic distinction in terms of functional neuroanatomy. One must bear in mind, though, that different patterns of activation may reflect distinct types of information retrieved rather than different retrieval systems per se.

1.1.4 A further distinction: encoding versus retrieval

Neuropsychological studies have tended to be cautious about distinguishing between the stages, as opposed to the types, of memory. This is natural given that the neuropsychological approach is not suited to making such a distinction. However, certain types of task design, applied in the setting of brain lesions may provide clues about whether the resulting impairments occur at encoding or retrieval (or, perhaps, in the consolidation process that acts somewhere between the two). This field is reviewed by Kopelman (Kopelman, 2002). The evidence for stage-based dissociations in memory impairment due to frontal damage is not strong, although, as described below, ingenious attempts have been made to explore this area (Incisa Della Rochetta and Milner, 1993). Functional neuroimaging, however, though lacking the capacity to draw an intimate, causal link between regional damage and psychological impairment, is very well suited to making broad temporal discriminations since it is possible to scan separately at learning/encoding and at remembering/retrieval stages. While there are ambiguities attendant upon this separation (each episodic encoding event might also be a semantic retrieval event; each retrieval might also produce encoding), this possibility is exploited and explored in all of the neuroimaging experiments reported in subsequent chapters.

Since memory encoding occurs irrespective of whether or not subjects are aware that their memory will be later tested (indeed, irrespective of whether or not their memory **is** later tested), the definition of an 'encoding' study is complex. At the outset, it is important to consider what, precisely, is meant by the term encoding. It may be suggested that encoding processes (or processes that promote encoding) are reflected in subsequent retrieval measures. That is, we recognise that they have been operative when we test whether material is subsequently recalled. This description is circular and incomplete. There are a number of factors that influence retrieval, not all of which occur at the encoding stage and consequently we must be wary of defining encoding

processes purely in these terms. Moreover, such a description may not address the true nature of the encoding processes. Many cognitive operations may correlate with subsequent retrieval abilities and this does not make them encoding operations. While a careful observation of how different cognitive operations performed on study material influence the extent to which that material is later recalled, is potentially valuable, one must nevertheless acknowledge that differential brain activations may reflect the different nature of these cognitive operations and may be interpretable only indirectly in terms of memory encoding. An alternative approach, and one that it has been possible to exploit fully only with the introduction of event-related fMRI, has been to define an encoding state, on a trial by trial basis, according to whether or not it is predictive of subsequent retrieval. In addition, the brain regions that are predictive of subsequent retrieval success may be compared across different task settings. This approach too produces some ambiguity since it may be it may ultimately prove difficult to specify the processes occurring during the study phase that are predictive of subsequent success during the test phase.

It is easier to specify when an item or event has been retrieved than when it has been encoded since the subject is aware of the retrieved memory coming into consciousness. Of course, this may occur whether or not the subject was searching for that item and there may be varying degrees of richness of retrieval and of confidence with which the subject identifies whether or not retrieval is correct. Nevertheless, in some ways the functional neuroimaging of episodic retrieval is less problematic than that of encoding.

1.2 Structure of Prefrontal Cortex (PFC)

It is helpful to consider at the outset what, precisely we mean, anatomically, by the term prefrontal cortex. It is not a descriptively useful term but has probably been rendered unassailable by its ubiquitous usage. PFC consists of the area of the frontal lobe that is anterior to the premotor cortex laterally and to the cingulate cortex medially. It is generally divided into three main parts: lateral, medial and orbital prefrontal cortex. There appears to be confusion with respect to the medial border: anterior cingulate cortex has been included (Zilles, 1990) and excluded (Passingham, 1993) from the general definition of PFC. Fuster has suggested that purely architectural criteria are insufficient for circumscribing PFC, defining it rather on the basis that it can be seen as the projection area of the mediodorsal nucleus of the thalamus. According to this definition, it is implicit that the anterior cingulate cortex, which receives mediodorsal nucleus afferents, in non-human primates at least, can be included in PFC (Fuster, 1997). It should be pointed out, however, that the view that PFC is defined as that region which receives mediodorsal nucleus afferents has been criticised as ''too broad and non-specific to be a useful guide to homologous cortical regions in cross-species comparisons'' (Preuss and Goldman-Rakic, 1991). What is interesting here is that, even at the broadest anatomical level, this region lacks a satisfactory definition. This is worrying, of course, with regard to the interpretation of functional neuroimaging studies, in which the spatial resolution is at the macroscopic level and therefore likely to be even more imprecise.

Notwithstanding some confusion in describing what we actually mean by PFC, it seems reasonable to define it, for the purposes of functional neuroimaging studies on macro anatomical basis described above. There are a number of consistent macroscopic features of PFC that are noteworthy. Perhaps most striking is that it accounts for a huge area of the cerebral cortex in humans and that, across species, its contribution to the

cortical mantle is related to phyllogenetic development (Fuster, 1997). The Gyrification Index, a measure of the degree of cortical folding, too, reaches the highest level in humans and this is most marked in PFC (Zilles et al, 1988). It appears therefore that the evolution of human cortex is stamped firmly on PFC. Of course, while caution must be exercised in drawing functional conclusions from such an observation, the idea that the PFC development is an important contributor to the higher functions of humans is compelling.

A brief description of the common macroscopic terminology of PFC is now outlined although one must bear in mind the emerging evidence that the relationship between macroscopic landmarks and the underlying cytoarchitectonic areal boundaries may be an approximate and unreliable one (Roland et al, 1997; Zilles et al, 1997). It is salutary to note, for example, that in a group of human subjects, the macroscopic extent of Brodmann areas 44 and 45 (thought to constitute Broca's Area) may vary tenfold and show a highly inconsistent relationship with gross anatomical landmarks (Amunts et al, 1999). Presumably, therefore, the macroscopic features have a variable relationship with functional sub-divisions too. This is a key consideration with respect to the functional neuroimaging approach in which task-related activations are located onto gross anatomy and assumptions are sometimes made about the underlying architectonics (usually in terms of Brodmann areas). Furthermore, group studies are predicated upon the idea that macroscopically overlapping activations across different subjects are reflective of similar cognitive processes occurring in those subjects.

The lateral landscape of PFC (Damasio, 1991), while highly variable in specific terms, can be sub-divided (by the superior and inferior frontal sulci into the superior, middle and inferior frontal gyri. The superior frontal gyrus curves around the superior

and anterior aspects of PFC and, along with the cingulate cortex, makes up a large portion of the medial PFC. The inferior frontal gyrus, the larger part of which is often referred to as the frontal operculum (the *lid* that lies over the insula) contains three noteworthy sub-divisions: the Pars Opercularis, Pars Triangularis and Pars Orbitalis. One further point with regard to generally used terminology is that the inferior frontal sulcus, which divides the middle from the inferior frontal gyrus is used to mark the border between the dorsolateral and the ventrolateral PFC (DLPFC and VLPFC, respectively). As will be seen, the division between DLPFC and VLPFC may be an important one with respect to function. The inferior surface of PFC, referred to as orbitofrontal cortex, consists of orbitofrontal gyri, most prominent of which is the Gyrus Rectus. Medially, the orbitofrontal gyri make up the lower part of medial PFC, along with anterior cingulate and superior frontal gyrus.

1.3 Function of prefrontal cortex

1.3.1 Unity or parcellation of function?

It is interesting that frontal lobes are frequently discussed in terms of an overarching unity of function. It is perhaps a little surprising, too, in view of their relative vastness and the clear evidence for anatomical sub-divisions within PFC at the microstructural level. The concept of the frontal lobe as a functional entity has some historical basis in the (mainly clinical) use of the term "frontal lobe syndrome": a convenient short-hand description of the clustering of a loose group of symptoms that tend to co-occur in the presence of frontal lobe damage. The vocabulary that has arisen from this (we have frontal behaviour, frontal tasks, even a frontal lobe riddle (Teuber, 1964)) is practical and convenient but potentially misleading if used beyond its intended scope. The first problem that comes with such a usage is a fundamental one: it has been

suggested (Baddeley and Della Sala, 1998) that the term "frontal syndrome" is flawed in that it stresses anatomical location rather than function. This is an unusual approach, and one that may mislead. It subtly removes emphasis from the careful and thorough description of function, instead describing behaviours primarily in terms of anatomical location. The problem is compounded by the fact that many of the functions that are attributed to frontal lobes are not fully understood. They are often high-level, metaphorical descriptions of complex behaviours and, as such, there are many inherent difficulties in attempting to map them onto the brain. For example, it is highly likely that the sorts of planning and strategic processes assumed to be upheld by PFC are distanced from observed behaviours (Burgess, 1997). That is, it is not a simple stimulus-response relationship, but rather a modulation of this linkage, with the result that they can be extremely difficult to quantify or to manipulate confidently. There is thus an ever-present danger of making unjustified assumptions based upon the observations of behaviours that are only indirectly linked to the processes under study. This covert and uncertain link between behaviour and process may foster an unintentionally procrustean approach. Such dangers are increased by the implications made in accepting the idea of a "frontal lobe syndrome" and its related vocabulary. A second and related danger in the use of such terminology is that it strongly localises function. It implies that specific cognitive processes or operations are carried out in discrete anatomical modules. While there is no doubt that this approach captures brain organisation in part, it is also true that a fuller understanding of brain function requires a consideration of functional integration: that is, of function emerging from the interactions of connected though anatomically separate modules (Tononi et al, 1992). Intuitively, it seems that the sorts of functions supported by PFC will be understood more completely in light of an understanding of brain integration rather localisation. This is a crucial consideration with respect to the existing vocabulary. If PFC functions

are to be understood in terms of interaction rather than localisation then the idea of a frontal lobe syndrome must be cast in a different light and may be ultimately unhelpful.

Dispensing with the term, however, while it may clear the ground a little, must not obscure the views that PFC displays a degree of functional homogeneity. Broadly speaking, intact PFC is important for dealing with situations that are novel and where automatic or routine ("unthinking" behaviour) is insufficient. While this view suggests one way in which PFC may be united functionally, it is, of course, frustratingly unspecific. If it does describe a unity of PFC function, a further series of questions concerning the nature of this unity are immediately raised: for example, is it the case that all regions of PFC subserve the same function with the different regions carrying out this function in different domains (Goldman-Rakic, 1998)? Conversely, do different regions of PFC support different processes with unity arising out of the fact that these processes come together to produce a cogent functional entity (e.g. the central executive (Baddeley, 1986; Baddeley and Della Sala, 1998) or the Supervisory Attentional System (Norman and Shallice, 1986; Shallice and Burgess, 1998)). Could it be the case that PFC is made up of multiple regions each subserving different functions and in varying domains with unity arising out of a complementarity of these functions (Petrides, 1994; Fuster, 1997; Petrides, 1998). In fact, all of these viewpoints are current. All of them would predict, too, that the sequelae of frontal lobe damage would traverse many domains of behaviour and cognitive function. Of relevance to the experiments and results that follow are the findings with respect to tests of episodic memory. These are discussed below.

1.3.2 Memory deficits following PFC lesions

1.3.2a Organisation, searching and monitoring.

The study of the functional neuroanatomy of memory began, and has continued, through systematic studies of lesions in humans and animals. While animal lesions may be planned, inflicted and controlled with great temporal and spatial precision, the study of their effects is highly limited with regard to the implications for humans. Lesion studies in humans, though more directly relevant, lack, in the majority of cases, spatial precision and the conclusions that may be drawn from such studies must be correspondingly imprecise. Notwithstanding these limitations, a large and broadly consistent picture of brain regions and systems implicated in memory function has accrued over the last 3-4 decades. The following section summarises some of the findings with respect to the PFC.

Many aspects of memory function are preserved in the face of widespread frontal damage. However there is strong evidence that damage is associated with a characteristic pattern of defects. This pattern is a complex one. Such patients tend to show normal recognition memory and cued recall task performance, though there are exceptions (see below). However, in more demanding tasks, where subjects are required to remember features of the encoding events, such as the order in which study material was presented, deficits are more prominent. Speculating that the core deficit in such frontally related memory impairment lies in the inability to initiate a sequence of responses in a given situation and to carry them out with constant monitoring of their execution, Petrides and Milner (Petrides and Milner, 1982) devised a task aimed at engaging such processes, rather than requiring simply the recall or reproduction of memorised material. Subjects were presented with arrays of study material (either verbal or visual) and instructed to point to each and every item within an array, in the order of their choice, without pointing to any single item twice. In order to avoid the

use of a spatial strategy, the locations of the items within the array were changed from response to response. It was found that patients with frontal lobe lesions were significantly impaired compared to controls.

Further studies have explored the importance of frontal deficits in organising material at both the learning and recall stages (Incisa Della Rochetta and Milner, 1993) and have emphasised their roles in memory function - roles that more traditional tests of memory have failed to elucidate. In addition, some experimenters have speculated upon a lateralisation in function of the frontal lobes. Petrides and Milner (Petrides and Milner, 1982) suggested that the self-ordered pointing task described above was impaired with respect to verbal and visual material in left frontal damage but only with visual material in right frontal damage. However, this was observed only when each of the groups was compared separately with control subjects and a direct comparison between the left and right frontally damaged groups showed no differences. In a study in which subjects were required to categorise and subsequently recall picture stimuli, both left and right frontal damage was associated with impairment at both stages (Incisa Della Rochetta and Milner, 1993). In right frontal damage, performance at the recall stage was inversely related to the number of items that they had been unable to categorise (that is, poor categorisation when material was presented was associated with poor subsequent recall). The authors took this to suggest that right frontal damage was associated with a defective ability to categorise and that this would have resulted in an impoverished representation of the set of items, resulting in poor recall. They speculated that the right frontal lobe damage was having its effect at the learning stage. Conversely, the impaired retrieval in people with left frontal damage showed no clear relationship with poor categorisation. They interpreted this observation as indicating that left frontal damage resulted in a recall deficit since even the items that had been

correctly categorised during the learning stage were vulnerable to a retrieval deficit. They further speculated that the role of the left frontal lobe lies in conducting an effective search of material stored in memory. It has been suggested that there is a distinction between 2 types of memory search: an associative or cue dependent memory search and a strategic memory search (Moscovitch, 1989). The frontal lobes, Moscovitch suggests, are important in the latter type of search. Incisa Della Rochetta and Milner posit a role for the left frontal lobe in such a search (Incisa Della Rochetta and Milner, 1993). They based this upon the observation that left frontal damage, when compared to right frontal and MTL (bilateral) damage and to controls, is associated with a deficit in free recall even when material has been presented in an organised way during a previous learning phase. If at retrieval, subjects with left frontal damage are provided with cues to organise their memory search, then the impairment disappears. Such an interpretation however, whilst ingenious, can be criticised and highlights the difficulties in speculating on the stages of memory on the basis of neuropsychological observation. It could equally be argued that the right frontal pattern of deficits could reflect the role of this region in retrieval - those regions that have been correctly classified may be more easily retrieved in a (right frontally mediated) memory search while unclassified items are less accessible and therefore vulnerable to the effects of right frontal damage. The deficit pattern associated with left frontal damage might simply reflect that items are weakly encoded irrespective of whether they are categorised or not so that the pattern of retrieval will be unrelated to the encoding task.

A further suggestion made on the basis of lesion data is that an impairment in free recall in frontal damage reflects a deficit in the use of organisational strategies (at both the learning and the recall stages) (Gershberg and Shimamura, 1995). This has been tested explicitly using measures of the extent to which patients subjectively

organise studied material and the extent to which they recall items in organised clusters. In order to examine this phenomenon Gershberg and Shimamura tested free recall of word lists in controls and frontal patients. They examined the ways in which subjects tended to cluster items at recall in a number of ways. First, with regard to their serial position within the presented list - since organisational strategies would more specifically affect the items held in long term memory systems then one might expect a deficit in recall of items from the initial and mid-stages of the studied list . (Of course, it is also true that the frontal lobes have been implicated in WM function and one might also expect difficulties in the later items in the list - those possibly reflecting WM). They also examined the ways in which subjects tend to cluster items together according to their own organisation scheme. Finally, they examined the extent to which the order of items recalled reflected the order of items presented (predicting that, since such serial organisation was explicitly available to the subject, this would place less demand on executive processes and thus the serial ordering in frontal damage might be comparable with that in control subjects). They found that, aside from the overall level of performance, the only difference between recall in the frontally damaged and the control subjects lay in the degree of subjective organisation. Extending this finding, lists in which words fell into sub-categories were presented and it was found that frontal damage produced a diminished tendency to cluster items according to category at subsequent retrieval. A further experimental paradigm, in which subjects were alerted to the list structure and given instructions on its use (at encoding or retrieval or both), showed that frontal damage did not impair the ability to make use of this information in clustering the items at retrieval (even though the overall level of performance remained impaired). They concluded that frontally-related memory deficits occurred at both encoding and retrieval and reflected subjects' failure to adopt organisational strategies at either or both of these stages. Interestingly, the results also show that, given explicit

information, performance improves, perhaps suggesting that the frontal damage impairs the adoption more than the use of the strategies.

A further study (Stuss et al, 1994) examined recognition and recall, together with subjective organisation and clustering on 3 types of word list: A categorised list in which material was presented in a blocked format (that is, items belonging to the same categories were presented together); a categorised list that was presented in an unblocked format (items presented in a pseudo-random order so that items from each category were distributed throughout the list) and an unrelated list (in which words could not be grouped into any obvious set of categories). Patients with frontal lobe lesions showed deficits in both recognition and recall. It was noted that the total mean correct score for the recall condition showed a greater deficit in the left frontally damaged patients compared to other frontal patients when the list was blocked during the encoding stage. For the blocked list, all patients showed impaired recall compared to the controls. When the material was presented in an unblocked way or when the unrelated list was tested the bilateral and left frontal patients showed impairment whereas the unilaterally right frontally damaged patients did not. Since each of the types of list was presented across 4 trials, the differential profiles of improvement across each of the groups for each type of list could also be analysed. For the blocked list, only the unilaterally left frontally damaged group improved (having started from a lower level). On the unrelated list, the control group and unilateral right groups improved and bilateral patients did not improve on any list. A further analysis, exploring the number and types of errors on free recall, showed that the unilateral right patients showed the highest score for intra-list repetitions or perserverations. Finally, an analysis of the degree of organisation used at recall showed that, for the blocked list only, the control subjects showed a greater degree of organisation than all the frontal

groups. A within-group analysis showed that, for both the controls and the unilateral right group there was superior performance when the list had been blocked at encoding. This was not the case for the unilateral left and bilateral groups. Stuss and colleagues concluded that the left-sided and bilateral patients were unable to use the external support to improve the degree to which they organised material at recall.

The above studies are described in detail since the cognitive models and experimenal paradigms have informed the experiments reported in subsequent chapters. In particular, I have attempted to determine, using functional neuroimaging, whether the frontal lobes are engaged during tasks that require organisation of material during memory encoding (experiment 3), and the implementation of a strategic and monitored search at retrieval (experiment 6). In the following, and final, sections, I will briefly mention some of the episodic memory abnormalities also reported in association with frontal damage.

1.3.2b Source memory

Memory for the source of an item requires that subjects recall not merely whether or not they have been presented with an item during a prior study phase but also some other attribute based upon the context in which it was presented. For example, it may have been presented before or after some specified time point (temporal source) it have have appeared in a particular position on a computer screen (spatial source). Other aspects of source memory include the requirement to ascertain what colour the item may have been or which of two voices spoke a word.

Frontal damage has been associated with disrupted memory for the source of items. Janowsky, Shimamura and Squire showed that such patients were able to

retrieve newly learned facts one week after presentation but were unable to recall the context in which these facts had been learned (Janowsky et al, 1989b). Further, though indirect, evidence for the roles of frontal lobes in source memory comes from investigations into elderly subjects, since it has been held that age-related changes are primarily in frontal cortex. Source difficulties are prominent in the elderly (Mcintyre and Craik, 1987).

1.3.2c Remembering and knowing

The distinction between a rich recollective experience that characterises some memory retrieval and the less elaborate, and possibly more impersonal, retrieval in other situations has been described in terms of "knowing" and "remembering" respectively (Gardiner and Richardson-Klavehn, 2000). This distinction has some resonance with one between recognising and recalling information and also with the difference between episodic and semantic memories (the former usually involving a rich, personalised experience the latter a simple knowledge without attendant autobiographical information). The distinction can be operationalised within a recognition memory task by asking subjects simply to distinguish between recognised words that they *remember* (i.e. words whose prior presentation they can consciously re-experience) and those that they *know* (i.e. those that they simply feel compelled to designate as studied, even in the absence of a re-experience of the presentation). Patients with frontal lesions, while showing little impairment on standard recognition memory tasks show pronounced reduction in the number of items to which they can make a *remember* response (Wheeler, 2000). Furthermore, ageing subjects in whom there are signs of deteriorating frontal function, show a deficit of the same nature (Parkin and Walter, 1992). These findings may indicate that, although subjects with

frontal deficits may perform recognition tasks to normal levels, the retrieval that they experience is somewhat impoverished.

1.3.2d Altered serial position learning.

The serial position effect has been suggested to have a number of components contributing to it, notably interference across the learning of a word list, WM and LTM processes and a subjective tendency to "organise" material on the basis of order and other intra-list associations. Since such organisation requires active/executive processes, it might be expected that the profile of the serial position effect would alter in the face of frontal damage. Eslinger and Grattan tested this across several trials of word list learning in frontally damaged and non-frontally damaged (temporal, parietal and occipital) patients (Eslinger and Grattan, 1994). They found that first-trial learning in frontal damage showed a preserved serial position curve. This effect was lost across subsequent trials (although it remained in non-frontal lesions). Frontal damage was also associated with a diminished tendency to produce a consistent sequential organisation at recall. The latter effect was confined to patients with dorsolateral as opposed to orbitofrontal lesions. The authors suggest that, to some extent, the serial position effect is governed by stimulus *distinctiveness*, with the initial and final items in a list being more distinctive and, thus, more easily bound within memory. If it is the frontal lobes that mediate such binding, producing clusters or structures during recall, then one would expect such a disruption of the serial position effect in cases of damage.

1.3.2e Susceptibility to interference.

Proactive interference refers to the way in which learning of one set of associations to stimuli interferes with learning new associations to the same stimuli. Gershberg and colleagues showed that, as well as finding it difficult to organise

encoded stimuli, patients with frontal damage are more susceptible to the effects of proactive interference (Gershberg and Shimamura, 1995). Using the learning of 2 lists of paired associates, with an A-B A-C design (e.g. On list 1 "River...Pond"; List 2 "River...Brook"), they showed that unilaterally frontally damaged patients were relatively impaired in learning the second list. They also produced a higher proportion of intrusion errors during recall (incorrectly producing an item from list 1 in response to a cue requiring an item from list 2). The authors interpret this phenomenon as an indication that the frontal lobes function as an on-line control of irrelevant or competing memory associations acting as a "general gating or filtering mechanism".

Experiments 5a and 5b (chapter 5) are of relevance to the proactive interference effect in frontal damage.

1.3.2f Confabulation and false memories.

Related, perhaps, to phenomena such as monitioring and susceptibility to interference is the increased tendency of patients with frontal lesions to confabulate - to produce false memories while asserting their veracity. Kopelman has suggested that frontal dysfunction may very well be a necessary (though not a sufficient) condition for confabulation that arises spontaneously (i.e. confabulation that is persistent and unprovoked) (Kopelman, 2002). He differentiates this spontaneous confabulation from *provoked* confabulations (Kopelman, 1987) that are perhaps the result of memory gaps and arise from the attempt to reconstruct memories during retrieval (Kopelman, 2002) an effect that may be seen in healthy volunteers. This formulation relates to Moscovitch's differentiation between a strategic (frontally-mediated) and a cue-dependent memory search although Moscovitch proposes that confabulation related to

frontal-damage arises from a deficit in the strategic access to memories (Moscovitch, 1989).

In both of the types of confabulation suggested by Kopelman, frontal lobe function may be relevant, particularly when one considers the origins of this memory deficit in terms of underlying processes considered to be crucial to the control of memory retrieval. Thus, for example, in order to access, identify and then proffer a response to a simple question testing episodic memory retrieval, one would have to generate the candidate memory, perhaps through an organised or strategic search, one would then have to ascertain its veractity and/or distinguish it from competing but false responses. Competing responses may differ in that they are paritally correct but have, say, a different source. Thus, for example, Kopelman suggests that confabulation may have, as at least a partial basis, a source monitoring difficulty (Kopelman et al, 1997; Kopelman, 2002). Alternatively, competing responses may share semantic attributes: a phenomenon that has been shown to elicit false recollection even in healthy volunteers: the 'Deese Effect' (Deese, 1959).

Relevant to confabulation and to the Deese effect, is the possibility that patients with frontal damage may show an increased level of false recognition (Delbecq Derouesne et al, 1990; Parkin et al, 1996; Schacter et al, 1996b). For example, patient BG (Schacter et al, 1996b), following a right frontal infarction, showed pathological false alarm rates for a variety of stimuli and these responses were accompanied by high levels of confidence (that is, BG incorrectly states that he has already been presented with certain stimuli and he does so with a strong feeling of remembering them: this latter observation is relevant to a possible "metamemory" deficit: see below). Interestingly, in those cases where healthy subjects are more likely to have high levels

of correct recognition and where they have high levels of confidence in their reports (when a deep encoding task has been used at study), then their levels of reported recognition and their confidence in this recognition are higher than in BG, lending weight to the authors' assertion that BG is not simply predisposed to identifying items as old and to reporting high confidence levels irrespective of the material or the condition. The authors enlarged on these results using stimuli in different modalities (visual and auditory, verbal and non-verbal). BG's deficit was found to be consistent. A further experimental manipulation was made to test whether BG's tendency to produce false alarms was affected by the extent to which a new (previously unstudied) item had an associative relationship to the previously studied ones. The results showed no evidence that false recognition was disproportionately provoked by using associative lures. In addition, as well as suggesting that BG's abnormal performance was not based on some form of associative interference, the authors explored the possibility that he was unable to distinguish experimentally presented items from those to which he had been exposed outside the context of the experiment. Thus, a "new" word within the experiment might be classified as an old word (that is "recognised") because it was a familiar word: a word that he had seen or heard pre-experimentally. A recognition task using non-words, which he was unlikely to have ever seen before, disproved this possibility. Finally, using both words and pictures, they examined the possibility that his false recognition was based upon a tendency to confuse items on the basis of categories to which they belonged. Thus, an incorrect report of recognition may occur simply because it belonged to the same broad category of a word that had actually been studied. Study items belonging to simple categories were presented. At test, new items came from different categories. This manipulation eliminated BG's false alarms entirely. Schacter and colleagues concluded that BG's deficit arose from an over-reliance upon general characteristics and a failure to retrieve item-specific memories.

Interestingly, Parkin's patient JB, who suffered left frontal damage also showed pathological levels false recognition A major difference, however, between these two patients lies in the fact that JB, unlike BG, does not show high levels of confidence (Parkin et al, 1996).

1.3.2g Metamemory

This refers to a "feeling-of knowing" (Metcalfe, 2000), something experienced by many people even when they are unable to recall a specific fact or item (for example, in the Tip-of-the-Tongue phenomenon (Brown and Mcneill, 1966)). It has been suggested that frontal damage will result in a disproportionate impairment in the ability to gauge the contents of memory: a metamemory deficit. Janowsky and colleagues showed that, in patients with frontal damage, while cued recall and recognition were at normal levels, there was a decreased correlation between subjects' feeling of knowing and their actual measured ability to recognise words on subsequent testing, after an extended delay (Janowsky et al, 1989a). In the concluding chapter I will refer to functional neuroimaging work that has produced futher evidence for the involvement of frontal lobes in metamemory through a manipulation of the tip-of-the-tongue phenomenon.

In brief the patterns of memory impairment associated with frontal lobe damage may be complex and subtle. They are most obvious when the retrieval of memories is not highly specified by an external cue, as would be the case, for example, in a recognition memory task. Such a task, due to the provision of 'copy cues' is less likely to require a strategic and monitored search of the contents of memory, whereas a free recall task, at which frontal lobe patients are impaired, requires a number of executive operations for optimal performance. The existence of frontal-damage associated

deficits in source memory and metamemory, together with an increased susceptibility to interference, confabulation and marked impairments when task demands become greater (including requirements to adopt strategies and to organise material) are all suggestive that frontal lobes play a complex but crucial role in laying down and facilitating access to memory and knowledge. Questions regarding the nature of this role drive the functional neuroimaging work that follows.

1.4 Summary of chapter.

This chapter has described some anatomical and neuropsychological data relating to frontal lobe function. Both fields are relevant to the functional neuroimaging studies that follow since the results of such studies attempt to link cognition and neuroanatomy. PFC forms a huge and relatively well developed area in humans. It probably encompasses a large number of functional sub-divisions and, in addition, each prefrontal area is densely and reciprocally connected with other prefrontal areas and with cortical and sub-cortical regions. These broad anatomical features suggest that it is likely to be involved in many cognitive processes: a prediction upheld by neuropsychological studies. Although, the host of tasks that have been linked to PFC function defies summary, it might be considered that a common deficit in PFC damage lies in an impaired ability to plan, concatenate and monitor the outcome of actions and to re-evaluate or suppress actions that are inappropriate to the needs of the task at hand. These general features of function appear to be crucial in the memory domain. In the next chapter, two of the functional imaging techniques, PET and fMRI are described and their potential advantages and disadvantages with respect to the question of prefrontal contributions to memory are discussed.

Chapter 2

Exploring PFC functions using neuroimaging.

Introduction.

The experiments in the following chapters were designed to explore the contribution of different brain regions, with a particular emphasis on PFC, to episodic memory. Because of the nature of such an experimental approach, which is to measure brain activity evoked by a specific stimulus or task, it generally proves more convenient to explore the neuronal correlates of well-defined memory stages. For this reason, the emphasis has been on the encoding or retrieval stages of memory rather than upon the period that occurs between these two, more temporally circumscribed, stages. This does not mean that functional neuroimaging techniques do not allow the possibility of exploring the transitional stages. They may do this through exploring time- and experience-dependent changes in brain activations as a reflection of learning (e.g. (Raichle et al, 1994; Kopelman et al, 1998; Fletcher et al, 1999). However, the experiments reported in the subsequent chapters are concerned with measuring brain activity at the encoding and retrieval stages separately. These terms are used here to refer to the collections of processes (possibly overlapping) that occur when subjects study material or attempt subsequently to retrieve it. The onus is ultimately upon the experimenter to establish what, more precisely, are the processes that compose any given encoding or retrieval task.

2.1 Advantages of functional neuroimaging.

Functional neuroimaging techniques are proving increasingly powerful in the study of cognitive functions. The spatial precision of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), coupled with the temporal resolution of the latter have created new possibilities for cognitive assessment. The application of increasingly sophisticated statistical techniques for the analysis of large functional imaging time series has enabled exploration of data both in terms of spatially

segregated brain function and of the integration of function across different regions. In combination with established experimental psychology, neuropsychological and psychophysical work, the techniques offer much to the study of human memory and especially of frontal lobe contribution to memory. This assertion is based upon a number of factors. First, neuropsychological studies deal with lesions that often differ markedly in size and location across different patients. PET and fMRI offer a more precise, spatial characterisation of functional differentiation across PFC. Second, the memory deficits produced by frontal lesions tend to be subtle, and it is likely that the sorts of memory processes subserved by PFC are some distance 'upstream' of observed behaviours (Burgess, 1997). Patients may, for example, achieve comparable behavioural performance with varying degrees of frontal mediation and compensatory strategies. Functional neuroimaging offers the possibility of detecting differences in the strategies that subjects or patients employ. Third, functional neuroimaging techniques can elucidate different stages of a memory process. As discussed, they can examine separately encoding and retrieval of memories; a dissociation that cannot be made with confidence in neuropsychology. Finally, PFC is unlikely to function independently of other brain systems with which it interacts (Fuster, 1997). Neuropsychological study can show whether a region is necessary for a given task, but not usually the broader system of which that region forms a part. Acquisition of whole brain images enables characterisation of spatially distributed functional networks of activity. Moreover, analytical techniques have been developed that allow characterisation of the effective connectivity between different brain regions during task performance (Mcintosh and Gonzales-Lima, 1994; Buchel and Friston, 1997).

With regard to the question of the necessity of a region for a given task, it has been suggested that a regional activation observed in functional imaging tells us little

(Price et al, 1999; Fletcher, 2000). For example, a number of studies of healthy subjects show frontal activation in association with recognition memory (Tulving et al, 1994b; Rugg et al, 1996) while neuropsychological studies (Stuss et al, 1994) have indicated that such tasks may be performed relatively normally even in the face of widespread frontal damage. One possibility is that such activations are "epiphenomenal", in the sense that they are not directly task-related. A more interesting possibility however is that the functional imaging data contain important additional information about the way healthy subjects perform the task. It might be viewed as providing an indication of more occult behaviour. For example, two subjects might be performing at ceiling upon a recognition memory task but, in the face of their indistinguishable behaviour, one may show activation of PFC the other may not. To argue on this basis that the PFC activation was epiphenomenal would be specious if it could be shown for example, that the former subject made recognition judgements on the basis of a rich recollection of the study episode whereas the latter did so merely on the basis of a vague feeling of familiarity. In such a case, it might be argued that the imaging difference reflects a psychological distinction that is hidden in the standard behavioural test. We must acknowledge that, like most observations, behavioural measures are limited in sensitivity and specificity and that discrepancies between functional imaging and neuropsychological data may point to flaws in our cognitive models of how tasks are performed and how performance is measured. In this sense, such discrepancies may represent a strength of the functional imaging techniques rather than, as has been suggested, a weakness. Ultimately, functional neuroimaging provides a new behavioural measure, one that adds information to more overt behavioural responses and that may even be observable in their absence.

2.2 Theoretical problems accompanying functional neuroimaging

One must also be realistic about the difficulties in applying the techniques and in interpreting their results. Some of these are profound, particularly with respect to the exploration of frontal function. A fundamental problem lies in the rudimentary state of current understanding of the types of processes subserved by PFC. In most functional neuroimaging experiments, changes in the haemodynamic response of a region are correlated with a manipulation of the subject's task. This change is attributed to a specific psychological process supposedly isolated by the task manipulation. A pattern of brain activity is therefore only meaningful to the extent that the psychological theory of task performance is valid. A specific example of this problem is the assumption that a task manipulation changes only a single cognitive process, leaving other processes unaffected. This assumption of ''pure insertion'' is particularly relevant to simple subtractive methods of analysing imaging data (Friston et al, 1996), where mean brain activity during performance of one task (the control) is subtracted from that during performance of another task: one that is assumed to differ only in that it engages the psychological process of interest. This assumption is dangerous: the difference between the two tasks may in fact be accompanied by numerous cognitive changes (which may not be evident from behavioural measures alone). This is why the ''activations'' reported by neuroimaging experiments cannot be evaluated without reference to the control task. This problem may be particularly relevant to the relatively high-level (non-automatic) and inter-related processes generally believed to be associated with PFC.

It is important, at the outset, to raise this problem: that neuroimaging ''activations'' are only interpretable in the context of a particular theory of task performance and with respect to a specific control. Neuroimaging activations are almost always described in terms of one or more conventional labels and within the

context of specific theories. For the technique to have real impact, its findings must be capable of informing as well as reflecting existing theories and models. In the final chapter, I will reconsider this point and attempt to offer a re-evaluation of the imaging findings in episodic memory (reported here and elsewhere) within a modified theoretical framework.

There are a number of problems with tests purporting to engage PFC and with the attempts to use these tests in the understanding of the functional characteristics of PFC (Burgess, 1997; Shallice and Burgess, 1998). These problems stem from the relatively impure nature of the tasks held to engage PFC. Taxing operations that control or modulate lower level processes would necessarily engage those processes too. This is summed up in Fuster's suggestion that PFC, by itself, doesn't actually "do": it modifies (Fuster, 1997). Furthermore, the results of this modification can be extremely difficult to measure since they are observed only indirectly. In addition, if an important aspect of PFC function lies in the response to novel situations then it must be acknowledged that any given task can only be novel for a finite period. Functional neuroimaging has indicated that a task that initially engages PFC no longer does so when that task is practised and made routine (Raichle et al, 1994; Fletcher et al, 2001). Yet another problem lies in the multi-faceted nature of executive tasks and in the necessary inter-linking of the sub-processes that are held to comprise modulatory or controlling processes. Thus, for example, in the Hayling sentence completion task a key process thought to be tapped is the inhibition of an automatic response (Burgess and Shallice, 1996b). However, there is evidence that healthy subjects may utilise a strategy that minimises their need to perform this inhibition. If they prepare a response before the context of the sentence has been made clear then they can produce this response after a peremptory check that the response is acceptable (that is, inappropriate to the

sentence's meaning). A patient with prefrontal damage may have difficulties with this task either through problems in inhibiting an automatic response or through a failure to recognise or use such a strategy (or due to both factors). Whatever the true state of affairs, the point is that the sub-processes are not easily dissociable and this theoretical constraint places major limitations upon the interpretation of imaging findings.

A further reason for caution in interpreting the results of such studies lies in the fact that they map functional attributes onto macrostructural features – lobes, sulci and gyri - of the brain. While gross anatomical features are likely to relate, to a degree, to the underlying cytoarchitectonic and myeloarchitectonic features, this relationship is neither certain nor consistent (Roland et al, 1997; Zilles et al, 1997; Amunts et al, 1999). As I have suggested in chapter 1 (1.2), it is very likely the case, these microstructural features have a greater bearing upon functional attributes than the macrostructural location. Thus, it is possible that group studies are prone to false negative results since they identify activations that occupy the same location across subjects but may ignore activations that might be considered microstructurally homogeneous but have varying locations with respect to the sulci and gyri.

I shall return to some of these difficulties in chapter 7 and attempt to show that, nevertheless, useful insights may be provided by PET and fMRI. At the outset however, it is important to look more closely at the techniques themselves from a practical and methodological view point. The following sections provide a brief outline of the two techniques (PET and fMRI). The aim of the description is to highlight certain characteristics of each approach. This will provide the basis for a consideration of how the technical characteristics of PET and fMRI shape the design of experimental tasks and the analytical methods.

2.3 The Techniques.

A more precise technical summary of the experiments carried out in the following chapters will be described in the Methods section of each experiment since there were some differences, across experiments, in the technical details and in the modelling and analyses. The following sections are concerned with the more general features of the techniques.

2.3.1 Positron Emission Tomography.

PET, as part of a cognitive activation study, provides a relatively precise, in vivo, 3-dimensional map of brain activity through tracking concentrations of an internally administered positron-emitting radioisotope, the cerebral distribution of which is measured using a gamma camera. The positron emitter used varies depending upon the nature of the question asked. The current work is concerned with studies of cognitive function using ^{15}O. In all experiments reported here, this is given as ^{15}O-labelled water administered intravenously. Internally, it emits positrons, which, in tissue, collide with electrons resulting in the emission of two bursts of gamma radiation at 180^{o} to each other. Recording these bursts of radiation using a coincidence detector allows average cerebral distribution to be measured. This measurement is made over a period of approximately one or two minutes. Since it is freely distributed with the blood, then an integrated measurement of its cerebral distribution is an indicator of cerebral blood flow and, indirectly, of cerebral synaptic activity.

2.3.2 fMRI.

Magnetic resonance imaging derives from the field of Nuclear Magnetic Resonance (NMR) in which a material's magnetic properties are used to derive a signal. (MRI became a more popular term in the 1970s due to the connotations of the word "Nuclear"). These magnetic properties arise from nuclear spins. Nuclei usually consist of protons and neutrons which have spins of equal and opposite angular momentum, cancelling each other out. In unpaired ones (most notably, Hydrogen) there is a resulting angular momentum and, therefore, a net spin. Much MRI is based upon molecules containing hydrogen and the biggest contributor to MRI signal are those hydrogen atoms bound to water. If an external magnetic field is applied, a proportion of magnetic moments align themselves with this field. Some are parallel to it, others are anti-parallel. Since the former is the lower energy state, a slight majority choose this alignment. (It is only a small proportion – at 1.5T, 1 in 10^5 of the dipole moments become aligned, the rest are randomly orientated. However, while the proportion is small, the actual number is great). The result is an overall net magnetisation. The axis of spin of a proton actually precesses around the net axis of that proton. A key part of generating the signal is in the application of a radio-frequency pulse that changes the alignment of the net magnetisation. This pulse exerts its effect through a characteristic frequency that enables it to affect the protons' precessions by resonance absorption. Having absorbed this energy, which changes their alignment, the spins return to the lower energey state through two types of relaxation

2.3.2a T1 Relaxation (Spin-Lattice relaxation)

This refers to the longitudinal return of the net magnetisation to its initial state (for that particular magnetic field).

2.3.2b T2 Relaxation – Spin-Spin relaxation

The transverse RF pulse, as well a producing a flip of the net magnetisation, leads to a phasing of precession that produces a net transverse magnetisation. The unphasing of precession is the T2 and T2* relaxation. T2 is affected by interaction with surrounding protons. T2* is affected by local field inhomogeneities.

The key point is that T1 and T2 are different in different types of tissue and are therefore potentially informative about the different tissue types. Most relevant, T2 relaxation is sensitive to local changes in the Oxyhaemoglobin-Deoxyhaemoglobin ration which is, itself sensitive to blood flow and, indirectly, to cerebral activity: most likely cerebral synaptic activity (Logothetis et al, 2001). This information can be linked with spatial information by the application of a magnetic field gradient, which will affect angular frequencies and phases differently at different points. The combined information of "what" and "where" is provided by T_2 relaxation time and angular frequency and phase measurements.

2.3.3 PET versus fMRI

Both PET and fMRI are dependent upon the haemodynamic responses to cerebral synaptic activity. Every attempt to map brain function using these techniques is ultimately dependent upon the characteristics of this sluggish response and is, thus, severely limited with respect to its temporal resolution. Much has been made of the advantages deriving from increased speed of acquisition of fMRI images over PET, and this has indeed added great power and flexibility to the design of functional imaging experiments and to the questions that they may address. However, the ultimate temporal resolution of both techniques is limited by their reliance upon measuring a response that occurs over seconds rather than at the millisecond level of neuronal firing.

2.3.3a Advantages of PET

PET's main advantage over fMRI concerns the problems of signal loss in certain brain areas when fMRI is used. Due to local inhomogeneities in the magnetic field. These are produced by interfaces between tissue and air, which lead to local magnetic field inhomogeneities. Thus cerebral regions behind the frontal sinuses and above the sphenoid sinuses are subject to loss of signal. The result is that, for some of these brain regions, notably inferior temporal cortex and orbitofrontal cortex, PET remains, in the eyes of some, the method of choice for some types of cognitive activation studies e.g. language studies that may activate inferior temporal cortex, or studies of emotional processing that are predicted to engage orbitofrontal cortex.

A further, unique potential of PET for exploring cognition is through linking it to underlying neurotransmitter function through ligand displacement studies: a technique that shall not be discussed further in this thesis.

2.3.3b Advantages of fMRI

A major advantage of fMRI over PET lies in increased spatial and temporal resolution. The possibility of acquiring far more scans (there is no theoretical limitation upon this since no radioactive ligand is necessary) over shorter time periods (one whole brain MRI image may be acquired in a matter of seconds, compared to over a minute for a PET scan), with each scan having finer spatial resolution than is obtainable with PET, enables cognitive activations to be more powerfully measured. Furthermore, since a sufficient number of measurements can be acquired to observe activations in single subjects, even greater spatial resolution may be obtained since it is no longer absolutely necessary to merge scans from several subjects. FMRI data from a single subject,

mapped onto that individual's high-resolution structural MRI (without the need for spatial normalisation), produces highly accurate localisation of foci of activation. This freedom also means that a single subject can be scanned on several occasions which, of course, has implications for attempts to plot brain changes reflecting relapsing or remitting symptoms in patient studies.

Additionally, the increased number of scans that may be acquired per unit time has liberated functional imaging from the need for blocked designs. A further discussion of the advantages of this is given below and in the discussion of experiment 5b (chapter 5).

2.4 Task Design in functional neuroimaging experiments.

2.4.1 Cognitive subtraction

Cognitive subtraction is the essence of functional neuroimaging as it is most commonly applied. Virtually every image of brain activity presented in the literature is a difference image. That is, the image is the result of a subtraction of the activity associated with a reference condition from an image acquired in the setting of a task of interest. The practical and theoretical implications of this are considered below.

2.4.1a Linking processes to brain regions

The characteristics of the techniques place a number of constraints on experimental design. In many ways, these constraints are no different to those that must be considered in any psychological experiment where one is trying to establish the existence of a relationship between an independent/explanatory/predictor variable and a dependent/outcome variable. In most cases, the explanatory variable in functional neuroimaging experiments is a cognitive sub-process. The dependent variable is the

estimated regional cerebral blood flow or the BOLD signal at each location (voxel) in the brain. If it can be established that the level of measured signal varies significantly in association with the presence, absence or level of the cognitive sub-process (manipulated through requiring the subject to perform two or more psychological tasks), then this relationship may, with certain caveats, be interpreted as an indication of the functional role of that brain region in the cognitive sub-process. This simple approach has been at the heart of the "cognitive subtraction" design of imaging experiments.

2.4.1b The "baseline" task.

To rehearse a point made above: for both techniques, an estimate of synaptic activity in association with a given task is only meaningful when compared to baseline or reference conditions, the ideal baseline task being one that is identical to the activation task in all respects save for the cognitive component of interest. Thus, the baseline condition in a memory activation study should be balanced for the visual, auditory-verbal, movement, etc. components of the activation task but would not engage memory systems to any significant degree. The design of the baseline task is as critical as that of the activation task. Failure to control adequately for the incidental (uninteresting) activations associated with the task in question will result in measured brain activations that have little or nothing to do with the process under study. Conversely, it should be borne in mind that even the most apparently simple of tasks can engage higher cognitive function to a considerable degree. Aspects of attention, memory and language pervade many tasks and may produce false negatives (with regard to brain regions activated) when brain activations associated with such tasks are used as a baseline. This point is well illustrated with reference to the most apparently simple of tasks: "rest". While such a baseline condition merely requires subjects to lie

still during the scanning procedure, it is not possible to control for the thought processes that necessarily accompany this apparently inactive state. It is possible that the trains of thought that run during a resting condition involve a number of high level, and probably frontally-mediated processes such as the automatic retrieval of autobiographical memories and the subjective attempt to suppress such memories recall in order to try and comply with the experimenter's admonition to "lie still and think of nothing". For example, in an early PET study of long-term memory Grasby and colleagues found that memorising a 15-word list produced marked, bilateral prefrontal activation when compared to memorising a 5-word list but not when compared to a resting condition (Grasby et al, 1993). This suggests that frontal activity is at least as great during rest as it is during long-term memory. Partly for this reason, none of the experiments that I report use rest as a baseline.

2.4.2 Parametric Designs.

It may be possible to refine the assessment of task-related brain activations through the use of a parametric design in which, across all scans, subjects perform qualitatively similar tasks but with the incorporation of a variation or gradation in the cognitive component of interest. Thus, a study of the encoding and retrieval of auditory-verbal memory (Grasby et al, 1994) employed, across 12 PET scans, a gradation in "memory-load" with subjects having to learn word lists consisting of between 2 and 13 words inclusive. This design made it possible to assess significant changes in brain activity in response to increasing (and decreasing) memory requirements and to ignore those activations that were common to all scans and unaffected by the experimental manipulation. Such an approach has also enabled experimenters to interrogate data with respect to more specific questions about memory systems, for example memory-load related brain changes occurring only within the

supra-span (or LTM) portion of the scans. It has enabled, too, the more effective use of memory performance as a covariate with which to examine cerebral changes. It should be remembered, however, that, in essence, the parametric approach is, conceptually, almost identical to the cognitive subtractions described above insofar as it relies on possibility of manipulating the component of interest while holding other factors constant.

2.4.3 Factorial Designs.

A potential drawback of the cognitive subtraction and the parametric manipulation approach is that they are both based upon an assumption of "pure insertion" (Friston et al, 1996). They adhere implicitly to a belief that a given cognitive component can be inserted or removed without affecting the activations produced by the other components of the task. Thus, in a memory study in which the activation task requires the learning of verbal material and the baseline task involves the presentation of the verbal material without the associated mnemonic requirement, the assumption of pure insertion is that, during the activation task, there is no interaction between the memory and the language processes. More simply put, such a design assumes that subtracting brain activity acquired during a language task from that acquired during a language-plus-memory task will result in the elucidation only of brain systems associated with memory. The reasoning behind this may be specious. It may very well be that the words are processed in a different way when they are the part of an explicit memory task compared to when they are not. The only way to assess whether the initial assumption (of no interaction) holds true is to manipulate the two factors (memory and verbal processing) separately.

Such a factorial design is now popular in the study of memory, not only because it may help to clarify the extent to which the assumptions of cognitive insertion are upheld, but also because the interactions between factors at the neurophysiological level are themselves potentially interesting. Experiments 1, 3, 5b and 6 used factorial designs, relating effects of interest largely to the interaction terms.

2.4.4 Event-related designs.

In a blocked experimental design (necessary with PET due to the slow data acquisition and popular in fMRI due to the impressive signal-to-noise ratio (SNR)) multiple repetitions of the same trial type occur in succession (usually in blocks of 30 seconds-1 minute). The average activity in each voxel may then be computed and is considered to be representative of the activity associated with that trial type. Event-related designs are not conceptually different to blocked designs in that they are subject to all of the constraints and possibilities associated with cognitive subtraction, parametric and factorial designs described above. They do, however, offer an increased flexibility to the experimenter allowing trials to be presented in a randomised and unpredictable order. (The value of this, and the extent to which it may overcome some of the interpretational uncertainty surrounding the block design will be discussed in the chapters 4 and 7, with particular reference to one of my experiments (4) and to memory studies in general). Furthermore, they allow an experimenter to analyse data on the basis of unpredicted occurrences or post hoc analyses. Thus for example, if a subject is presented with a list of words to learn, subsequent retrieval measures will indicate that some of the words were successfully encoded while others were not. There is no way of knowing this information in advance (without the addition of an explicit experimental manipulation) and so a block design could not be used to look at the neurophysiological differences between subsequently remembered and forgotten words. An event-related

design is, however, suitable for such an analysis (Brewer et al, 1998; Wagner et al, 1998c) and this is a major advantage. An alternative possibility is that one can restrict one's analysis to, say, correct trials occurring in two conditions in order to ensure maximum comparability. This was the approach used in the event-related experiment presented here (experiment 4).

2.5 General considerations in functional neuroimaging analysis.

All experiments reported in subsequent chapters have been analysed using statistical parametric mapping (SPM) which, essentially, constitutes a set of standard statistical techniques that ultimately enable between-scan voxel-by-voxel univariate contrasts producing spatial representations of statistically significant differences. The approach involves a number of pre-processing steps. Since there are subtle differences across the set of experiments reported, the precise nature of actual analyses will be described in the Methods section of each. However, it will be useful to consider each of the steps in general terms with regard to their purpose and their implications for issues such as spatial resolution and activation detection. I will therefore provide a general consideration of the steps common to each of my experiments under the following headings: spatial pre-processing, model design/fitting and statistical inference.

2.5.1 Spatial pre-processing.

The spatial pre-processing implemented in subsequent chapters consists of three main stages: image realignment, spatial normalisation and spatial smoothing. Images from a subject are realigned to a reference image, spatially normalised into a standard space, and smoothed to improve SNR.

2.5.1a Realignment

Subject movements are inevitable through the course of an experiment. The resultant misalignment could mean that a voxel by voxel comparison across scans within a subject would be meaningless (since one might be comparing different volume elements (voxels) across successive images). The standard realignment programme in my studies used a minimisation of sums of squares approach in order to define the parameters required to align each image to a reference image (in most cases, the first image acquired). Having ascertained these parameters, a six-parameter affine transformation was performed on each image (except the reference image). The six parameters consisted of three translations (x, y and z movements) and three rotations (roll, pitch and yaw). Following this registration of images, interpolation of voxel values was used in the writing the new, realigned images. This interpolation is necessary but, it should be remembered, produces a degree of spatial smoothing that necessarily leads to a reduction in spatial resolution.

2.5.1b Spatial normalisation

Subjects have different-sized and shaped brains. A group analysis, carried out on a voxel by voxel basis, makes an assumption that a given "group" voxel, representing a specific brain locus for that group is made up of comparable voxels from each of the constituent individuals. This can only be achieved through a warping procedure such that individuals' brains are transformed to occupy a reference space. This is carried out, for each subject, in a two-step procedure. The first, and least complex, is a twelve-parameter affine transformation of a representative image from that subject to a template image occupying the desired reference space (three translational and three rotational parameters as in the realignment stage plus three zoom parameters and three shear parameters). A non-linear transformation using a set of

basis functions is then applied in order to map the sulci and gyri of the subject's image, as far as is possible, onto those of the template image. The stored parameters are then applied to the whole set of subject images for that subject in order to ensure that each occupies the same space (as each other and as the other members of the groups and, indeed, as individuals from all studies that have used the same template images).

This is a computationally difficult procedure and prone to a number of errors. Furthermore, it will necessarily lead to a further reduction in spatial resolution, partly due to the interpolation required when writing the new, normalised images and partly due to the fact that there will be, in the group images, a blurring of the unique features of individuals. This is the price that must be paid for group data but one should not forget that the whole idea of a group analysis makes certain assumptions about homogeneity across individuals: of macrostructure, of micro-structure and, critically, of the macro-micro structure relationship, as discussed above.

2.5.1c Spatial smoothing

Functional neuroimaging data are noisy. Spatial smoothing is introduced in order to increase the SNR on the basis that very high spatial frequency signal is more likely to represent noise than true activation. That is, a cluster of activated voxels is considered more plausible as a brain response than a single voxel. Smoothing is carried out with a gaussian kernel. The size of this kernel is often arbitrary but may perhaps be selected upon the basis of regions in which activation may be expected e.g. a smaller smoothing kernel is perhaps more appropriate when activation in smaller structures is expected. Once again, this step results in a reduction in effective spatial resolution.

2.5.2 Model design and fitting.

Despite the complex technical problems that accompany it, a functional neuroimaging study is usually very simple in that it explores the presence of a relationship between the cognitive manipulation, embedded in the experimental conditions, and the response at each and every voxel or brain locus. The significance of the relationship is determined by a numerator (size of effect in that voxel) and a denominator ("noise" or standard deviation in that voxel). The challenge, therefore, is to estimate each of these two effects and to determine whether or not the resulting response in that voxel (expressed, say, as a t value) is significant (and, by implication, whether the brain locus at that voxel is involved in the process of interest). Ultimately, the success of this will be determined by the task design and by the psychological models driving the experiment (see discussion above and in the concluding chapter). However, steps may be taken at this stage of the analysis to optimise signal detection and to reduce the impact of noise.

Modelling of conditions in PET is quite simple: each measurement can be considered independent and the regional response produced by each condition may be estimated by evaluating the average activity in each voxel for that condition compared to the average activity for the baseline task. Since measures are independent, standard error may be calculated easily and is uncontaminated by, for example, serial autocorrelation. One fact that does need to be taken into account is the global brain activity that accompanies each measurement. This could produce spurious activations (if higher levels of global activity co-occurred with the activation task) or it could conceal true activations (if global activity showed the reverse effect). Global effects are best dealt with by an experimental design that counterbalances the order of conditions and varies them across subjects but the effect may also be modelled and partialled out at this stage.

In fMRI the modelling is more complex since a continuous time series is usually acquired. This means that, in modelling the signal, one needs to pay attention to its likely shape as well as its magnitude. For example, in a commonly used "box-car" design in which blocks of activation task alternate with blocks of baseline task, the pattern of activation is likely to lag behind the experimental design by a few seconds (due to the sluggishness of the haemodynamic response). The brain activation signal will therefore be more efficiently found using a model that accounts for this effect. Similarly, when an event-related design is used (see experiment 4) the way in which we model the likely haemodynamic response to individual trials will have a great impact upon what we find. Furthermore, the acquisition of a continuous time series has an impact upon error estimation (and, therefore, upon statistical inference). Since serial autocorrelation contributes to the error term, for a variety of reasons, this may produce a spurious reduction in the error estimate, leading to an unjustified inflation of t values and resultant type I statistical error. Additionally, as with PET data, fluctuations in global activity may act to produce or conceal activations. These are generally dealt with in fMRI using some form of high-pass filtering in which low frequency signal (i.e. of markedly lower frequency than the frequency inherent in the experimental design) is modelled and consigned to the error term.

2.5.3 Statistical Inference.

Classical statistical inference is an inexact business and some have criticised its essentially arbitrary nature (Hunter, 1997), a criticism that has been made, too, in the setting of functional neuroimaging (Friston et al, 2002b) with the suggestion that a Bayesian approach may prove more useful: i.e. one that eschews the assignment of p values (the likelihood that a region was not activated), instead opting for an expression

of the likelihood that a given size of effect truly reflects activation (Friston et al, 2002a; Friston et al, 2002b). These developments are at an early stage and the more standard, classical inferential procedure has been used in the experiments that follow. Below, I describe briefly two of the problems that accompany this.

2.5.3a The multiple comparisons problem.

The main problem with statistical inference in functional neuroimaging arises from the multiple comparisons problem (Bland and Laltman, 1995). Simply put, a voxel by voxel standard imaging analysis involves thousands of simultaneous t tests. The likelihood of erroneously refuting the null hypothesis (that there is no activation) for any given voxel is thus much greater. In standard experiments this may be guarded against by correcting the calculated p value with respect to the number of comparisons carried out (by multiplying the p value by this number). This is only appropriate where separate t tests are independent. If they are non-independent (as in the case in functional neuroimaging by virtue of the smoothness of the images) then the standard Bonferroni correction will be too conservative. For this reason, in SPM, a modified version of the correction is applied by calculating the number of effectively separate comparisons (having taken into account the smoothness). However, the use of both the Bonferroni approach, and this modification of it, is open to the criticism that it is over-conservative (Perneger, 1998; Turkheimer et al, 2000) and even irrational (Perneger, 1998). For this reason, other approaches are currently being taken up: for example, the use of the "False Discovery Rate" (Benjamini and Hochberg, 1995; Genovese et al, 2002) or the application of Bayesian approaches, which are unaffected by multiple comparisons (Friston et al, 2002b).

2.5.3b Modelling inter-subject variability

A second consideration with respect to statistical inference concerns inter-subject variability. In order to ensure that the results of a study are plausibly generalisable to the population as a whole (or at least the population of people with the same characteristics as the participants), one must show that the measured effects are present not only in the group as a whole but also that these effects are reflected within individual subjects (i.e. that they are not carried by strong effects in a minority of subjects). In order to be sure of this, inter-subject variability should be explicitly modelled. This is a serious issue when inter-subject variability in the observations is large compared to intra-subject variability. Such is not the case in PET where, within subjects, observations tend to be very variable from scan to scan. For this reason, I have used the standard PET analysis approach of treating inter-subject variability as a "fixed effect". In the fMRI studies, since a formal analysis treating inter-subject variability as a "random effect" was unavailable at the time that these data were analysed, I have used an approach that addresses this point simply by ensuring that, at the level of each individual within the group, the reported group activation was found, thus guarding against the problem described. In experiment 4, I did this by looking at each subject's data set separately and have actually presented the data from all six individual subjects. In experiment 5b, I carried out a formal 'conjunction' analysis (Price and Friston, 1997), which ensures that reported activations are, indeed, common to all subjects.

2.5.3c The approach to statistical inference used here.

To summarise the model fitting and statistical inference: parametric statistical models are assumed at each voxel, using the General Linear Model to describe the data in terms of experimental and residual variability. Hypotheses expressed in terms of the model parameters are assessed at each voxel with univariate statistics. This gives an

image (a "statistical parametric map") of activation s surviving a pre-specified statistical threshold.

My approach to observations in the experiments that follow has been underpinned by the belief that we will never find a balance between the likelihoods of type I and type II error that satisfies everybody and every situation. Ultimately, with regard to the question of inference, the validity of a finding is determined by its replicability and by its compatibility with other studies exploring similar phenomena in the field. The extent to which we must be wary of the two types of error is perhaps guided by the overall theme of our experimental enterprise. Clearly, when testing a new, expensive and potentially hazardous drug over older well-established treatments, a false positive (the erroneous statement that the new drug is significantly more beneficial than the old one) is perhaps a more serious error than a false negative and we must be more on guard against the former error than the latter. Functional neuroimaging, however, seems a more exploratory field and I suggest that false negatives are likely to be as confusing and serious as false positives. Reviewing the memory literature from the memory field recently (Fletcher and Henson, 2001), I was struck by the number of activations that would not have survived had a stringent correction for multiple comparisons been used but which, when viewed in the context of other studies that replicated them or with which they were highly consistent, they gained plausibility. For this reason, I have chosen to report a number of findings here that would not survive the Bonferroni-type correction and my general approach (with certain exceptions, all of which are detailed in the individual Methods sections) has been to use an uncorrected threshold of $p<0.001$ in the belief that, while this increases my vulnerability to false activations, it reduces the risk of hiding real effects that, when viewed in the context of all the experiments, are plausible and meaningful.

2.6 Summary of chapter.

The purpose of this chapter has been to consider some of the characteristics of the functional neuroimaging techniques. They have a number of features (in vivo measurement, spatial and temporal resolution, experimental flexibility) that make them a very useful addition to the neuroscientific toolbox and enable them to provide unique insights into structure-function relationships in the brain. Nevertheless, they are subject to a number of practical and theoretical constraints and are ultimately limited in the questions that they may pose and the interpretations that they allow. For these reasons they must be seen as a complement to, rather than a replacement of, existing techniques and approaches.

I have suggested that the analytical procedures in the neuroimaging field, still evolving, may be contentious and may defy any simplistic or universal approach. Additionally, they are based upon a number of assumptions about the reliability of the guiding theoretical models and the consistency, or otherwise, of structure-functions relations across individuals. It is unlikely that all of these assumptions are valid in all circumstances. Finally, with respect to statistical inference and to our views about the reliability of findings, we must acknowledge that there are no hard rules and that, ultimately, the plausibility of a single experiment, and of the field as a whole, will arise from observations of internal consistency and of consistency with findings from other techniques.

Chapter 3

Dissociating brain systems for episodic memory encoding and retrieval

Experiment 1 – paired associate encoding

Experiment 2 – paired associate retrieval

General Introduction.

With certain exceptions (Squire et al, 1992), in the earliest PET studies of episodic memory (Grasby et al, 1993; Petrides et al, 1993a; Petrides et al, 1993b; Grasby et al, 1994) study (encoding) and test (retrieval) phases occurred within the same scanning period. Such a combination, while experimentally convenient, fails to take advantage of one of the main advantages of functional neuroimaging: the possibility of exploring, separately, the encoding and retrieval stages of episodic memory. Experiments 1 and 2, reported in this chapter, aimed at examining these stages with respect to the presence of dissociable neuronal systems for the two stages. In addition, in experiment 2, an attempt was made to dissociate semantic and episodic memory retrieval in terms of the brain systems activated, thus providing experimental support for the episodic-semantic distinction (Tulving, 1983). In both experiments, word paired associates, each consisting of a category together with a relevant exemplar of that category, were used.

3.1 Experiment 1 - Brain systems associated with encoding of word paired associates

3.1.1 Introduction

In exploring the brain regions activated in association with episodic memory encoding, it is necessary to take into account the influence of other memory processes contributing to task performance. Brain changes associated with priming processes, for example, may be elicited, particularly when pair members are closely semantically related. The design of this study attempted to reduce this contribution, as much as possible, through the use of low frequency category-exemplar pairings and, more importantly, by means of a dual task design. The logic of this latter aspect of the study is that a concurrently performed motor distracting task will interfere with episodic memory encoding but not with priming processes (Jacoby et al, 1993). The use of a difficult concurrent task should therefore selectively attenuate brain activations associated with episodic memory encoding but leave priming systems relatively intact. By contrast, episodic memory should be less impaired when subjects perform a structurally similar, but attentionally less demanding, task.

3.1.2 Materials and Methods.

Six right-handed male subjects took part in the study. All subjects were fit, healthy and free of any significant previous or current medical, neurological or psychiatric illness. The study involved the administration of 7.2 mSv effective dose equivalent of radioactivity per subject and was approved by the Administration of Radioactive Substances Advisory (ARSAC) committee of the Department of Health, U.K. Subjects gave informed written consent and the study was approved by the joint

research ethics committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London.

3.1.3 PET Scanning

Scans of rCBF were obtained using a CTI model 953B-PET scanner (CTI Inc, Knoxville, Tenn., U.S.A.) with collimating septa retracted. For each scan, subjects received a 20 second bolus of $H_2{}^{15}O$ at a concentration of 55mBq/ml and a flow rate of 10ml/minute through a forearm cannula. Twelve consecutive PET scans were collected at 10 minute intervals, each beginning with a 30 second background scan before delivery of the bolus. The integrated radioactivity counts accumulated over the 90 second acquisition period, corrected for background counts, were used as an index of rCBF. Subjects were scanned in a quiet, darkened room, with eyes fixed on a computer screen, suspended approximately 40cm from their face.

3.1.4 Tasks

3.1.4a Memory task.

Prior to scanning, subjects were instructed that they would be read a list of category-exemplar pairs and that they should try to remember them for a later test of recall. Rare category-exemplars were chosen (Battig and Montague, 1969). An example is given in the appendix to this chapter. During scanning, subjects were presented with a list of 15 pairs, read by the experimenter at a rate of one pair per three seconds. In the five minutes following the presentation/scanning stage, a 'stress and arousal' questionnaire was completed verbally by the subject (this comprised a list of questions concerning the subject's anxiety and well being and was primarily introduced to prevent list rehearsal). Retrieval was then tested by presenting categories (at a rate of one per three seconds) and subjects were asked to recall the relevant exemplar at each

prompt. If unable to recall an item, the subject said, "pass". In total, six different paired associate lists were presented across six different scans. Three of the paired associate lists were administered in association with a "high distraction" motor task and three with a "low distracting" task (see below).

In addition, a control task was administered an equal number of times in association with the motor tasks (i.e. three times in association with the "high distraction" task and three times with the "low distraction" task). In this control task, subjects were presented with an identically paced auditory input but with no mnemonic component. The input comprised the words "One thousand...Two thousand" read repeatedly once every three seconds, a total of fifteen times.

3.1.4b Distraction Tasks

Subjects received prior instructions and practice in the use of a joy-stick placed beside their right hand. They were required, during scanning, and while they were listening to the memory pairs or the control task, to use the stick to move a cursor, as rapidly as possible, into boxes appearing randomly (in the "high distraction" task) in one of four positions on the screen in front of them. An interval of 0.25 seconds separated successive appearances of boxes. In order to control for the number of boxes appearing to the subject across scans, the total time for each trial was kept constant (1.1 seconds). A 'Low distraction' task was carried out in half of the scans. This was identical in very respect to the High distraction task apart from the fact that the boxes appeared in an entirely predictable way, moving successively clockwise around the four positions on the screen. This task summarized is in figure 1. It was ascertained, through pilot testing, that the high (unpredictable) distraction task produced a deficit in subsequent cued retrieval compared to the low (predictable) distraction task.

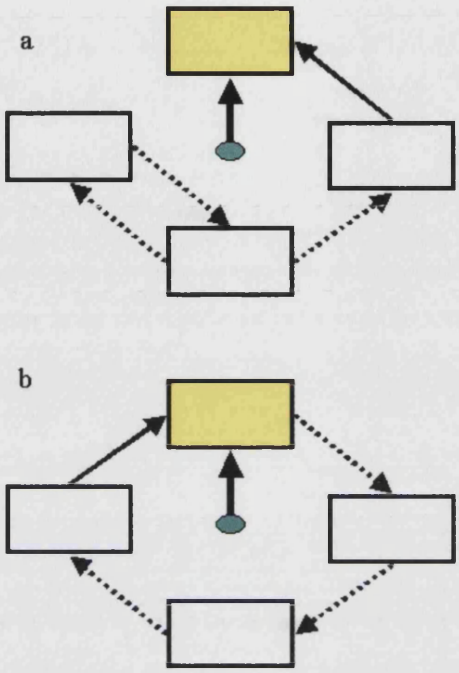

Figure 3.1 Diagrammatic representation of high-distraction (a) and low-distraction (b) tasks. A four-box array was presented on the screen and subjects were required to use a joystick to move a cursor into the highlighted box. The box that was highlighted changed at a rate of once every second. In the case of the more distracting task, there was no predictability in the pattern of change. In the low-distraction task the pattern was entirely predictable.

3.1.5 Summary of task design and data analysis.

Thus, in this experiment, there were four possible combinations of task administered to the subjects:

- Memory encoding with high distraction task (M+D+).
- Memory encoding with low distraction task (M+D-).
- Control task with the high distraction task (M-D+).
- Control task with the low distraction task (M-D-).

The memory-induced cerebral activations were examined in the presence of both distraction tasks. The comparison of rCBF associated with the M+D+ task with that associated with the M-D+ task identifies the brain regions sensitive to encoding in the presence of the High distraction task. In this case, an attenuation of episodic memory

encoding (and relative preservation of priming processes) was predicted. The comparison of rCBF in the M+D- task with that associated with the M-D- task represents the neuronal activity associated with encoding in the presence of the Low distraction task. In this case, brain activity associated with episodic memory encoding was predicted to be relatively unaffected. The interaction term, comparing, the differences between these two comparisons would therefore identify areas specific to episodic memory encoding.

Images were reconstructed into 63 planes, using a Hanning filter, resulting in a 6.4mm transaxial and 5.7mm axial resolution (full width half maximum). The data were analysed with statistical parametric mapping (SPM) (Friston et al, 1995a; Friston et al, 1995b) using SPM software from the Wellcome Department of Cognitive Neurology, London (http://www.fil.ion.ucl.ac.uk) implemented in Matlab (Mathworks, Sherborn, MA). After initial realignment, the scans were transformed into standard stereotactic space. The scans were smoothed using a Gaussian filter set at 12mm full width at half maximum. The regional cerebral blood flow (rCBF) equivalent measurements were adjusted to a global mean of 50 ml/dl/min. A blocked (by subject) ANCOVA model was fitted to the data at each voxel, with a condition effect for each of the conditions, using global CBF as a confounding covariate. Predetermined contrasts of the condition effects of each voxel were assessed using the t statistic, giving a statistic image [SPM(t) transformed into an SPM(z)] for each contrast. The chosen threshold of significance for main effects of conditions was $p<0.001$ (uncorrected for multiple comparisons).

3.1.6 Task Performance

3.1.6a Memory task

The mean number of exemplars recalled in response to category-cueing following the M+D- task was 12.5 (s.d. = 1.5), i.e. 83.3%. The M+D+ task was followed by significantly ($p<.001$) impaired retrieval levels, as expected, of 10.3 (s.d. = 1.3), 68.7%.

3.1.6a Distraction task

Performance of the high distraction task, during concurrent memory encoding produced a mean reaction time of 512 milliseconds (s.d. = 71). Performance of the same distraction task in association with the control (passive listening task) was associated with an average reaction time of 453 milliseconds (s.d. = 59). Performance of the low distraction task, during concurrent memory encoding showed a mean reaction time of 426 milliseconds (s.d. = 84). Performance of the same distraction task in association with the control (passive listening task) was associated with an average reaction time of 366 milliseconds (s.d. = 63). Thus, the difficult distraction task was associated with a significant slowing of reaction times ($F(1,5) = 32$, $P<.001$). The interaction with memory encoding did not reach significance ($F(1,5) = 6$, $P = .058$) but there was a clear trend.

3.1.7 Imaging results.

3.1.7a Memory encoding - high distraction.

A comparison of scans in which subjects performed the control task in association with the high distraction task with those in which they performed memory encoding in the presence of the same distraction task (i.e. M+D+ versus M-D+), revealed significant activations in superior temporal gyri bilaterally and left anterior cingulate cortex. Data are presented in table 1 and figure 3.2

3.1.7b Memory encoding - low distraction.

A comparison of the control task in the presence of the low distraction task with memory encoding in the same condition (M+D- versus M-D-), identified activation in superior temporal gyrus (left only) and anterior cingulate cortex as seen in the comparison above. In addition, activation was seen in the retrosplenial area of posterior cingulate cortex and in left ventrolateral PFC. See table 1 and fig . 36

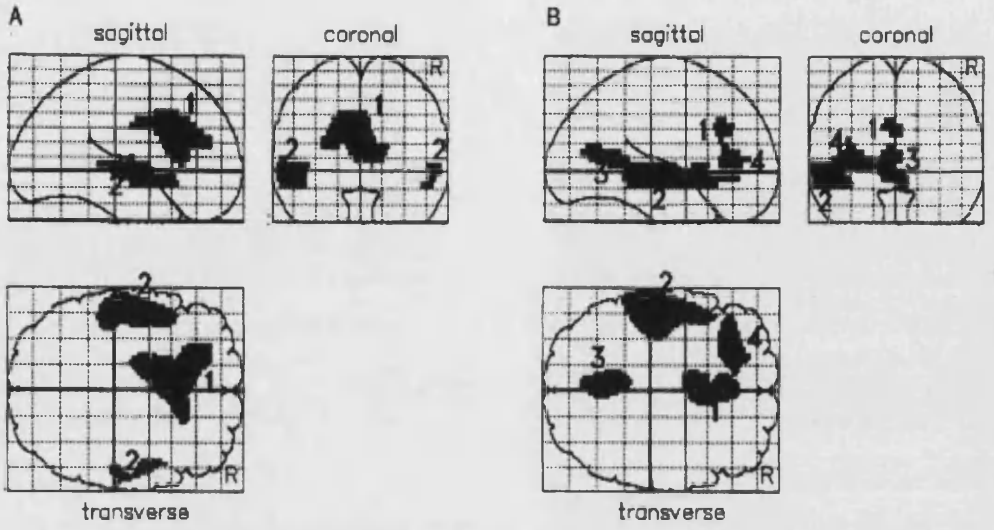

Figure 3.2 Encoding-related activations.

Statistical parametric maps of: SPMs of (a) Memory encoding activations in the presence of the high-distraction task. (M+D+ vs M-D+) and (b) Memory encoding in the presence of the low-distraction task. (M+D- vs M-D-). Activations are seen as orthogonally viewed 'glass brains', from the right (*top left*), from behind (*top right*) and from above (*bottom left*). The statistical threshold was set at $P < 0.001$.

Figure 3a shows activation of anterior cingulate cortex (1) and bilateral temporal cortex (2). Figure 3b also shows activation of (1) and (2) and, in addition of posterior cingulate cortex (3) and left inferior frontal gyrus (4)

Table 3.1 **rCBF increases associated with the encoding task compared to auditory control**

Region		Location (X,Y,Z)	Z Score		Location (X,Y,Z)	Z Score
	High Distraction			*Low Distraction*		
Left Superior Temporal Gyrus		-54, -6, 0	5.2		-56, 0, -4	5.0
Right Superior Temporal Gyrus		48, 4, -8	4.1		54, -8, -4	2.5
Left Anterior Cingulate Cortex		-4, 22, 28	5.4		-2, 28, 28	4.0
Medial frontal cortex		-22, 36, 20	4.0		---	-
Left Prefrontal Cortex		---	-		-32, 34, 8	4.1
Posterior Cingulate Cortex		---	-		-2, -62, 12	4.1

31.7c Interaction: encoding and distraction

([M+D- vs. M-D-] versus [M+D+ vs. M-D+]).

In this comparison, patterns of memory-induced activation in the presence of the low distraction task were contrasted with those in the presence of the high distraction task. Thus, it identified regions significantly attenuated by distraction and, therefore, by the logic of the experimental design described above, specific to episodic memory encoding. To reduce the number of voxels analysed (and thus, to reduce the risk of type I error due to multiple comparisons) this comparison was constrained to a "mask" of

those regions identified by a combined (M+D+ versus M-D+) and (M+D- versus M-D-) comparison. That is, this analysis of the interaction was confined to a system of regions found to be involved in the memory encoding tasks as a whole.

The comparison identified left PFC (in a ventrolateral region) and posterior cingulate cortex. Data are presented in table 2 and figure 3b. In addition, the regions showing an interaction in the opposite direction are shown (table 2 and figure 3b).

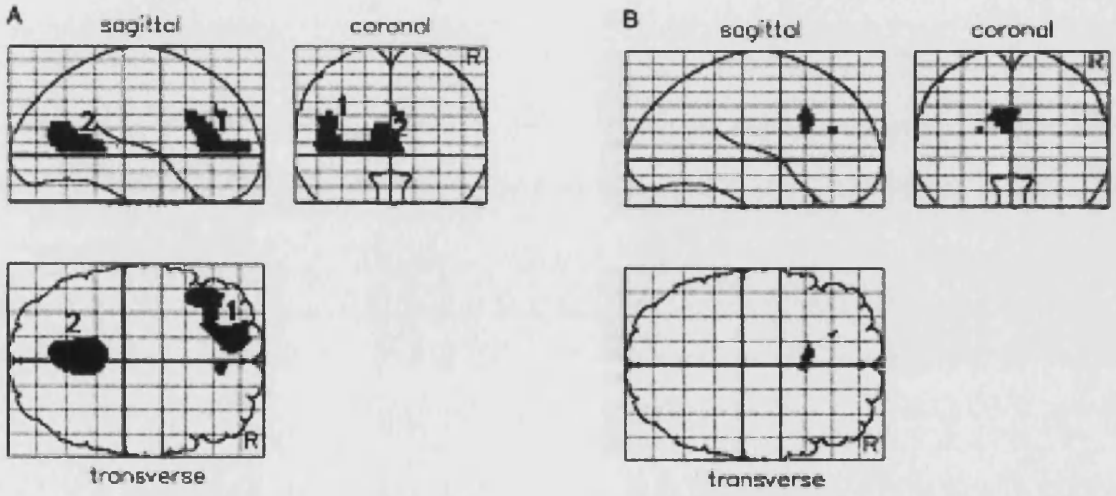

Figure 3.3 Regions showing an interaction between encoding task and level of distraction.
a. Regions in which encoding related activation (M+ vs M-) was significantly greater in the presence of the low-distraction task. Alternatively this may be considered to reflect regions in which the high-distraction task produced an attenuation in encoding-related activations. This contrast was masked as described in the text. These regions are left inferior frontal gyrus (1) and posterior cingulate cortex (2).
b. Regions showing an interaction in the opposite direction (i.e. regions in which encoding-related activation was significantly less in the presence of low distraction or, alternatively formulated, where encoding-related activation was augmented in the high-distraction task). Anterior cingulate cortex is the only region showing this effect.

Region		Location (X,Y,Z)	Z Score
	Decreases in memory-induced activations produced by distraction		
Left Prefrontal cortex		-48, 34, 8	2.7
Posterior Cingulate Cortex		-6, -50, 8	2.8
	Increases in memory-induced activations produced by distraction		
Left Anterior Cingulate Cortex		-12, 0, 32	3.6

Table 3.2 Interactions between encoding and distraction

3.1.8 Summary of experiment 1 results.

Comparison of verbal paired associated encoding with control conditions produced activation in superior temporal cortex bilaterally and in left anterior cingulate gyrus. These activations were present whether or not subjects were distracted. Specific to encoding under the low distraction condition was left PFC and posterior cingulate cortical activation. A direct contrast between the two sets of encoding related activations showed that left PFC and posterior cingulate are the sites of a significant interaction between verbal encoding and distraction. By the logic driving this experiment, this makes them likely candidates for parts of the episodic memory encoding system. In addition, this neurophysiological effect was associated with a behavioural interaction in which subsequent retrieval performance was significantly worse when encoding had occurred under high distraction. This suggests that the two regions attenuated by distraction may be important to the encoding process.

Experiment 2 – Brain systems associated with the retrieval of paired associates.

3.2.1 Introduction.

The purpose of this experiment was to explore, in terms of brain responses, the retrieval component of the encoding experiment described above. A dual-task design was not used in this study but, otherwise, a similar design, involving the encoding and retrieval of category-exemplar word pairs was used. Two control tasks were used, a simple word repetition task introduced to control for auditory-verbal components of the activation tasks and a further 'semantic generation' task. The purpose of the latter was to attempt to distinguish episodic from semantic memory retrieval.

3.2.2 Materials and Methods

Six right-handed male subjects took part in the study. All subjects were fit, healthy and free of any significant previous or current medical, neurological or psychiatric illness. The study involved the administration of 7.2 mSv effective dose equivalent of radioactivity per subject and was approved by the Administration of Radioactive Substances Advisory (ARSAC) committee of the Department of Health, U.K. Subjects gave informed written consent and the study was approved by the joint research ethics committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London.

3.2.3 PET Scanning

PET scans were obtained as described above for the encoding study.

3.2.4 Tasks

Two memory tasks were used, namely episodic memory and semantic memory retrieval.

3.2.4a Episodic memory retrieval.

In the episodic memory retrieval task, subjects were presented, five minutes before the scan, with a list of 15 category-exemplar pairs (at a rate of one pair per 3 seconds). In the 5-minute period between list presentation and the beginning of the scan, a stress and arousal questionnaire was administered (as with the encoding experiment, the primary purpose of this was to prevent list rehearsal). During scanning, subjects were prompted with each category from the list, at a rate of one per 3 seconds, and required to recall the exemplar with which each word had been paired. If unable to recall an item, subjects said, "pass".

3.2.4b Semantic memory retrieval.

In the semantic retrieval task, subjects were presented with a list of 15 previously unseen categories and required to provide a relevant exemplar of their choice for each. Categories were, again, presented at a rate of one per 3 seconds.

3.2.4c Control task.

A third condition, introduced as a control task, required simply verbal repetition of words (categories and exemplars) read out by the experimenter at the same rate.

The episodic (E), semantic (S) and repetition (R) conditions were presented, across the twelve scans, in four blocks of three as follows: R E S S E R, etc. to prevent order effects.

3.2.5 Data analysis.

This was identical to that used for experiment 1 (section 3.1.5). Three conditions (episodic memory retrieval, semantic memory retrieval and control task) and compared using t tests with the threshold set at $p<0.001$).

3.2.6 Task performance.

The average number of exemplars correctly recalled in the episodic retrieval task was 12.1 (s.d. 2), that is 80.8%. (This is virtually identical to post-scan retrieval following encoding in the presence of the easy distracting condition in experiment 1 above). During the semantic memory task, performance was 100% for all subjects.

3.2.7 Imaging results

3.2.7a Episodic memory retrieval

A comparison of the scans in which subjects performed the control task with those in which they carried out cued exemplar retrieval was associated with significant activations in left anterior cingulate cortex, right prefrontal cortex (PFC), thalamus (bilaterally) and medial parietal cortex bilaterally (in an area known as 'precuneus'). See table 3.3 and figure 3.4a.

3.2.7b Semantic memory retrieval

This comparison produced significant activations in left anterior cingulate cortex and the thalamus bilaterally. See table 3.3 and figure 3.4b.

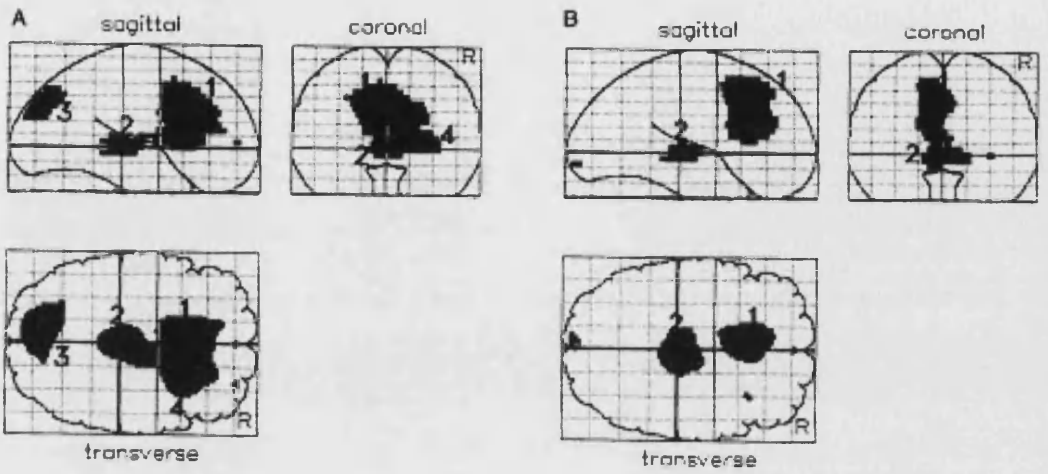

Figure 3.4 Main effects of memory retrieval tasks versus the control (repetition condition).
a Regions in which the episodic memory retrieval task produced significant activation compared to the repetition task.
b Regions in which the semantic memory task produced activation in comparison to this condition. Both contrasts produced activation of anterior cingulate cortex (1) and thalamus bilaterally (2). The episodic vs repetition condition produced, in addition, activation of medial parietal cortex (precuneus – 3) and right PFC (4).

Table 3.3 Regions activated in association with episodic and semantic memory retrieval

Region		Location (X,Y,Z)	Z Score
	Episodic Retrieval vs Control Task		
Left Anterior Cingulate Cortex		-2, 18, 36	9.4
Right Thalamus		2, -22, 0	7.5
Left Thalamus		-2, -22, 8	5.1
Right PFC		18, 28, 24	4.4
Left Precuneus		-6, -68, 36	6.1
Right Precuneus		12, -72, 28	4.0
	Semantic Retrieval vs Control Task		
Left Anterior Cingulate Cortex		-2, 20, 36	6.9
Right Thalamus		6, -20, 0	6.4
Left Thalamus		-8, -24, 12	4.1
	Episodic vs Semantic Retrieval		
Right PFC		30, 42, 24	4.0
		18, 30, 24	3.4
Left Precuneus		-6, -68, 36	6.1
Right Precuneus		12, -72, 28	5.6

3.2.7c Episodic versus semantic retrieval

This comparison revealed that two regions of right PFC (in dorsolateral and ventrolateral regions) showed significantly greater activation in episodic than semantic memory retrieval. In addition, precuneus, bilaterally, was associated with greater activity in episodic than semantic retrieval. See table 3.3 and figure 3.5.

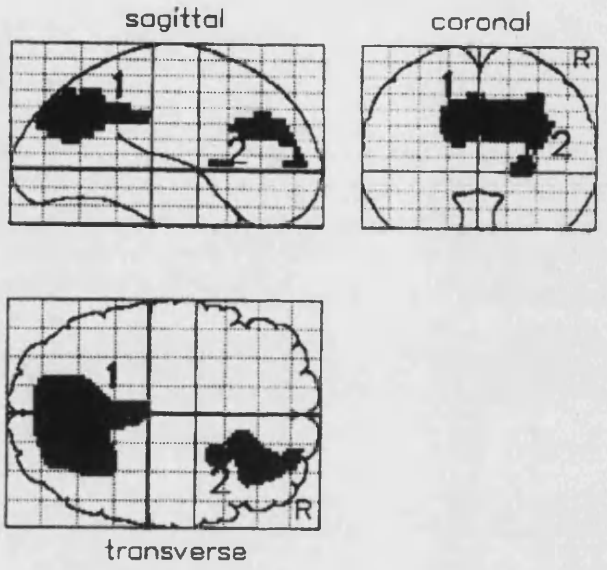

Figure 3.5 Comparison of episodic and semantic memory retrieval tasks
Episodic memory retrieval is associated with greater activation in precuneus (1) and right PFC (2). Two right frontal regions are seen a more dorsal and a more ventral one.

3.1.9 Summary of experiment 2 results

Common activations were seen for episodic and semantic retrieval, relative to a control repetition memory task, in thalamus bilaterally and left anterior cingulate cortex. In addition to these, the episodic memory task produced activation in right PFC and precuneus. A direct comparison between episodic and semantic memory retrieval tasks showed significantly greater activity in right PFC (ventrolateral/insula and dorsolateral) and in precuneus. Thus, the Episodic versus Semantic contrast produced a dorsolateral PFC activation that wasn't seen (at the threshold of $p<0.001$) in the Episodic versus Control comparison. At a lower threshold ($p<0.01$), this activation was seen in the latter comparison. It seems possible, therefore, that the control task may simply be a noisier condition with a resulting diminution in power for contrasts involving it. Since I believe the best contrast for isolating episodic retrieval-specific activations comes from

the comparison of this task with the semantic retrieval condition, I shall confine the discussion to findings from this contrast.

3.2 Discussion of experiments 1 and 2.

These preliminary experiments indicate that separable brain regions are involved in the encoding and retrieval stages of episodic memory. The experimental design aimed at isolating episodic memory processes as purely as possible; in the case of encoding, this was done through the use of a dual task method; at retrieval, it was done through inclusion of a semantic processing task as a control condition. Regions that were observed to be specifically sensitive to episodic memory encoding processes were left VLPFC and posterior cingulate cortex. Regions specifically sensitive to episodic memory retrieval were right PFC (dorsolateral and ventrolateral) and precuneus.

Taken together, the areas found to be active in experiments 1 and 2 comprise all those areas activated in a previous study in which Grasby and colleagues compared episodic encoding and retrieval (both occurring during the same scanning phase) to a working memory task (Grasby et al, 1993). This study showed bilateral prefrontal activation and the findings from the current pair of studies suggest that the involvement of the right and left frontal lobes may be dependent upon the memory stage. This observation will be taken up in the concluding discussion section (chapter 7). The experiments also identified activation of anterior cingulate cortex (in both encoding and retrieval), superior temporal gyri (encoding) and thalamus (retrieval) but these activations were not specific to the episodic memory component.

3.3.1 The use of the dual task design.

Dual task methodology has been used widely to explore the extent to which tasks rely upon separate or overlapping brain systems (Shallice et al, 1985). The present application was based upon specific findings that a secondary task will interfere with the encoding of episodic memory but not with other more automatic processes (Jacoby

et al, 1993). Experiment 1 shows that this effect may be reflected at a neurophysiological level in the attenuation of memory-induced activation in left VLPFC and posterior cingulate cortex.

A potential pitfall of the dual task approach, however, lies in the possibility that the secondary (motor) task could produce a degree of cerebral activation that was sufficient to mask any change due to the memory task. That is, if rCBF changes induced by the performance of the high distraction task were of such magnitude and generality that the additional influence of memory encoding would be nugatory. However, this is unlikely since a comparison (not reported) of the M-D+ with M-D- showed only small changes, none of which were in the areas identified by the planned comparisons. This suggests that the high distraction task, alone, does not have a huge effect on rCBF, thus making it unlikely that the M+D+ versus M-D+ comparison is subject to a ceiling effect. However, this suggestion would, ultimately, it must be admitted, only be provable through a separate experiment, in which the two distracting tasks were performed alone and compared directly,

Thus, the use of the dual task design has enabled a separation of episodic memory from priming processes and suggests that left VLPFC and posterior cingulate cortex activations are truly associated with episodic memory encoding processes.

3.3.2 PFC involvement in encoding and retrieval.

These findings are clearly in agreement with previous (and subsequent) functional neuroimaging studies highlighting the involvement of frontal lobes in memory. Moreover, they are in keeping with the neuropsychological data (see chapter 1) implicating frontal lobes in episodic memory function. The differential engagement

of right and left PFC in encoding and retrieval respectively would not be expected on the basis of neuropsychology however, although it is in keeping with other functional imaging studies (e.g. (Kapur et al, 1994; Tulving et al, 1994b) see chapter 7). This finding is notably compatible with the "HERA" (Hemispheric Encoding Retrieval Asymmetry) model of prefrontal involvement in memory (Tulving et al, 1994a). As discussed in chapter 1, some speculative attempts have been made, on the basis of neuropsychological data, to differentiate the roles of left and right frontal lobes. Incisa Della Rochetta and Milner suggested that left PFC is specifically involved in memory retrieval since subjects with left frontal damage perform normally on category cued word list recall but poorly when cues are not provided (even when an organisational strategy has been provided during the encoding stage (Incisa Della Rochetta and Milner, 1993). This finding is, at first glance, incompatible with the above findings and with the HERA model generally. However, the retrieval task used in experiment 2 differs from that used by Incisa Della Rochetta and Milner insofar as it involved recall in response to external cues such that a strategic search requiring left frontally-mediated generation of categories would be unnecessary. Moreover, it seems clear that the functional imaging approach is more suited than the neuropsychological approach to separating the encoding and retrieval stages, no matter how subtle and ingenious the latter may be.

The clear question that arises from the observation of patterns of prefrontal involvement in experiments 1 and 2 concerns the nature of the psychological processes that they reflect. With regard to left PFC, one important point is that, whatever these processes are, they are likely to be important to subsequent retrieval since the distracting task that is associated with an attenuation in left IFG activity, presumably through interfering with processes mediated by this region, also produces a decrement in

subsequent, post-scan retrieval. These processes are further explored in experiments 3 and 4 described in the chapter 4 together with two further studies attempting to address the specific contribution of left PFC to verbal episodic memory encoding (chapter 5).

With regard to the right PFC activation seen during episodic memory retrieval, it is suggested that its activation is not absolutely specific to retrieval (or, indeed, even to memory) but rather reflects the processes that tend to predominate at this stage. One possibility is that right PFC is necessary to the monitoring/verification processes suggested to be an important part of successful retrieval (Shallice, 1988; Burgess and Shallice, 1996a). Indirect evidence for this comes from the observation that perseveration, which may reflect a failure in such monitoring processes may predominate in right-sided frontal lesions (Stuss et al, 1994). A follow-up experiment addressing these suggestions is described in chapter 6.

Appendix

Category-exemplar pairs used in experiments 1 and 2.

Category	Exemplar
Animal	Goat
Prime minister	Asquith
Butterfly	Fritillary
Island	Mauritius
Aircraft	Wellington
Philosopher	Hume
Hat	Trilby
Bread	Cottage Loaf
Vegetable	Leek
Precious Stone	Sapphire
Car	Vauxhall
Elective Office	Councilor
Toy	Top
Fruit	Lime
Money	Cent

Note: Data from this chapter have been presented in the following publications

Shallice T, Fletcher PC, Frith CD, Grasby PM, Frackowiak RSJ, Dolan RJ.
Brain regions associated with acquisition and Retrieval of verbal episodic memory.
Nature 1994 368: 633-635

Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RSJ, Dolan RJ.
Brain systems for encoding and retrieval of auditory-verbal memory: An *in vivo* study in humans.
Brain 1995 118: 401-416

Chapter 4

A further exploration of PFC function in episodic memory encoding

Experiment 3: a PET study of PFC and organisational processes.

Experiment 4: an fMRI study of semantic relatedness in paired associate encoding.

General Introduction

The following pair of experiments, one carried out with PET the other with fMRI, are related to each other in their use of the semantic relatedness between encoded words as a means of manipulating the requirements of the encoding task. The first (experiment 3) was similar to the encoding experiment (experiment 1) reported in the last chapter in that it used a dual task design in order to isolate selected processes as purely as possible. The influence of a distracting motor task upon three encoding tasks was explored. The three tasks required subjects to organise encoded material, according to its semantic characteristics, at three different levels with the hypothesis that the previously observed left PFC activation, if it does indeed reflect organisational processes that optimise encoding would be sensitive to this manipulation.

In experiment 4, a simple manipulation was used to explore the effects of semantic processing upon episodic memory encoding. An 'event-related' fMRI design was used in which the two types of event differed in terms of the semantic relatedness linking members of encoded word pairs. The purpose of this study was to attempt to ensure that frontal activations related to the semantic processing could be interpreted in isolation from any of the confounding factors produced by the standard PET 'blocked' design.

4.1 Experiment 3

Exploring the role of left prefrontal cortex in episodic memory encoding.

4.1.1 Introduction.

In functional neuroimaging studies (see chapters 3 and 7), an unpredicted, but highly consistent, lateralisation of frontal lobe function has been observed in encoding and retrieval studies. Left PFC shows predominant activation in association with learning or encoding tasks and the right PFC in association with recall tasks (Kapur et al, 1994; Tulving et al, 1994b; Fletcher et al, 1995). The functional significance of the left PFC activation at encoding is unclear although it appears that it is not necessarily associated with the intention to encode information, since an incidental encoding task, which produces high levels of subsequent retrieval (Kapur et al, 1994), is associated with activation in left PFC. Furthermore, a critical link to encoding processes may be indicated by the observation that, when encoding is performed with a concurrent distracting task, there is an impairment in subsequent recall and an attenuation of activation in left PFC (see chapter 3).

It has been suggested that activation of left PFC in association with encoding may reflect the fact that the encoding is not independent of subjects' knowledge or semantic memory (Tulving, 1983). Thus, to learn a word within the context of an encoding experiment necessarily entails knowledge of that word's meaning. The use of such knowledge has been suggested to underlie the left PFC activation seen in functional neuroimaging studies of memory encoding (Tulving et al, 1994a). This suggestion is consistent with the observation that tasks requiring subjects to make judgements about word meanings are associated with higher degrees of subsequent recall of those words than tasks emphasising non-semantic aspects of the words (e.g.

phonological or orthographic features) (Craik and Lockhart, 1972). This observation has been highly influential and the close association between such tasks and optimal learning is reflected in the fact that tasks emphasising meaning continue to be referred to as "deep" encoding tasks.

A relevant observation, in this context, is that there are major advantages in subsequent recall when subjects are required to organise study material (Segal and Mandler, 1967). Neuropsychological studies indicate that an important aspect of the prefrontal contribution to memory function is in the organisation of material (Incisa Della Rochetta and Milner, 1993; Gershberg and Shimamura, 1995). The use of functional neuroimaging in this experiment enabled a more specific exploration of such process in the setting of memory encoding.

The term "organising" when applied to neuropsychological tasks, generally refers to the grouping of items on the basis of shared semantic attributes (Gershberg and Shimamura, 1995). Thus, a task that requires organisation of material will overlap considerably with a "deep" encoding task insofar as it will emphasise meaning. However, organising has the additional requirement of manipulating material on the basis of its similarities to, or differences from, other material in the same study block. The hypothesis driving this experiment was that the previously seen activation of left PFC in encoding tasks reflects, at least in part, a tendency or necessity to organise study material on the basis of semantic attributes. Subjects were required to learn 16 item word lists with the prediction that, in conditions where they were required to generate an organisational structure to facilitate encoding, a greater degree of left PFC activity would be observed than in conditions where material was already organised. Three levels of organisational requirement were used and this aspect of the design enabled a

determination of whether left PFC activation reflected the semantic abstraction process or more general demands of mentally manipulating the study material (which would involve, for example, the active maintenance of the list structure in working memory).

A further consideration is the possibility that activations are not directly associated with the experimental manipulation but reflect some associated, but incidental, features of the tasks. This was addressed using a dual task paradigm in which subjects were required to carry out a concurrent distracting procedure. Such a requirement can interfere specifically with the ability to encode material (Baddeley et al, 1984; Jacoby et al, 1993; Craik et al, 1996). As discussed in association with experiment 1, if left PFC is associated with the organisation of material at encoding, then a simultaneously performed distracting task, as well as producing subsequent impairments in retrieval, would reduce the level of left PFC activity. Furthermore, distraction-induced reductions in activation specific to some encoding conditions but not to others, indicates process specificity for encoding-related PFC activations.

4.1.2 Material and methods

7 healthy, male, right-handed subjects (mean age 27 years, age range 20-48) were scanned. Each subject underwent 12 separate scans. No subject had a history of past psychiatric or neurological illness and all gave informed consent. The studies were approved by the local hospital ethics committee and Administration of Radiation Safety Advisory Committee (UK). Subjects gave informed written consent and the study was approved by the joint research ethics committee of University College, London.

4.1.3 PET Scanning.

Scans of the distribution of $H_2{}^{15}O$ were obtained using a Siemens/CPS ECAT EXACT HR+ (model 962) PET scanner operated in high sensitivity 3-D mode. Subjects received a total of 350Mbq of $H_2{}^{15}O$ over 20 seconds through a forearm cannula. Data were acquired over 90 seconds for each scan. Attenuation-corrected data were reconstructed into 63 image planes with a resulting resolution of 6mm at full-width-half-maximum.

4.1.4 Tasks.

Study material comprised three types of word list (all lists consisting of 16 words). The features of the three encoding tasks, together with a sample list from each, are summarised in the appendix. Lists were presented auditorily and varied according to the degree of organisation that subjects were required to perform in order to facilitate encoding.

4.1.4a Organise 1.

This was the least demanding condition with respect to the organisational requirements. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading and 4 sub-headings, with 4 items belonging under each sub-heading. They were told what the heading and sub-headings would be. They were further informed that presentation would be blocked (that is, that words coming under each subheading would be presented successively). Subjects were instructed to try to learn all items and informed that bearing in mind this list structure would be helpful. 5 minutes after the scan, free recall was tested.

4.1.4b Organise 2.

This was more demanding than Organise 1 with respect to organisational processes. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading and 4 sub-headings, with 4 items belonging to each sub-heading. They were told what the heading and sub-headings would be. They were further informed that presentation would be unblocked (that is, that words would be presented in a random order with respect to the sub-headings). Subjects were instructed to try to learn all items and informed that bearing in mind this list structure would be helpful. 5 minutes after the scan, free recall was tested.

4.1.4c Organise 3

This was the most demanding condition with respect to organisational processes. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading and 4 sub-headings, with 4 items belonging to each sub-heading. They were told what the overall heading would be but that they would be required to work out what the sub-headings were. They were further informed that presentation would be unblocked. Subjects were instructed to try to learn all items and informed that being able to work out the list structure (that is, the 4 sub-headings) would be helpful to their subsequent recall. 5 minutes after the scan, free recall was tested. (See summary, Appendix 4.1).

4.1.4d Distraction Task.

As in the previous study (experiment 1, chapter 3), a dual task approach was used, involving both a high distraction and a low distraction condition. The former specifically affects episodic encoding by interfering with active organisation processes.

Subjects were required to watch a screen, suspended on a cradle approximately 45cm away. On the screen was a photograph of a left hand. Sequentially, one of the four fingers was highlighted (rate once per second) and subjects were required to press the corresponding button on a keypad placed under their left hand. In the more distracting version, stimuli (and therefore button presses) followed an unpredictable order. In the less distracting task, there was a predictable sequence, moving from one finger to the next.

4.1.5 Summary of task design and data analysis.

Thus, this experiment constituted a 3 X 2 factorial design, with the first factor (organisation of encoding material) having 3 levels (Organise 1, Organise 2 and Organise 3) and the second factor (motor distracting task) having 2 levels (high distraction and low distraction). Consequently, there were 6 conditions with, for every subject, 2 scans per condition. The effects of the organisational requirements upon brain activity were explored both in the setting of the low and high distraction tasks. The prediction was that the most demanding organisational task (Organise3) would be most vulnerable to the effects of distraction and that this behavioural interaction would be mirrored at the neurophysiological level. Left PFC was predicted to be the site of this interaction.

Data analysis was the same as that used in experiment 1 (see 3.1.5).

4.1.6 Task performance

Recall performance was tested in each subject after every scan and is given in table 1. With the less distracting motor task, performance was comparable across all word lists. Non-parametric testing showed that the effect of distraction differed

significantly across conditions (Friedman two-way analysis of variance by ranks: Xr^2 (DF = 6) = 39.7; $p<0.001$). In the presence of the more distracting task performance in the Organise 3 condition was impaired (Wilcoxon; $t=0$; $p<0.02$).

In Organise 3, where category sub-headings were unknown prior to list presentation, subjects were, in almost every case, able to report the appropriate list structure when debriefed after each scan. A measure of the extent to which subjects used the organisational structure to aid retrieval was provided by counting the number of times they shifted category unnecessarily during free recall. Since there were 4 categories, at least 3 shifts were necessary to cover them all. Table 1 shows the number of unforced category shifts following each of the encoding conditions. It can be seen that there were more unforced shifts following Organise 3, in the presence of the more distracting task than with the distracting task or in either of the other encoding conditions.

	Organise 1	Organise 2	Organise 3
Performance at retrieval (s.d.)			
High distraction at encoding	12.6 (2.9)	11.8 (2.4)	10.3 (2.8)
Low distraction at encoding	12.7 (2.1)	12.1 (2.1)	12.2 (2.1)
Number of unforced category changes at retrieval (s.d.)			
High distraction at encoding	0.5 (0.7)	0.8 (0.9)	2.1 (1.1)
Low distraction at encoding	0.4 (0.4)	0.9 (0.9)	0.9 (0.5)

Table 4.1 Performance measures

Post-scan recall performance (maximum = 16) and post-scan deviation from organisational structure for the three types of encoding task under conditions of high and low distraction.

4.1.7 Imaging results.

4.1.7a Organisational requirements

Initially, regions specifically responsive to the need to organise study material were examined i.e. activations occurring to a significantly greater extent in Organise3 when compared, in separate contrasts, with the Organise 2 and Organise 1 conditions. The only region surviving the pre-set threshold ($p<0.001$) was in left PFC (located roughly in middle frontal gyrus on the upper bank of the inferior frontal sulcus). The focus of activation, was mapped onto a series of structural magnetic resonance images from eight separate subjects (images which had been stereotactically normalised into the same space). In every case, it lay just above the inferior frontal sulcus and may, thus, be

termed dorsolateral. For this reason I shall refer to this region as DLPFC but its proximity to the inferior frontal sulcus (i.e. the border between DLPFC and VLPFC) should be borne in mind. This contrast is shown in table 4.2 and figure 4.1a.

4.1.7b Organisation-distraction interaction.

In this analysis the search volume was confined to voxels that were significantly more active in the condition making the greatest organisational demands on the subjects. This analysis thus addressed the question of whether regions activated in association with organisational requirements would show a relative attenuation of activation in the presence of the more distracting task (which impairs such organisational processing). A distraction-associated attenuation was observed in an overlapping left PFC region. Crucially, with regard to memory performance, the distracting task had no effect on Organise 1 or Organise 2 but produced a significant impairment in Organise 3. (See table 4.2 and figure 4.1b). The parallel profiles of the neurophysiological reduction and the impaired behavioural performance allow the inference that, in Organise3, a critical function, whose instantiation involves the left DLPFC, relates to organising study material

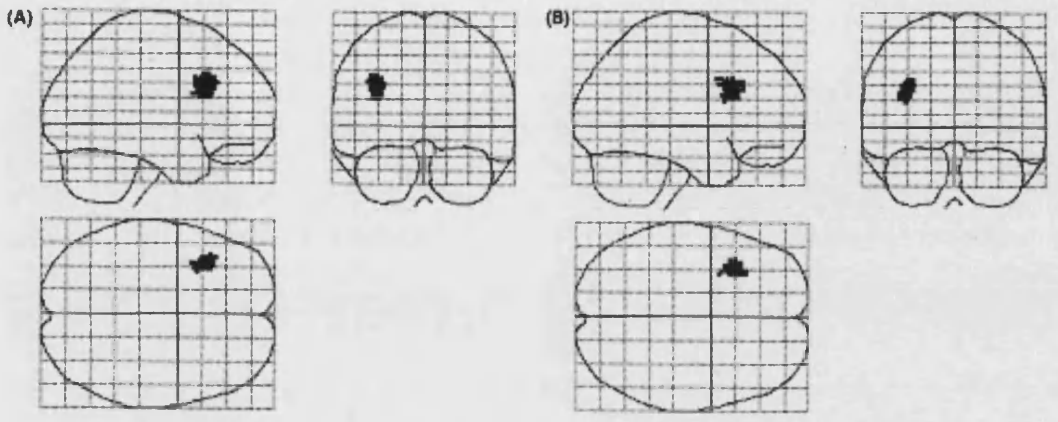

Figure 4.1 Organisation at encoding and distraction-by-organisation interaction ($p<0.001$).

SPMs are presented as orthogonal 'glass brains' showing activations associated with (a) increasing demands for organisation and (b) the interaction between organisational demands and the motor distracting tasks. In both cases, it can be seen that left PFC is the region sensitive to the comparisons.

	Memory in the presence of the less distracting task		Attenuating effect of distraction	
Comparison	Localisation (X,Y,Z)	Z score	Localisation (X,Y,Z)	Z score
Organise 3 vs Organise 2	-36, 22, 30	2.3	-36, 24, 28	2.1
Organise 2 vs Organise 1	-34, 14, 22	3.2	----	----

Table 4.2 Regions sensitive to Organisational requirements and to interaction between organisation and distraction.

In order to illustrate this pattern of results graphically, I have plotted the estimated rCBF from a left PFC voxel (located at X, Y, Z = -36, 24, 28) showing the pattern of activity increasing across the three levels of organisational demand in the presence of the more and less distracting motor tasks. This is shown in figure 4.2.

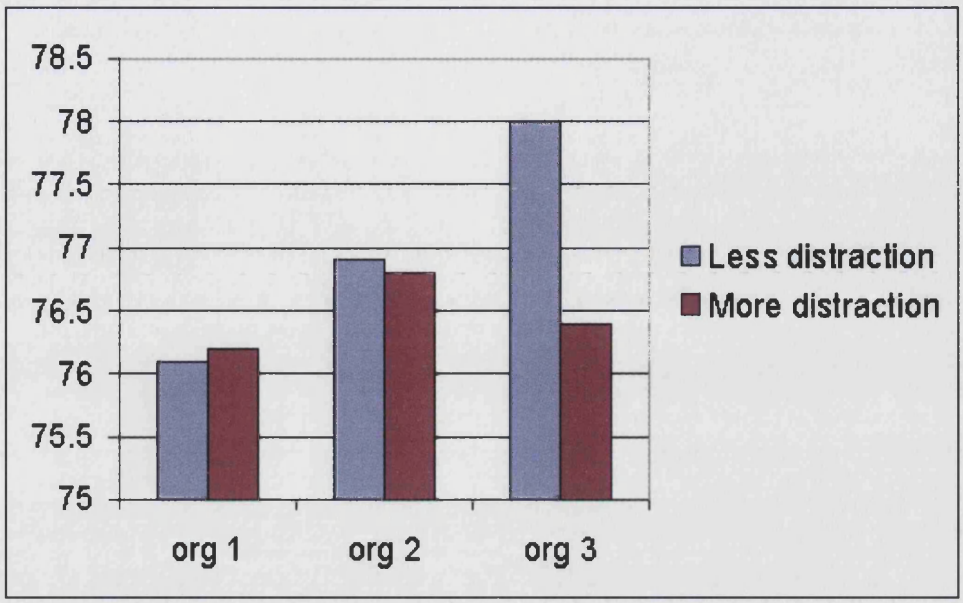

Figure 4.2 Plot of the average (across subjects) estimated rCBF (ml/dl/min) from a left PFC voxel

In this voxel (located at X, Y, Z = -36, 24, 28), activity increases from the least demanding (Org 1) to the most demanding (Org 3) organisation condition. In the presence of the high distraction motor task, this task-related increase is attenuated.

4.1.8 Discussion of experiment 3.

The findings support the hypothesis that a left PFC activation observed during memory encoding tasks reflects processes involved in deriving commonalities in meaning among the words presented in order to create an organisational structure. The type of abstraction necessary in the critical condition in this study has been shown to enhance encoding (Segal and Mandler, 1967; Craik and Lockhart, 1972). Such abstraction processes are known to be impaired in association with prefrontal lesions (Benton, 1968; Bornstein and Leason, 1985). The interpretation that left PFC activation is important for creation of an organisational structure gains support from a key finding in experiment 3: activation in this condition (only) was attenuated by distraction. It is

noteworthy that the more distracting task, as well as leading to an attenuation in left prefrontal activation, was associated a large increase in the number of unforced category shifts during retrieval subsequent to the Organise 3 condition. These post-scan behavioural effects perhaps indicate a linkage between this activity and the organisational sub-processes engaged by the task.

A key aspect of the abstraction/organisational processes engaged in this study lies in the requirement to assess study material with respect to its semantic properties. This demand was maximised in the Organise 3 condition where subjects were required to use the presented material to create the structure de novo. Thus, in this condition, subjects were required to consider a broader range of semantic attributes of presented words than in the two conditions where the organisational structure had been provided by the experimenter. In this respect, it is noteworthy that studies emphasising semantic processing of material, in the absence of any specific memory encoding component, have been associated with left PFC activation (Kapur et al, 1994). The functional imaging evidence strongly suggests that left PFC activation is consistent in studies that emphasise the requirement for processing study material according to its meaning. I will return to this observation in chapter 7.

Why should the more distracting task selectively affect the Organise 3 condition? It has been shown that a variety of tasks, thought to be subserved by intact PFC function, are impaired in the presence of a demanding sensorimotor task that, in itself, does not engage PFC function (Moscovitch, 1994). Moscovitch argued that carrying out such a sensorimotor task produces the analogue of a frontal lobe syndrome in the normal subject. The results obtained in experiment 3 are in accord with this. In association with the less distracting condition, Organise 3 is associated with greater left

PFC activation than Organise 1 and Organise 2. Organise 3 is the condition, too, where distraction significantly impairs performance both quantitatively (in terms of the number of items subsequently recalled) and qualitatively (in terms of the degree of organisation at recall). This impaired post-scan performance appears to be predicted, during the scan, by an attenuation of left PFC activation.

What processes are involved in the interference effect? Since carrying out the more distracting task is associated with this attenuation in left PFC activation (in association with Organise 3) it seems implausible that interference occurs because the high distraction task requires the same resources as the primary task. Perhaps, rather, the constraint on processing lies in the use of attentional resources. It may be that the supervisory and working memory functions of PFC cannot be adequately utilised unless the subject is able to attend to the memory task. The high distraction task prevents this attention.

Of course, all of the memory tasks used in this study make demands upon the working memory processes required for active maintenance of list structure in order, where necessary, to carry out manipulations of presented material. However, an explanation of these results purely in terms of maintenance processes is difficult to sustain. The study design enabled a dissociation of the activation associated with the semantic abstraction necessary to the generation and use of an organisational structure from those activations associated with the maintenance, in working memory, of such a structure. The latter is likely to be prominent in both the Organise 3 and the Organise 2 conditions, perhaps even more so in Organise 2 where the list structure was known at the outset and would therefore be maintained in full throughout the scanning period. Thus, from the logic of the subtractive methodology, since left PFC activity was higher

in Organise 3 than Organise 2 one might infer that the activity in this region does not, in any simple sense, reflect maintenance purely. Moreover, it is unlikely that this activation can be attributed to a non-specific increased difficulty or effort since the condition which subjects found most effortful (Organise 3 in the presence of the more distracting task) was associated with the attenuation of left PFC activation.

It is interesting that there were no effects of distraction in the Organise 2 condition. One explanation for this is that the apparent specificity of distraction fits with a distinction between the processing and storage aspects of working memory under dual task conditions (Craik et al, 1990). Thus Organise 3 emphasises processing demands and was significantly affected by distraction but Organise 2, which has equivalent (or even, possibly, greater) storage demands, does not. Therefore the lack of a distracting effect on Organise 2 compared to Organise 1 perhaps reflects that a more prominent difference between these two conditions lies in storage rather than processing demands.

In summary, experiment 3 has provided evidence that the encoding-associated left PFC activation forms part of the brain system mediating the formation of an organisational structure and, more specifically, with the abstraction of the relevant semantic attributes of study material. This abstraction enables an assessment of the commonalities and differences allowing the segregation or grouping of material in order to optimise encoding. The region found to be sensitive to the experimental manipulations lies more dorsally than that seen in the encoding tasks in experiment 1. This is perhaps an indication of a ventral-dorsal distinction, a theme that I shall discuss more fully in the concluding chapter.

4.2 Experiment 4

fMRI study of the influence of semantic relatedness in paired associate encoding.

4.2.1 Introduction.

In this fMRI experiment, an alternative approach to verbal memory encoding was used, exploiting the possibilities afforded by event-related or trial-specific fMRI design (Buckner, 1998; Buckner et al, 1998a; Friston et al, 1998). These enable an exploration of the brain responses to single items (verbal paired associates). This is not possible with PET, which must use a blocked design due to the slow acquisition of scanning data. The event-related experimental design has many advantages over blocked designs (Josephs and Henson, 1999). Most notable of these, with regard to the current study, is the opportunity to randomise the order in which different experimental stimuli or tasks are presented. This enables a disambiguation of activity produced by the processes of interest from those that may arise (in a blocked design) due to the repetition and predictability of the experiment. Such effects could be seen both as a decrease in activation (e.g. due to habituation) or as an activation that is not directly related to the processes under study (e.g. if the subject, on the basis of knowing precisely what sort of trial is about to occur, is able to adopt an optimising strategy). With randomised order of trials, these effects may be removed and activations interpreted with greater confidence.

A further advantage of the event-related design in encoding studies lies in the selective averaging of trials on the basis of post hoc measures. This has been used to great effect in studies of activations that reflect a difference predicting subsequent memory performance [(Wagner et al, 1998c; Kirchhoff et al, 2000; Otten et al, 2001). It

was used slightly differently in the current study. Specifically, in exploring the effects of semantic processing within the context of episodic memory encoding, it is possible that differences due to the semantic manipulation (in this case 'close' versus 'distant' semantic relations between word-pair members) will produce different subsequent memory performance and may thus differ too in terms of the strength of encoding. The current experimental design and analysis included an attempt to mitigate this through dropping from the analysis all trials in which encoding proved to be unsuccessful as measured by subsequent cued retrieval.

4.2.2 Materials and Methods.

MRI scanning was carried out on 6 volunteer subjects (age range 24 – 32 years; mean age 27 years). All subjects were fit and healthy with no history of neurological or psychiatric illness or of drug/alcohol abuse. All subjects gave informed consent and the study was approved by the local hospital ethics committee.

4.2.3 fMRI Scanning.

A Siemens VISION system (Siemens, Erlangen) operating at 2 Tesla was used to acquire both T1 anatomical and gradient-echo echo-planar T2* weighted image volumes with blood oxygenation level dependent (BOLD) contrast. For all subjects, data were acquired in one scanning session lasting approximately 20 minutes. Aside from 6 'dummy' volumes, which were subsequently discarded to remove T1 equilibration effects, a total of 196 functional volumes per subject were acquired. A TE of 40 ms was used. Volumes were acquired continuously every 4800 ms. Each volume comprised forty-eight 3mm axial slices with in-plane resolution 3x3mm positioned to cover the whole brain.

4.2.4 Tasks.

During scanning, subjects were presented visually with word pairs, at a rate of one pair per 12 seconds, projected onto a screen comfortably within subjects' field of view. Pair members were presented successively each word remaining on the screen for 1 second. Thus, there was an inter-stimulus interval of 10 seconds. When the second word in a pair had been presented, it was replaced with a fixation cross. Subjects were instructed to read each pair and to consider the concept or word that linked its two members. They were warned that, following scanning, cued retrieval would be tested. Sixty pairs were presented during each scanning session. 30 were designated as closely

related (e.g. king...queen) and 30 were designated distantly linked (e.g. prince...skull). Order of presentation of close and distant pairs was randomized across subjects. Pairs were generated according to simple criteria. They were designated as closely related when members of a pair showed an immediate and obvious link, such as belonging clearly to the same category. When the shared semantic attributes were accessible only through the use of indirect semantic mediation, they were designated as distantly related. Thus, an informal, but clear, categorisation of pairs was used. Words used in the study did not differ systematically in concreteness, frequency or familiarity. Unfortunately, it is unavoidable that some pairs that had been deemed distantly related would be found, by subjects, to be closely related (or vice versa). However, this would likely generate type II error in the imaging data. I believe that this does not, therefore, affect the reliability of the reported activations.

4.2.5 Summary of task design and data analysis.

Data were analyzed using Statistical Parametric Mapping (Friston et al, 1995a; Friston et al, 1995b). All volumes were realigned to the first volume and resliced using a sinc interpolation in space. Each volume was normalised to a standard EPI template volume (based on the MNI reference brain, (Cocosco et al, 1997)) of 3x3x3mm voxels in a standard space (Talairach and Tournoux, 1988) using nonlinear basis functions. The T1 structural volume was coregistered with the mean realigned EPI volume and normalised with the same deformation parameters. Finally, the EPI volumes were smoothed with a 8mm FWHM isotropic Gaussian kernel to accommodate further anatomical differences across participants, and proportionally scaled to a global mean of 100.

Stimuli were classified into three event-types: pairs with a close semantic relationship, those with a distant semantic relationship and finally those that were not associated, subsequently with successful cued retrieval. The latter items were modeled in the treatment of the fMRI data but were not further analysed.

Treating the acquired volumes as a time series, the haemodynamic responses (to the onset or presentation of the second word in the pair) for each event-type were modeled with a canonical, synthetic haemodynamic response function and its first-order derivative with respect to time (Josephs et al, 1997). The inclusion of the derivative caters for small deviations in the onset of the haemodynamic response (Friston et al, 1998). These functions were used as covariates in a general linear model, together with a constant term and a basis set of cosine functions with a cut-off period of 90 seconds to remove low frequency drifts in the BOLD signal (Friston et al, 1998). The parameter estimates for the height of the canonical response for each event-type covariate results from the least mean squares fit of the model to the data were obtained. Pair-wise contrasts between the height parameter-estimate for event-types were tested by voxel-specific, repeated measures t-tests across participants. These were subsequently transformed to the unit normal Z-distribution to create a statistical parametric map (SPM) for each contrast. Given that differential activity in left PFC was predicted on the basis of previous studies of paired associate encoding and was the subject of our a priori hypothesis, an uncorrected threshold, as for experiment 1, was set ($p<0.05$). In fact, the left PFC effect reported below survived correction for multiple comparisons.

Having carried out the group analysis event-related responses were plotted for all 6 individual subjects in order to ascertain that any reported findings were common to all subjects and not produced by an especially strong response in only a sub-group. The

purpose of this analysis was to provide a qualitative approximation to the "random-effects" analysis that was unavailable at the time these data were analysed and would be inapplicable with only seven subjects.

4.2.6 Task performance

The mean performance for subsequent cued retrieval of closely linked pairs was 28/30 (range 24 – 30, s.d. = 2.0). The mean performance for subsequent cued retrieval of distantly linked pairs was 27.4/30 (range 25 – 30, s.d.=1.4). These performance measures did not differ significantly. Subjects were debriefed with respect to their ability to generate semantic mediators in order to link pair members. In virtually all cases, subjects were able to recall a concept or word that they had generated in order to do so. There was no evidence that their success at doing so differed across the two conditions but all reported that the Distantly related pairs required a less clear and obvious mediation in order to produce a link.

4.2.7 Imaging results.

In a number of regions, distantly linked pairs were associated with significantly greater activity than Closely linked pairs (see Table 4.3 and figure 4.3).

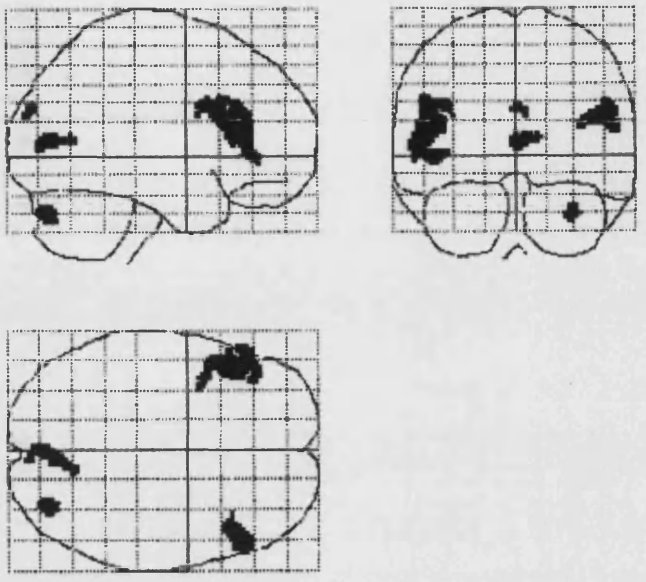

Figure 4.3 Effective of semantic distance at encoding.

Statistical parametric map (SPM) of regions showing a significantly greater BOLD response ($P < 0.001$) for Distantly linked than for Closely linked pairs in experiment 4.

Region	Location (X, Y, Z)	Z Score
Left Inferior Frontal Gyrus	-44, 26, 18	5.0
	-50, 32, 16	3.2
	-40, 8, 28	4.7
Left Inferior Frontal Gyrus	54, 30, 22	4.8
Right Cerebellum	32, -78, -32	4.3
Right Occipital Cortex	6, -72, 8	3.9

Table 4.3 Regions showing differential responses for Distantly-, compared to Closely-related, word pairs.

The only region to survive correction for multiple comparisons was left VLPFC. The left prefrontal region is shown in more detail in figure 4.4 and the individual BOLD responses for each event type for each of the 6 subjects are shown in figure 4.5. It can be seen that, across all of the subjects, the BOLD response was greater for the Distantly than the Closely linked pairs. This consistency is reassuring with respect to he generalisability of this finding (see discussion in chapter 2: 2.5.3b). A region of right PFC also showed a difference between the two event types (see table 4.3 and figures 4.3 and 4.5) but the plots for individual subjects showed that this effect was only present in

3 of the 6. In view of this, and the fact that the activation did not survive the correction for multiple comparisons, this area will not be discussed further.

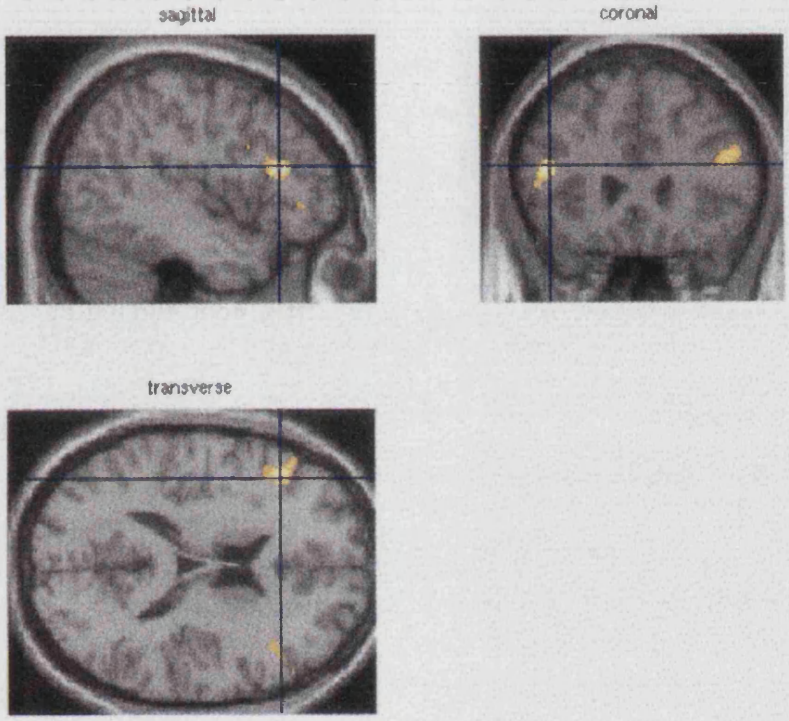

Figure 4.4 Location of left VLPFC activation.

This figure shows orthogonal sections of a T1-weighted anatomical image that conforms to a standard stereotactic space. Superimposed on these sections is the SPM ($P < 0.001$) shown in Fig. 3, indicating regions showing a significantly greater BOLD response for Distantly linked than for Closely linked pairs. Sections have been chosen at the voxel of maximal difference (coordinates x, y, z= -44, 26, 18) to show the left PFC region.

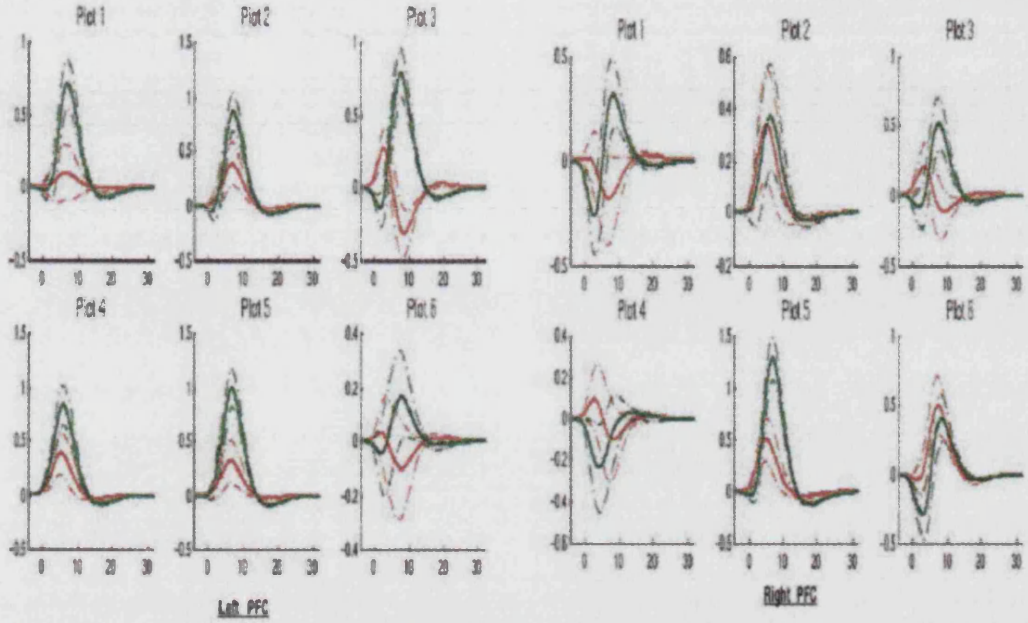

Figure 4.5 **Plots of the individual BOLD responses from left and right PFC** (chosen from voxel of maximal difference [-44, 26, 18 and 54, 20, 32]) for each of the six subjects. The average within-subject BOLD response for a distantly linked pair is shown in green with the standard error (broken green line). The average within-subject BOLD response for a closely linked pair is shown in red with the standard error (broken red line). It can be seen that the left PFC response is consistently greater for the former across all six subjects. The right PFC difference, although it survives a statistical threshold of $P < 0.001$, is found in only half of the subjects.

The reverse comparison (that is, Closely linked pairs versus Distantly linked pairs) showed no regions surviving correction for multiple comparisons.

4.2.8 Discussion of experiment 4.

This experiment showed an activation of left VLPFC (in left inferior frontal gyrus) in association with more demanding semantic processing during episodic memory encoding. This finding is consistent with previous functional imaging studies relating left inferior frontal activation to semantic processing (Petersen et al, 1988; Petersen and Fiez, 1993; Kapur et al, 1994; Demb et al, 1995) and with experiment 1 presented in chapter 3 which showed that left frontal cortex appears sensitive to the requirement to form meaningful associations between verbal stimuli within the setting of explicit encoding instructions. While the result in itself is largely a replication, one may now be more confident, on the basis of the current observation that the left PFC activation, seen in verbal semantic processing tasks and in verbal episodic memory tasks, is not directly related to the confound produced by systematic blocking of tasks.

In considering the functional significance of the observed pattern of results in left PFC, I initially distinguish between intentional and incidental encoding tasks. The former are preceded by instructions that there will be a later memory test whereas, in the latter, the memory test phase is administered without prior expectation. The observation of left PFC experiment 4 was made in the context of an intentional encoding task but it is likely that similar PFC activity would be evident in incidental tasks where subjects attend to semantic attributes but are not given explicit encoding instructions. For example, in a PET study of incidental encoding, attending to the meaning of items was associated with higher left PFC activity than attending to orthographic features (Kapur et al, 1994).

4.3 General Discussion

These two studies together present a further exploration of the left prefrontal involvement in semantic aspects of episodic memory encoding. The PET study (experiment 3) is primarily concerned with organisation of material based upon semantic characteristics. The fMRI study (experiment 4) presents an attempt to establish that the encoding-related activation in PFC may be interpreted in isolation from the potential confounds that accompany a 'blocked' experimental design.

With regard to the precise localisation of the left PFC activation and the possible semantic processes mediated here, more detailed discussion will be set out in the concluding section (see chapter 7). First, it should be pointed out that the location of maximal activation differed between experiments 3 and 4. In the former, the effects of increasing organisational demand were associated with a more dorsolateral response (although, as stated, the close proximity to the inferior frontal gyrus suggests that caution should be exercised in using the dorsolateral-ventrolateral dichotomy). In fact, the finding from experiment 4 is more typical insofar as it shows an encoding-related activation in inferior frontal gyrus (ventrolateral PFC). In addition to the findings in experiment 1, there has been a strong degree of consistency of localisation of prefrontal activation across a number of tasks engaging intentional and incidental memory encoding (Kapur et al, 1994; Kapur et al, 1995; Kopelman et al, 1998). Common to these tasks has been an emphasis on the semantic attributes of material and the finding of left VLPFC activation is compatible with other functional neuroimaging tasks engaging semantic processing both explicitly (Petersen et al, 1988; Raichle et al, 1994; Demb et al, 1995; Ricci et al, 1999) and implicitly (Petersen et al, 1990). Further, it has been shown that this region of left PFC is increasingly responsive to presentation of consonant strings as they acquire "meaning" within the context of an artificial grammar

system (Fletcher et al, 1999). The region also appears to be sensitive to semantic processing irrespective of whether material is verbal or pictorial (Vandenberghe et al, 1996). However, experiment 3 shows that, when the demands go beyond processing of meaning and extend to the requirement for higher order organisation of studied material, it is a more dorsal region of lateral PFC that is active. This possible dissociation between dorsal and ventral regions of PFC will be discussed more fully in the concluding chapter.

Another point to consider is the observation that it is left, rather than right, PFC that is sensitive to these verbal encoding tasks. One must be cautious in interpreting the lateralisation of function observed in these experiments. While it is certainly an intriguing observation that, across a series of functional neuroimaging studies of verbal episodic memory, left sided frontal activation has tended to predominate at encoding and right-sided activation at retrieval (Tulving et al, 1994a), more recent evidence has suggested that it relates to modality of studied material rather than memory stage [(Kelley et al, 1998; Wagner et al, 1998b). Experiments 1, 2, 3 and 4 used solely verbal material and the lateralisation of the finding may reflect this. Moreover, with respect to experiment 4, as figures 3 and 4 show, there was a sub-threshold (but, across subjects, inconsistent) activation in right VLPFC. It is, unjustified, therefore, to consider this as a truly lateralised activation. The apparent lateralisation of frontal activations in association with memory encoding and retrieval tasks will be considered in the concluding chapter.

Appendix to experiment 3

The Organise 1 condition

Pre-scan instructions:

You will be read a list of 16 words at a rate of 1 word per three seconds. Listen to these words and try to remember them. The list will cover 4 categories, each represented by 4 exemplars. The over all list heading is Animals and the 4 sub-headings are Birds, Mammals, Invertebrates and Fish. The exemplars will be kept together in the groups to which they belong.

Kestrel

Osprey

Chaffinch

Quail

Pig

Gerbil

Gorilla

Hedgehog

Snail

Octopus

Worm

Jellyfish

Pike

Trout

Carp

Salmon

The Organise 2 condition

Pre-scan instructions:

You will be read a list of 16 words at a rate of 1 word per three seconds. Listen to these words and try to remember them. The list will cover 4 categories, each represented by 4 exemplars. The over all list heading is Drinks and the 4 sub-headings are Wines, Juices, Beers and Hot Drinks. The exemplars will be read out in a random order and you should try to allocate each successive exemplar into the appropriate category.

Hock

Carrot

Stout

Espresso

Bovril

Ale

Grapefruit

Burgundy

Mango

Chianti

Mild

Darjeeling

Apple

Cocoa

Sauterne

Lager

The Organise 3 condition

Pre-scan instructions:

You will be read a list of 16 words at a rate of 1 word per three seconds. Listen to these words and try to remember them. The list will cover 4 categories, each represented by 4 exemplars. The over all list heading is Foods. The exemplars will be read out in a random order. As you listen to the words, try to work out what the four categories might be and to allocate each successive exemplar into the appropriate one.

Grape

Sausage

Herring

Turbot

Croissant

Mango

Kipper

Ham

Raspberry

Venison

Bream

Nan

Pitta

Veal

Banana

Rye

Note: Data from this chapter have been presented in the following publications
Fletcher PC, Shallice T, Dolan RJ. The functional roles of prefrontal cortex in episodic memory. I Encoding. *Brain* 1998 121: 1239-1248
Fletcher PC, Shallice T, Dolan RJ Sculpting the Response Space"- An account of left prefrontal activation at encoding" NeuroImage 2000 12(4): 404-417

Chapter 5

Explorations of the effects of semantic interference in episodic memory encoding.

Experiment 5a – PET

Experiment 5b - fMRI

General Introduction

The role of medial temporal structures, including the hippocampal and parahippocampal formation, in episodic memory is well established with homologous left- and right-sided structures mediating verbal and visual aspects of memory respectively (Scoville and Milner, 1957; Squire and Cohen, 1984). By contrast functional neuroimaging data, consistent with the data that have been presented in preceding chapters, have emphasised the role of the prefrontal cortex in human memory (Fletcher et al, 1997; Fletcher and Henson, 2001). In discussing the motivation for the pair of experiments described in this chapter, it is worth briefly reconsidering the characteristics of the frontal response to episodic encoding/semantic retrieval that have emerged over the last few years.

First, left PFC activation is independent of the intention to memorise material (Kapur et al, 1994). Second, left PFC is linked to efficient encoding since a simultaneous distracting task (which interferes with encoding) is associated with attenuation of activation (see chapter 3 – experiment 1). More recently, event-related fMRI has shown evidence for a link between left PFC and encoding success (Wagner et al, 1998c; Kirchhoff et al, 2000; Otten et al, 2001). Third, the types of task associated with left PFC are those emphasising the meaning rather than surface features of study items (Kapur et al, 1994) (i.e. "deep encoding tasks" (Craik and Lockhart, 1972)) a finding that is in agreement with neuropsychological work (Incisa Della Rochetta and Milner, 1993; Gershberg and Shimamura, 1995). Furthermore, experiments 3 and 4 reported in the previous chapter also highlight the sensitivity of left PFC to semantic processing demands within the setting of an episodic memory-encoding task. Taken together, they also suggest tentative evidence for a degree of functional heterogeneity with a more ventral regional activation reflecting attention to semantic attributes of

word pairs and a more dorsal region, lying above inferior sulcus, active when the demand to organise words into groups, according to their semantic attributes, is emphasised.

Many questions remain concerning the specific roles of PFC at encoding. While, for example, organisation of study material is known to be important for optimal learning (Segal and Mandler, 1967), the specific role of left PFC in this type of semantic processing is unclear. Several possibilities have been suggested. These may be summarised as follows: first, it has been proposed that left PFC activation reflects the retrieval of semantic knowledge, (Tulving et al, 1994a). A second viewpoint is that left PFC's role lies in holding the semantic attributes of material in working memory (Gabrieli et al, 1998). A third view is that left PFC activation is associated with a higher level process concerned with the selection of semantic attributes that are relevant to the task at hand (Thompson-Schill et al, 1997; Thompson-Schill et al, 1999; Frith, 2000). This view, that left PFC is concerned with selecting rather than retrieving or holding semantic attributes has been tested experimentally (Thompson-Schill et al, 1997) and is implicit in proposals that left PFC activation in memory encoding reflects organisation of encoded material according to its semantic attributes (see experiment 3). Alternatively, it has been suggested that the crucial feature of left PFC activation lies in the formation of associations even in the absence of any semantic evaluation (Passingham et al, 2000). A broader view is that left PFC activations are associated with 'reflective activity' which comprises 'detailed, deliberative analysis ... maintenance of information while it is being evaluated, or the initiation of systematic self-cueing to retrieve additional information' (Nolde et al, 1997). This latter view is probably sufficiently broad to encompass all of the afore-mentioned accounts. One other suggestion is that the role of left (ventrolateral) PFC is in the control of retrieval

from semantic memory (Wagner et al, 2001). These views will be discussed further in the final chapter and the evidence for and against them considered more closely.

The two studies reported in this chapter seek to address ambiguities in the interpretation of left PFC activation at encoding. The first (experiment 5a) used PET; the second (experiment 5b) used a modified version of the same design in fMRI. Both attempt to characterise brain responses to the learning of new semantic relationships when different relationships to the same material had already been established. This situation may be considered as the activation state and can be compared directly with instances where semantic associations have been well learned and with cases where new semantic associations must be established in the absence of previously learned associations. In this way, selection processes may be dissociable from processes associated with retrieving and holding in mind semantic attributes since, it is suggested, the critical feature of setting up new semantic associations to verbal material that has already been repeatedly presented lies in the selection of new attributes. There is no reason to suppose that the actual amount of semantic information will exceed that in the semantic processing of entirely novel material. Thus, a significantly greater left PFC activation when pairs are familiar but rearranged (compared to when they are novel) may be attributable to selection rather than retrieval and maintenance processes.

5.1 Experiment 5a

PET exploration of the effects of semantic interference at episodic memory encoding

5.1.1 Introduction.

Because of fundamental differences in the temporal resolution and image acquisition capacity of PET and fMRI, slightly different designs were chosen for the two experiments. In the PET study, the experimental conditions were produced and defined by what had occurred during a pre-scanning period. Each condition was preceded by a 2-minute "lead-in" during which subjects repeatedly learned a list of word pairs. The sole reason that this lead-in period was not scanned was due to the temporal constraints upon PET and to the limited number of acquisitions available: constraints that did not apply to the fMRI experiment (5.2).

5.1.2 Material and methods

Six healthy male right-handed volunteers were studied. Each subject underwent 12 separate scans, each preceded by a lead-in learning period. No subject had a history of past psychiatric or neurological illness and all gave informed consent. The studies were approved by the local hospital ethics committee and Administration of Radiation Safety Advisory Committee (UK).

5.1.3 PET Scanning.

Scans of the distribution of $H_2{}^{15}O$ were obtained using a SIEMENS / CPS ECAT EXACT HR+ (model 962) PET scanner in 3-D mode with a 15 cm axial field of view. Relative rCBF was measured from the distribution of radioactivity after slow bolus i.v. injection of $H_2{}^{15}O$ (9 mCi per scan, each lasting 90 sec). Attenuation-corrected data were reconstructed into 63 image planes with a resulting resolution of 6 mm at full-width-half-maximum.

5.1.4 Tasks.

During a 2-minute lead-in period to each PET scan, subjects learned 16 category-exemplar pairings (read out successively at a rate of one pair per 4seconds). Each list was heard twice with the end of the second presentation timed to coincide with the beginning of the PET scan. This repeated learning served to create the context for the critical experimental manipulation that followed. During scanning, a list of 16 further paired associates was presented. The pairs were manipulated to produce 4 conditions:

5.1.4a New-New condition

Here, new categories and exemplars were presented, having no relationship to those that had been presented during the lead-in phase.

5.1.4b New-Old condition.

New categories were paired with old exemplars, i.e. exemplars that had been heard during the lead-in phase. So, for example, if the pair 'DOG...BOXER' was presented during the lead-in phase, this would be followed, during scanning, by 'ATHLETE...BOXER'.

5.1.4c Old-New condition.

Old categories were paired with new exemplars. So, for example, if the pair 'DOG...BOXER' was presented during the lead-in phase, this would be followed, during scanning, by DOG...DALMATIAN'.

5.1.4d Old-Old condition.

The same pairs that had been presented during the lead-in phase were re-presented during scanning. This condition served as the 'baseline' condition for most comparisons.

5.1.5 Summary of task design and data analysis.

The experimental design is summarised in figure 5.1. Subjects were instructed to listen closely to each list and told that a memory test would follow. They were not informed as to which stage of the presentation would coincide with the acquisition of the PET scan.

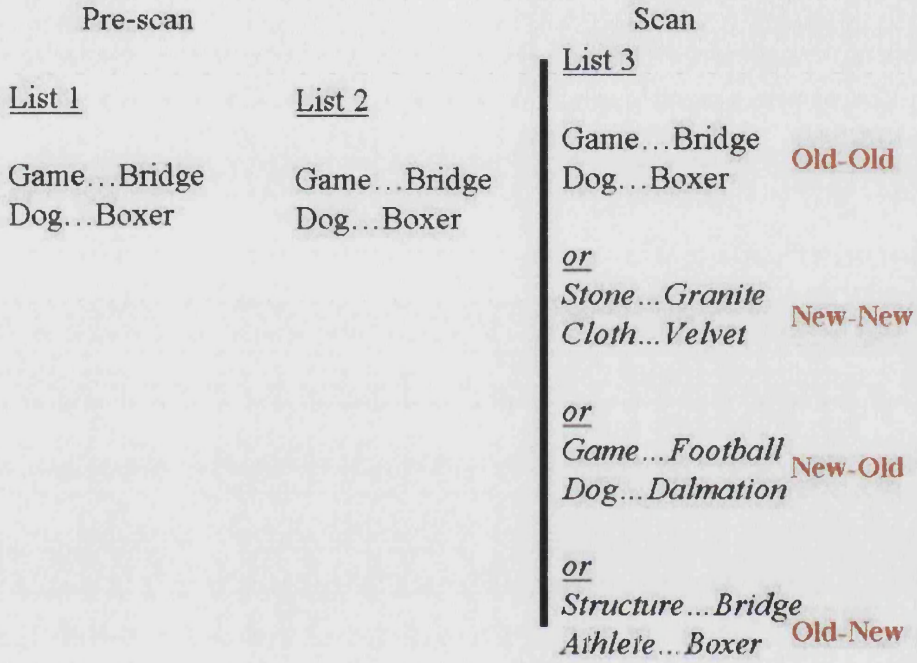

Figure 5.1 Design of experiment 5a.

During an initial lead-in period, 16 category-exemplar pairs were presented (two examples shown). Presentation was then repeated. Finally, at the time of scanning,, one of the four experimental list types was presented.

For each condition subjects were scanned three times, giving a total of 12 PET scans.. The order of the presentation of experimental conditions was counterbalanced both within and across subjects. The effectiveness of encoding was assessed through category-cued retrieval after a 5-minute period during which a distracting task (mental calculation) was administered to prevent rehearsal.

Statistical parametric mapping (Friston et al, 1995a; Friston et al, 1995b) software was used for image realignment, transformation into standard stereotactic space, smoothing and statistical analysis. All measurements for each condition were averaged across subjects. State-dependent differences in global flow were modelled using ANCOVA. Condition-specific effects (namely those of the New-Old and Old-New conditions compared to the New-New and Old-Old conditions) were assessed with contrasts of the adjusted task means using the t-statistic subsequently transformed into normally distributed Z statistic. The resulting set of Z values constituted a statistical parametric map (SPM{z}), which was then thresholded at $P<0.001$.

The analyses that I was particularly interested in with respect to the guiding experimental question were those identifying regions that were sensitive to the learning of new associations to experimentally familiar material. That is, I wished to ascertain where the New-Old and the Old-New conditions would produce greater activation than the Old-Old and the New-New conditions. The prediction was that this would be in left PFC.

5.1.6 Task performance

Recall was 95% for New...New, 83% for Old...New, 73% for New...Old and 93% for Old...Old. Performance for Old...New and New...Old was significantly worse than that for New...New ($p<0.01$ and $p<0.001$ respectively). Thus, the formation of a previous semantic association had a significantly deleterious effect upon the learning of a new association.

5.1.7 Imaging results.

Activation of left PFC (in the region of inferior frontal sulcus) was sensitive to a manipulation of the association between category and exemplar. Maximal activation in this region was seen in the two conditions involving a change in category exemplar pairings (Old...New and New...Old). Figure 5.2 shows a statistical parametric map of this activation for the contrast of these two conditions with the two conditions where there was no change (this effect survived a threshold of $p<0.05$, corrected for multiple comparisons). These data are also plotted in figure 5.2 where the mean adjusted activity in the left PFC is plotted for each of the four experimental conditions. It can be seen that maximal activation occurs in the two conditions involving a change in category-exemplar pairings compared to conditions where there is no change with respect to previously established pairings. The foci of activation produced by this comparison are shown in table 1.

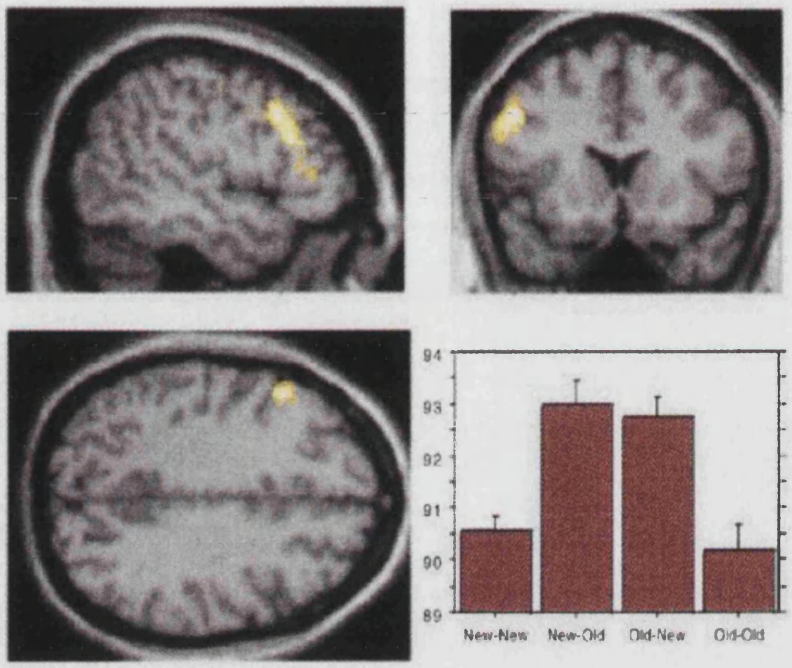

Figure 5.2 Comparison between the combined 'new...old' and 'old...new' and the combined 'old...old' plus 'new...new' conditions.

Activation is seen in the left PFC. The SPM has been rendered into standard stereotactic space and superimposed on to orthogonal sections, at voxel coordinates (x, y, z = -46,20, 30) of a magnetic resonance image. The inset graph shows rCBF equivalents (error bars shown) from the same coordinates. It can be seen that activation is significantly greater for the conditions involving a change in category–exemplar pairings than either of the two other conditions.

Region		Location (X,Y,Z)	Z Score
	[New-Old plus Old-New] versus Old-Old		
Left lateral PFC		-46, 16, 32	4.6
		-46, 26, 24	4.0
	[New-Old plus Old-New] versus [Old-Old plus New-New]		
Left lateral PFC		-46, 20, 30	5.3
		-46, 26, 24	4.7
Medial Parietal Cortex (precuneus)		0, -68, 50	5.8
Left Medial PFC		-32, 58, 0	4.3
Left infero-lateral Parietal Cortex		-58, -48, 34	4.0

Table 5.1 **Activations associated with new category-exemplar pairings.**

5.2 Experiment 5b

fMRI exploration of the effects of semantic interference at episodic memory encoding

5.2.1 Introduction.

As will be seen below, the improved capabilities of fMRI, in terms of a greater and more flexible image acquisition, has enabled improvements in the design of this experiment, which also serves as a replication of experiment 5a. In the study above, the manipulation of interest (i.e. formation of new semantic linkages) was always confounded with item novelty (i.e. a new pairing always involved the introduction of either a new category or a new exemplar. In this experiment, this confound was removed by holding stimulus familiarity constant in the re-pairing condition. I will return to a consideration of this improvement in the discussion section. In addition, scanning occurred throughouth the lead-in learning period and then on subsequent repeated presentations of target lists: a possibility not afforded with PET.

5.2.2 Materials and methods.

MRI scanning was carried out on 7 volunteer subjects (age range 23-36 years; mean age 28 years). All subjects were fit and healthy with no history of neurological or psychiatric illness or of drug/alcohol abuse. All subjects gave informed consent and the study was approved by the local hospital ethics committee.

5.2.3 fMRI scanning

A Siemens VISION system (Siemens, Erlangen) operating at 2 Tesla was used to acquire both T1 anatomical and gradient-echo echo-planar T2* weighted image volumes with blood oxygenation level dependent (BOLD) contrast. For all subjects,

data were acquired in 4 scanning sessions separated by a 5-minute rest period. Aside from 6 'dummy' volumes, which were subsequently discarded to allow for T1 equilibration effects, a total of 384 functional volumes per subject (96 scans per session) were acquired. A TE of 40ms was used and volumes were acquired continuously every 4800 ms. Each volume comprised 48 3mm axial slices with in-plane resolution 3x3mm positioned to cover the whole brain.

5.2.4 Tasks.

Twelve word paired associates were presented visually, at a rate of one pair per four seconds, on a projection screen placed comfortably within subjects' field of view. Members of each pair were presented successively, each member being presented for two seconds. Thus subjects would see, for example, the stimulus "Bird..." for two seconds followed by "...Note" for two seconds. When a list had been shown in its entirety, it was presented again (the same pairings in a different order to minimise the formation of between-pair associations). An individual list was presented a total of 4 times, alternating with a baseline control task. Scanning occurred throughout. The baseline task consisted of the presentation of identically paced paired items that were shown repeatedly (that is only two items were seen throughout the block – simply the items: *word1...word2*). Subjects were instructed to read the pairs silently in the memory-encoding task and to think about the word or concept that linked members of each pair. They were forewarned that, following scanning, a cued retrieval task would be administered. When the same list had been presented for the fourth time, the next baseline epoch was followed, without warning, by a second list. In this list, one of the following changes was made: Either 12 entirely new word pairs were presented or twelve pairs comprising the same words that had been learnt during the 4 initial presentations was presented but this time the pairings of individual words were

rearranged. In both cases, the new word pairs were presented a total of 4 times alternating with the unchanging baseline task. Thus, in effect, 3 conditions were produced:

5.2.4a Novel pairs.

The blocks of initial pair presentation (of the first list in each case and of the second list when new items rather than rearranged ones were presented) all contained material that was experimentally novel both in terms of the words themselves and the pairing that they were placed in.

5.2.4b Familiar pairs

By the fourth presentation of any pair list, both the words and the pairings in which they were set were highly familiar, forming a further baseline condition. Note too that, since scanning occurred throughout the list repetitions and intervening low level baseline task, it was possible to determine brain regions that showed reducing activation with increasing familiarity.

5.2.4c Rearranged pairs.

This was the condition of primary interest. Having established a set of stimulus pairings, these were broken and rearranged so that different semantic attributes of the same material were emphasised in the linkages.

Each subject was scanned through 4 four sessions, each of which consisted of the initial set-up phase (a set of pairs presented 4 times) and then either a novel pair condition (two sessions) or a rearranged pair condition (two sessions). The study design (giving examples of stimuli) is summarised in figure 5.3.

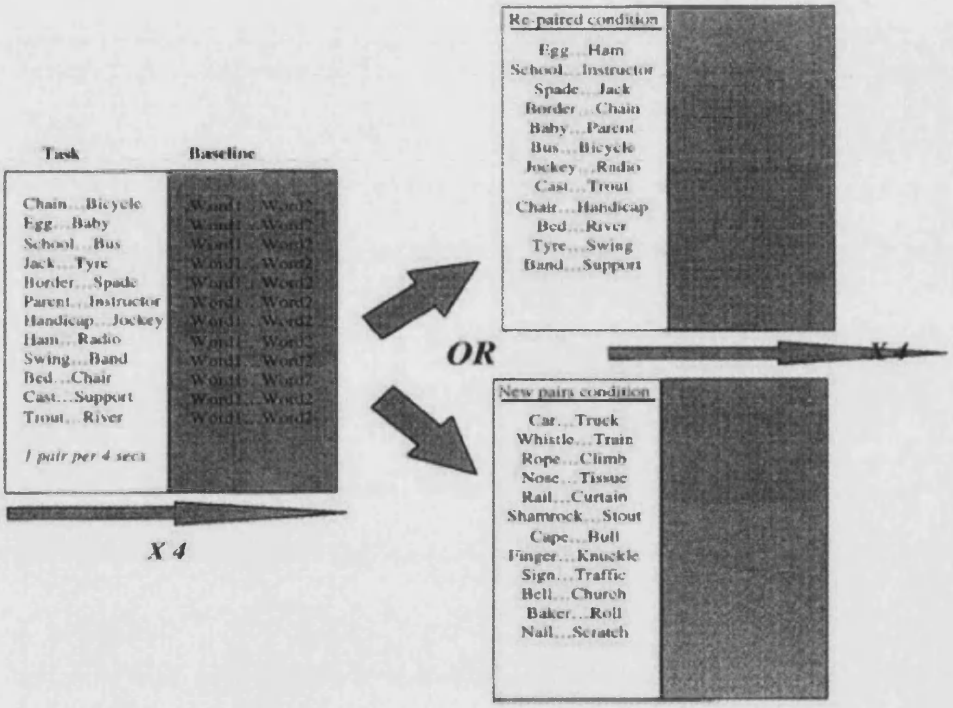

Figure 5.3 Study design for experiment 5b.

5.2.5 Data analysis.

Data were analyzed using Statistical Parametric Mapping (SPM97, Wellcome Department of Cognitive Neurology, London, UK; (Friston et al, 1995b). All volumes were realigned to the first volume and resliced using a sinc interpolation in space. Each volume was normalised to a standard EPI template volume (based on the MNI reference brain, (Cocosco et al, 1997)) of 3x3x3mm voxels in a standard space (Talairach and Tournoux, 1988) using nonlinear basis functions. The T1 structural volume was coregistered with the mean realigned EPI volume and normalised with the same

deformation parameters. Finally, the EPI volumes were smoothed with a 8mm FWHM isotropic Gaussian kernel to accommodate further anatomical differences across participants, and proportionally scaled to a global mean of 100. Blocks of task were modeled as 'box-car' functions convolved with a canonical version of the haemodynamic response to account for slight delays in BOLD response.

Simple subtraction of baseline from activation tasks enabled a definition of the non-time-dependent system associated with word pair encoding. It was also possible to estimate changes in activation (relative to this baseline task) as a function of increasing familiarity with study material were characterised. Furthermore, regions responding to a change in well-learned word lists (depending upon whether that change was in the items themselves or in the way in which items (individual words) were paired with each other) were identified. In order to do this, the activations (compared to the baseline) associated with the first presentation of rearranged pairs were compared with average activations (compared to baseline) for the initial presentation of these pairs prior to their rearrangement combined with activations associated with initial presentation of all other pairs (that is, all 'novel' conditions). That is, in brief, activations produced by re-pairing were compared with activations associated with novel items. In view of the fact that lists were not counter-balanced across subjects, a further comparison was carried out limited to those lists occurring in the re-pairing condition. This was identical to the re-paired versus novel comparison but used only those lists associated with the re-pairing condition. That is, activations, relative to baseline, after pair rearrangement, were compared to activations on initial presentation of this material. This was done to establish that activations were not merely the result of a systematic bias in the nature of the word lists across conditions.

In order to minimise a risk of false positives, and to ascertain that the regions reported all show true activation relative to the baseline condition, the first analysis (that is, all task blocks versus all low-level baseline blocks) was used to define a subset of voxels. The analysis of the interaction effects was applied only to this "mask" subset of voxels. In using this approach, one can be more confident that changes reported were changes in absolute activation (relative to baseline). Further, this use of a constrained subset of voxels constitutes a stricter approach with respect to the prevention of false positive results as it means that fewer voxel-wise comparisons are carried out. In the third analysis – the one addressing regions sensitive to a change in the pairing of already-learned words - this mask was also used. In view of the strong and spatially precise a priori hypothesis with respect to left PFC, an uncorrected threshold for this region ($p<.05$) was set. For all other regions, effects surviving a threshold of $p<.001$ are reported. The use of the mask rendered the standard SPM correction for multiple comparisons inappropriate

For all effects, subjects' data were modelled separately and group results are presented as the conjunction of activations across all 7 subjects (Price et al., 1997). In essence, this means that only changes common to all subjects are reported. The conjunction analysis indicates effects that do not differ significantly between subjects in terms of magnitude and location.

5.2.6 Task performance

Cued retrieval was tested after the scanning session. Subjects were cued with the first item in each pair and required to respond with the second. In some cases a given cue was associated with 2 responses (when pairings had been rearranged). In these cases, subjects were required to name both items with which the cue had been

paired. The cue was chosen as the one that had been presented first during the initial presentation of items. This means that cued retrieval following pair rearrangement occurred in a different setting from retrieval where no such rearrangement occurred. While this is not ideal with regard to the behavioural measurement, it had no bearing upon the neuroimaging results that we present. The mean scores were near ceiling: initially presented pairs 99.2% (range 91.7 – 100%); entirely novel pairs 98.3% (range 91.7-100%); old words rearranged 96.7% (range 83.3 – 100%). In essence, we found a ceiling effect: this occurred because every pair had been presented a total of four times. No significant differences were noted between new and rearranged pairs. In effect, the influence of semantic interference on post-scan retrieval is likely to be submerged by the effect of repeated learning. This does not affect the interpretability of the imaging findings.

5.2.7 Imaging results.

5.2.7a Encoding tasks versus baseline.

A number of areas were activated in association with this contrast, including, as predicted, left PFC. Results from this analysis are summarised in table 5.2 and figure 5.4.

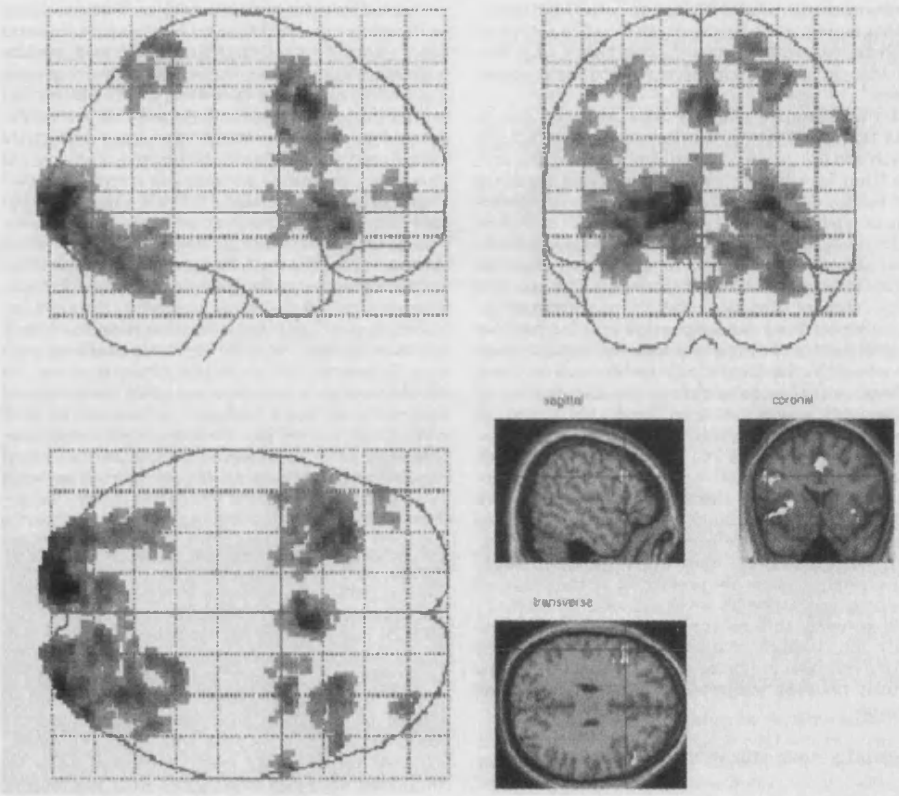

Figure 5.4 Comparison of all encoding conditions with baseline task.

Regions showing a significantly greater BOLD response ($P < 0.001$) for the encoding than the baseline task (irrespective of time-related changes) are shown. Results are presented as "Glass brain" projections. In the bottom right panel are orthogonal sections of a T1-weighted anatomical image with sections chosen at the left prefrontal voxel of maximum intensity (x, y, z = -44, 26, 18) onto which the SPM has been rendered to show in more detail the prefrontal activations.

5.2.7b Decreases in activation with familiarity.

The results of this analysis, in which changes in activation (compared to the alternating fixation baseline task) were modelled as a linear decrease, as pairs become more familiar (from presentation 1 to 4), are shown in table 5.2 and figure 5.5. Left

PFC (inferior frontal gyrus), occipital cortex and cerebellum showed significant time-dependent effects.

5.2.7c Pair rearrangement.

Here, the novel pair conditions were treated as the baseline task in order to identify activations in which the most prominent driving factor was not simply novelty but rather the need to form new associations in the face of existing associations to familiar material. The comparison exploring for regions showing a significantly greater response to pair rearrangement than pair novelty is shown in table 5.2 and figure 5.6. The effect in left PFC was subtle one, (significant at $p<0.01$, uncorrected). A contributory factor to its failure to survive a more stringent threshold is probably the reduction in the number of observations contributing to this comparison. Nevertheless, the activation lay within a reduced volume of search, produced by an orthogonally specified "mask" (at $p<0.001$) of encoding-related activations. This reduction in the search volume, accompanied by the strong prior data from experiment 5a and the a priori predictions, make this a noteworthy finding.

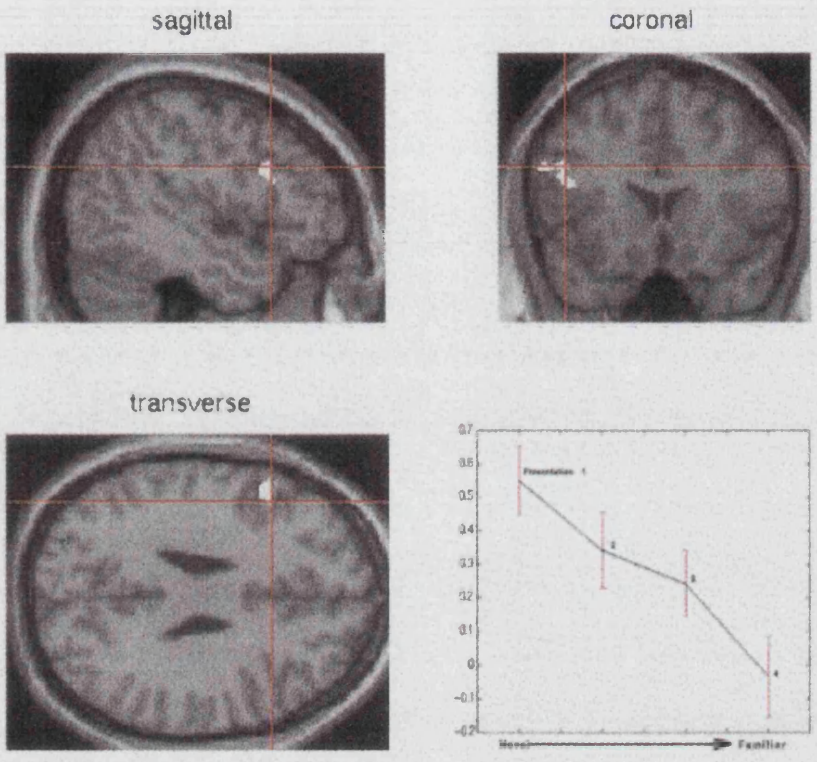

Figure 5.5 Left PFC region showing a decrease in activation in association with familiarity. Orthogonal sections of a T1-weighted anatomical image that conforms to standard stereotactic space. Superimposed on these sections is the SPM ($P < 0.001$) of regions showing a decrease in magnitude of activation (relative to the baseline condition) across successive word pair list presentations. The section has been chosen at the voxel that showed maximal effect with the contrast (x, y, z = -46, 18, 28). In the bottom right panel, the activations in this voxel, relative to the baseline task, are plotted (with error bars) for each the four presentations of the word list.

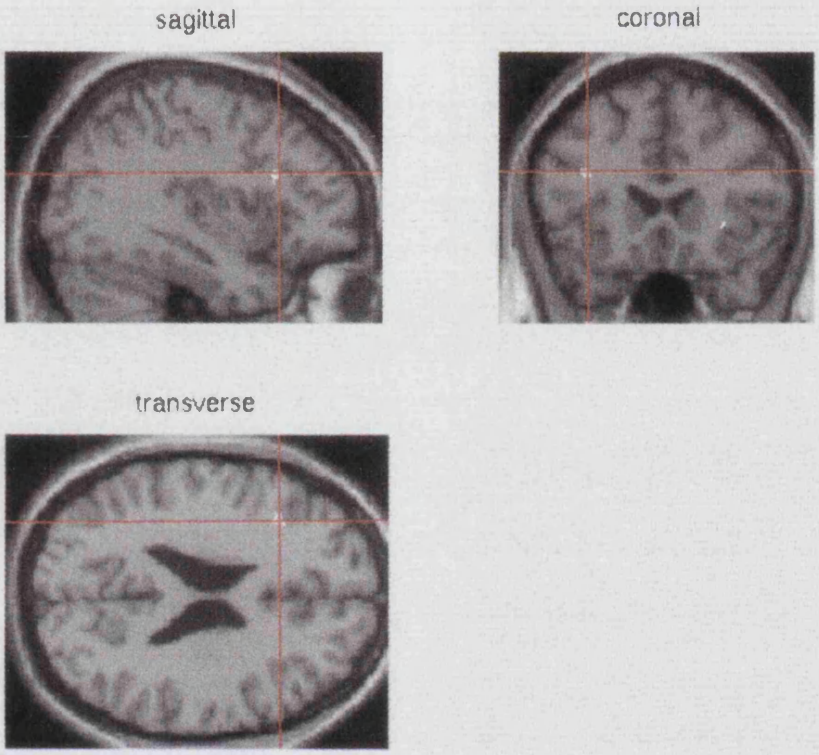

Figure 5.6 Pair rearrangement versus pair novelty.

Orthogonal sections of a T1-weighted anatomical image that conforms to a standard stereotactic space. Superimposed on these sections is the SPM (P , 0.05) resulting from the comparison of rearranged pairs to novel pairs in experiment 5b. The section has been chosen at the voxel in left PFC, which showed maximal effect with this contrast (x, y, z = -36, 20, 24). This comparison was "masked" with the contrast between activation and baseline tasks, shown in Fig. 5.4.

Region		Location (X, Y, Z)	Z Score
	Contrast of all activation tasks to baseline		
Left Inferior Frontal		-32, 30, -6	6.8
Gyrus		-52, 16, 30	4.8
Right Inferior Frontal		30, 24, 2	5.7
Gyrus		54, 24, 32	5.1
Left Occipital Cortex		-10, -96, 2	7.6
		30, -96, 4	7.3
Medial PFC/Ant.		4, 12, 46	6.0
Cingulate Cortex		-4, 8, 46	5.5
Parietal Cortex		24, -46, 66	5.5
		-28, -50, 40	4.0
	Regions showing decreasing activation with repeated list presentation		
Left Inferior Frontal		-46, 18, 28	5.1
Gyrus		-44, 18, 18	4.3
		-52, 12, 16	4.3

Occipital Cortex		-24, -92, 10	3.9
		24, -82, 22	5.2
Cerebellum		-40, -52, 14	4.6
		38, -62, -24	4.7
	Regions showing sensitivity to pair rearrangement (compared to new pairs)		
Left Inferior Frontal Gyrus		-36, 20, 24	2.3
		-46, 14, 28	1.7
		-52, 12, 30	1.7
Occipital Cortex		14, -80, -20	5.2

Table 5.2 Activations in experiment 5b

5.2.8 Summary of results

The pattern of findings with respect to the main region of interest, left PFC, may be summarised as follows: effects of interest provoke activations within left inferior frontal gyrus, although the propinquity of this region to the inferior frontal sulcus (and therefore to a more dorsal area of lateral PFC) should be noted. This region formed part of a system (including right PFC, occipital, pariteal and anterior cingulate cortex) that was active in association with the encoding task relative to the low level baseline task. Left PFC showed a reduction in this activation with pair repetition, and, when a novel set of pairs was presented, its activation was evoked once more. However, activation

was greatest not when new stimuli were presented but when old stimuli in new pairings were presented. In brief, this region is associated with episodic memory encoding and is maximally engaged in the face of semantic interference.

5.3 General Discussion

The experiments reported here, as well as using different neuroimaging techniques, show important design differences. First, in the PET study (experiment 5a), scanning occurred only during the crucial manipulation of semantic interference (i.e. on the third list presentation). In experiment 5b, since fMRI allows continuous data collection, scanning occurred during all presentations of lists. This enabled an evaluation of the change in frontal activity as the word lists became more familiar, before the re-pairing occurred. Two notable findings emerge from these data. First, an initial left PFC response to word paired associates is attenuated with repeated presentations of those pairs (figure 5.5). This is consistent with the finding that more practised tasks do not require frontal mediation (Raichle et al, 1994). It also suggests at least two possibilities. On one hand, it is conceivable that left PFC is responsive purely to the novelty of the study material (within the context of the experiment). By the fourth presentation, material had become familiar. An alternative possibility is that the reduction in left PFC activation reflects a decrease in processing demands for these word pairs after repeated presentations. These experiments have enabled a distinction between these two possibilities. Since re-pairing of familiar words evoked a response in left PFC that was significantly greater than when pairs were presented for the first time it may be argued that an explanation of left PFC activity purely in terms of item novelty is inadequate.

Another possibility is that the re-pairing condition is associated with the need to consider novel semantic attributes of the previously presented pairs. Thus, with reference to figure 5.2, an initial presentation of, for example, "Ham..." when paired with "...Radio" emphasises a set of attributes that changes when, following rearrangement, "...Ham" is paired with "Egg...". Nevertheless, I do not believe these

findings to be explicable purely in terms of novel semantic attributes *per se.* I suggest this firstly because processing of a new set of such attributes was necessarily a feature of processing novel as well as rearranged pairs. A second piece of evidence lies in the observation in experiment 5a that left PFC activity increases for both an "old category - new exemplar" condition (in which the nature of semantic linkage does not qualitatively change from the comparison "old category – old exemplar" condition) and a "new category – old exemplar" condition (in which there is a qualitative change in the nature of the link e.g. "Sportsman...Boxer" changes to "Dog...Boxer"). This finding that left PFC does not distinguish between these two conditions, but does distinguish between either of these conditions and a "new category – new exemplar" condition, seems to indicate that the crucial area of sensitivity lies in the requirement to create a new linkage in the face of an existing one, that is, in re-selecting the semantic attributes of relevance.

Another modification of the design in experiment 5b allowed a more confident interpretation of the left PFC pattern of activity. In experiment 5a, left PFC activation was maximal when new associations were made to familiar items (that is, when A-B; C-D, etc. had been learned and during scanning subjects were presented with A-X; B-Y, etc.). However, a potential problem in interpreting this is that changing semantic associations occurred in the presence of novel material (that is, when A-E and B-F were presented, items X and Y were novel). Thus, the results might be interpretable in terms of an interaction between item novelty and semantic processing. Experiment 5a removes this ambiguity by ensuring that a changing semantic linkage was not associated with item novelty (that is, A-B, C-D, etc. was learned and then presented as A-D, B-C, etc.). A further difference between the two experiments was that, in the former, stimuli were presented verbally and, in the later, visually. The degree of consistency in the results, with respect to the left PFC activation, is reassuring.

Thus, the findings from the two experiments concur in identifying left PFC as a region that is sensitive to conditions where the critical emphasis is upon semantic processing necessary for the formation of new associations. This manipulation must elicit a degree of interference from previously encoded pairings a phenomenon known as proactive interference. Interestingly, patients with prefrontal lesions show increased susceptibility to this interference effect (Shimamura et al, 1995) while isolated left prefrontal lesions result in an absent encoding advantage with semantic processing (Zattore and Mcentee, 1983). These results are compatible, too, with the findings from experiment 1 (chapter 3) and experiments 3 and 4 (chapter 4). In each of these, the formation of semantic associations was the key to the encoding process and, in each, left PFC showed activation. Moreover, this experiment may give grounds for relating left PFC activity more specifically to this semantic associative processing rather than to item novelty or to WM.

It is worth pausing to reconsider the precise localisation of the left PFC activations observed across this series of experiments. While I have, for simplicity, referred to them, collectively, as "left PFC", in actual fact they may represent functionally heterogeneous areas. Certainly, there is a degree in variability in localisation across different comparisons, with the most dorsal activation being produced by the manipulation of organisational processes in experiment 3. However, whether these admittedly subtle differences reflect true functional heterogeneity, with different brain regions sensitive to the different tasks used, or whether they simply reflect variations in the functional and structural anatomy of the different groups of subjects, must, at present, remain a matter for surmise. At present, one can safely say that all experiments were associated with lateral PFC activation and that this, in general

lay in the region of the inferior frontal sulcus, on some occasions localised in middle frontal gyrus (experiments 3 and 5a) and on others in inferior frontal gyrus (experiments 1, 4 and 5b).

One possible criticism of the chosen interpretation of these findings (i.e. *Selection* of semantic attributes rather than semantic *generation* or *maintenance*) is that the re-pairing condition might be associated with two sets of semantic information: one relating to the previous pairing of the words and one to the new pairing. The net result would be a greater level of semantic generation (and maintenance) in this condition. This argument is difficult to answer but does not, in my view, offer an entirely satisfactory explanation for the left FC activation in the re-pairing condition. The criticism rests upon the idea that the greater FC activation for rearranged versus novel pairings is produced by an additive effect (activation associated with old semantic features plus activation associated with new semantic features). However, by the fourth presentation of pairs, stimuli had ceased to engender activation in this region, i.e. activity had fallen to a baseline level (see figure 5.5). Thus, such an additive effect appears unlikely on the current evidence and does not directly account for the greater activation in left FC for rearranged compared to novel stimuli.

Finally, the critical question concerns a more specific description of the nature of the semantic processes that engender left PFC activation. As outlined, the main theoretical accounts are concerned with the role of left PFC in retrieval, holding on-line, selection or controlled retrieval of semantic attributes. Attempts to distinguish between these possibilities have met with difficulties in that the processes are, if real, highly reliant upon each other: thus, greater selection demands are invariably associated with greater retrieval and holding demands. One study attempting to address this used

"high" and "low" selection tasks in three different types of semantic decision making task: generation, classification and comparison **(Thompson-Schill et al, 1997)**. They found that, in the different tasks, broad areas of left PFC showed a preferential sensitivity to the high rather than the low selection condition and, further, suggested that these results could not be due to greater amounts of semantic information being retrieved and held on-line. Although it is difficult to be entirely confident that one can separate amount of semantic attributes from degree to which selection processes are engaged, their results are compatible, in this respect, with the current experiments. In a further study, analogous to these, Thompson-Schill and colleagues explored the effect of "competition" on a semantic generation task (Thompson-Schill et al, 1999). Having already learned to generate one type of response (e.g. colour) to a word, subjects were then required to generate another (e.g. action). It was found that left inferior PFC was particularly sensitive to this task demand. This finding may be interpretable in a similar way to the effect of pair rearrangement in the current experiment. The two experiments will be revisited in the context of the broader literature, in chapter 7.

In summary, I believe that this use of a 'competition' or proactive interference cognitive task may enable engagement of selection processes without increasing the retrieval or holding processes. Indeed, one might plausibly suggest that, in the setting of a proactive interference task, the semantic field must be narrowed. What is required is the suppression of previously learned associations and the selection of different attributes. It is this feature that is critically different in the two conditions. This is related to the idea that left PFC supports a supervisory system modulating routine processing in novel situations (Norman and Shallice, 1986). Frith suggests that left PFC is specifically associated with the selection of an appropriate set of non-automatic responses and, moreover, that a *sine qua non* for this is the creation of an arbitrary

category of appropriate responses and the suppression of responses which lie outside this ad hoc and temporary category. He refers to this as "sculpting of the response space." (Frith, 2000) Thus, in the selection experiments of Thompson-Schill and colleagues (Thompson-Schill et al, 1997), the subject is given a clue as to which dimension of the relation between a pair of words is relevant as the pair is presented. This may be seen as directly relating to Frith's "sculpting" operation. It is these two conditions of Thompson-Schill and colleagues where the activation maxima most closely resemble those of the experiments reported in chapters 4 and 5. Here, although no overt responses were required during scanning, subjects were carrying out an internal semantic operation: specifically, the generation of a semantic link between words. Thus, this operation was required to produce the internal "response." Common to the activation tasks associated with left PFC activation, in both experiments, was the novel/nonroutine nature of the semantic association that had to be produced. Thus, it seems that that a crucial component of the activation tasks in experiments 5a and 5b lies in Frith's "sculpting" requirement. The rearrangement of familiar material requires that, for each word, a previous "response space" becomes inappropriate and a new one is required. This sculpting, a combination of inhibiting the inappropriate and identifying the appropriate semantic features is, Frith argues, a vital function of left PFC. Processing of material in this way may be the key to optimal memory encoding. Perhaps an effective episodic memory trace is created if, and only if, this "sculpting of the response space" occurs, and that this trace is created even when the task does not explicitly have a memory component. This follows suggestions (Sussman, 1975; Shallice, 1988) that encoding in episodic memory occurs specifically in nonroutine situations. This type of processing may be the crucial feature of a deep encoding task (Craik and Lockhart, 1972) and the results from the experiments so far suggest that it is supported, at least in part, by left PFC.

Note: Data from this chapter have been presented in the following publications
Dolan RJ & Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 1997 388: 585 – 588
Fletcher PC, Shallice T, Dolan RJ Sculpting the Response Space"- An account of left prefrontal activation at encoding" NeuroImage 2000 12(4): 404-417

Chapter 6

Exploring the roles of right PFC in episodic memory retrieval.

Experiment 6 – Monitoring processes: free- versus cued-retrieval.

General Introduction

A number of suggestions have been made as to the functional significance of the right prefrontal cortical activation in association with episodic memory retrieval (see (Fletcher et al, 1997) for review). One is that the predominance of right PFC activation during retrieval experiments reflects the adoption of a "retrieval mode" necessary for the initiation and maintenance of retrieval processes (Kapur et al, 1995; Nyberg et al, 1995). However, it has also been argued that right prefrontal activation is sensitive to the degree of retrieval success (Rugg et al, 1996). Other evidence implicates this region in error-checking at retrieval (Fletcher et al, 1996) or in processes necessary for retrieval of information regarding feature rather than location information (Nyberg et al, 1996; Owen et al, 1996b).

In the discussion section in chapter 3 (3.3), I raised the possibility that this activation reflects processes that may optimise episodic retrieval, processes such as the monitoring and verification of responses that have been suggested to be an important part of successful retrieval (Norman and Bobrow, 1979; Burgess and Shallice, 1996a) From the perspective of neuropsychology, one suggestion is that PFC is particularly involved in such strategic control of memory retrieval (Shallice, 1988; Moscovitch, 1989). Thus in the paired associate retrieval study (experiment 2), the retrieval of a previously presented exemplar, given the category cue, may demand that a subject internally generates a candidate response, assesses its suitability and responds accordingly. If a putative response is deemed incorrect, then further possibilities may need to be generated and assessed.

An important and widely used neuropsychological task with regard to the notion of retrieval monitoring involves the retrieval of an organized list of words. This form of

un-cued retrieval, using an internally organized structure created from a single encoding trial, makes critical demands upon monitoring operations. Evidence indicates that frontal lesions interfere with an organized and monitored memory search, in that frontally damaged patients retrieve material in a relatively haphazard way (Incisa Della Rochetta and Milner, 1993; Gershberg and Shimamura, 1995). The first of these studies stressed the use of organization at encoding or retrieval by varying the amount of structure supplied to subjects at these stages, and found no significant difference between the left and right frontally damaged groups (Incisa Della Rochetta and Milner, 1993). However, the observation that repetition errors in free recall occur most in patients with right DLPFC damage (Stuss et al, 1994) may be suggestive of a role for this region in monitoring/checking processes at retrieval. The existence of a syndrome where confabulatory recognition difficulties occur in patients whose lesions principally affect the right PFC is also consistent with the suggestion of a critical role for this region in monitoring (Delbecq-Derouesne et al, 1990; Schacter et al, 1996b)

6.1 Experiment 6

Monitoring processes: free- versus cued-retrieval

6.1.1 Introduction.

The current study addressed the hypothesis that right PFC is important for a monitored memory search. Brain activity during verbal retrieval was explored using PET to differentiate activity associated with the use of a pre-learned structure to guide recall from that associated with a reference task in which recall was guided by the experimenter. The prediction was that right PFC activity would be greater in the task requiring a monitored search. To allow direct comparison with neuropsychological data, experimental paradigms were devised with reference to the tests used on frontal

lobe patients (Incisa Della Rochetta and Milner, 1993; Gershberg and Shimamura, 1995). The paradigm is also analogous to the manipulation at encoding reported in experiment 3 (chapter 4).

6.1.2 Material and methods.

6 healthy, male, right-handed subjects (mean age 29.5 years, age range 19-56) were scanned. No subject had a history of past psychiatric or neurological illness and all gave informed consent. The studies were approved by the local hospital ethics committee and Administration of Radiation Safety Advisory Committee (UK).

6.1.3 PET Scanning.

Scans of the distribution of $H_2{}^{15}O$ were obtained using a Siemens/CPS ECAT EXACT HR+ (model 962) PET scanner operated in high sensitivity 3-D mode. Each subject underwent 12 scans, receiving a total of 350Mbq of $H_2{}^{15}O$ over 20 seconds through a forearm cannula. Data were acquired over 90 seconds for each scan. Attenuation-corrected data were reconstructed into 63 image planes with a resulting resolution of 6mm at full-width-half-maximum.

6.1.4 Tasks.

Subjects performed two distinct episodic memory tasks.

6.1.4a Retrieval 1 – "Internally-cued"

Study lists were presented 5 minutes prior to scanning. Each list consisted of 16 words. Lists were structured, with an overall heading and 4 sub-headings with each sub-heading containing 4 unique items. The material was identical to that used in experiment 3 and examples of the list are given in Appendix 1 chapter 3 (note, though, that , unlike experiment 3, where lists were not always structured in the presentation, for the current experiment, all words were blocked into sub-headings at encoding). With subjects already having been alerted to the list structure and informed of the heading

and sub-headings, lists were presented auditorily. After a 5-minute gap (filled to prevent rehearsal), scanning began and recall was tested. Responses were paced by prompting subjects with the word "next" once every 4 seconds and, each time, subjects were required to produce a word from the pre-scan study list. Subjects were instructed, prior to the study, that using the list structure to guide retrieval would help their performance.

6.1.4b Retrieval 2 - "Externally-cued "

Study lists were presented 5 minutes prior to scanning. Each list consisted of 16 paired associate words, each pair consisting of a category and an exemplar. During scanning, subjects were presented with categories at a rate of once per 4 seconds and were required to generate the relevant exemplar.

6.1.4c Control tasks

For the *Retrieval 1* control task, subjects repeatedly heard the word "next" at an identical rate to the activation task and they were simply required to repeat it each time. For the *retrieval 2* control, subjects were presented with comparable items to those heard in the experimental condition (i.e. categories and exemplars) at the same rate, and were required to repeat each one.

6.1.5 Summary of task design and data analysis.

Thus, across the 12 scans, each task (*Retrieval 1*, *Retrieval 2*, 2 baseline conditions) was presented 3 times. A brief summary of the design, together with the performance data, is shown in table 6.1.

Data analysis was the same to that used in experiment 1 (see 3.1.5). The chosen threshold of significance for main effects of conditions was $p<0.001$ (uncorrected for multiple comparisons). An uncorrected threshold was chosen because of the *a priori* hypothesis with regard to the prefrontal cortex. The effects that were explored were: *Retrieval 1* versus its appropriate control task, *Retrieval 2* versus it control task and, most importantly the comparison of these two contrasts (i.e. [*Retrieval 1* versus control] versus [*Retrieval 2* versus control] and vice-versa). For the latter contrast, I reduced the search volume, and, therefore, the risk of false positives, through the use of masking. In this case, the mask used came from the data in experiment 2 (from the comparison of paired associate retrieval with the semantic retrieval condition: see 3.2.7c, figure 3.5 and table 3.3). In effect, I used the activations from the previous study to define the memory system that formed by regions of interest for this more specific experiment.

	Retrieval 1	**Retrieval 2**
Pre-scan List presentation	Blocked (1 heading, 4 sub-heading, 4 items in each sub-category)	Category-exemplar pairs
Cueing at Retrieval (during scanning)	"Next"	Category
Average number of items recalled (max. = 16)	11.2 (s.d. = 1.1)	14.2 (s.d. = 0.8)

Table 6.1 Task Design and retrieval performance - experiment 6.

6.1.6 Task performance.

Retrieval performance during scanning is shown in table 6.1. As can be seen, performance was significantly worse in the *Retrieval 1* (internally cued retrieval) condition ($p<.01$). A measure of the degree to which subjects utilised the semantic categorisation within the latter list was provided by recording the number of unforced category shifts (since there were four categories covered in each list, then at least 3

category shifts were required during recall). The high degree to which subjects used categorisation as an aid to retrieval as evidenced by the low number of unforced category shifts (mean = 0.3. Simulations of random list generation from a similar 4X4 structure were performed and this indicated that, in all cases, subjects were producing far fewer category shifts than would be expected if they were failing to use the list structure).

6.1.7 Imaging results.

6.1.7a *Retrieval 1* versus Control.

The structured free recall condition was associated with activation in right PFC (both dorsolateral and verntrolateral regions) and in medial parietal cortex (precuneus). These activations are presented in table 6.2

6.1.7b *Retrieval 2* versus Control.

The paired associate recall task produced activation in right PFC (dorsolateral and ventrolateral) and precuneus, just as with the *Retrieval* 1 contrast. In addition, activation for this comparison was seen in anterior cingulate cortex and thalamus. These activations are presented in table 6.2.

Region		Location (X, Y, Z)	Z Score
	Retrieval 1 *(internally cued)*		
Right Dorsolateral PFC (Middle Frontal Gyrus)		36, 44, 24	5.3
Right Ventrolateral PFC (Inferior Frontal Gyrus/Insula)		52, 18, 24	2.9
Medial Parietal Cortex		-24, -74, -36 28, -76, 36	5.6 4.8
	Retrieval 2 (externally cued)		
Right Dorsolateral PFC (Middle Frontal Gyrus)		38, 38, 24	3.5
Right Ventrolateral PFC (Inferior Frontal Gyrus/Insula)		38, 12, 0	4.8
Medial Parietal Cortex		-16, -70, 36 12, -72, 40	4.3 3.2
Anterior Cingulate Cortex		6, 24, 16	4.5
Thalamus		0, -18, 8	4.9

Table 6.2 **Retrieval tasks compared to their control tasks**

6.1.7c *Retrieval 1* versus *Retrieval 2*.

As described above, a subset of voxels, defined by experiment 2, was used as a mask in this comparison. Thus, this comparison, and the reverse one, reported below, was confined to a brain system already shown to be associated with the demands of an episodic memory retrieval task. Such an approach can improve the sensitivity of analysis while reducing the risk of false positive results, enabling us to address more specific questions about dissociations within this system in response to differing task demands. With regard to the prefrontal activation, this analysis revealed a significantly

greater right dorsolateral prefrontal cortex activation associated with *Retrieval 1* compared to *Retrieval 2*. This is shown in figure 6.1a and table 6.3.

6.1.7d *Retrieval 2* versus *Retrieval 1*.

This comparison, confined to the same mask showed that a more ventral PFC region, lying in the region of inferior frontal gyrus and insula, was significantly more active during *Retrieval 2*. This is shown in figure 6.1b and table 6.3.

Note: for these two contrasts, unmasked analyses were also performed, for completeness and the additional activations arecorded in table 6.3.

Region		Location (X, Y, Z)	Z Score
	Areas showing greater activity in Retrieval 1 than Retrieval 2 Masked Comparison		
Right Dorsolateral PFC		36, 34, 32	3.6
		42, 26, 32	3.5
Medial Parietal Cortex		24, -78, 36	3.3
	Unmasked Comparison		
No Additional areas seen			
	Areas showing greater activity in Retrieval 1 than Retrieval 2 Masked Comparison		
Right Insula/Ventrolateral PFC		22, 8, 0	3.6
		36, 18, 0	3.1
		34, 24, 8	2.4
Posterior Cingulate/Medial Parietal Cortex		-2, -48, 28	3.2
		8, -50, 24	2.6
	Unmasked Comparison		
Superior/Middle Temporal Gyrus		-52, -34, -4	4.6
		40, -14, 24	3.5
Inferior Parietal Cortex		60, -32, 8	3.2
Ventro-medial PFC		-10, 56, 4	4.4

Table 6.3 **Direct comparisons of *Retrieval 1* and *Retrieval 2*, masked and unmasked.**

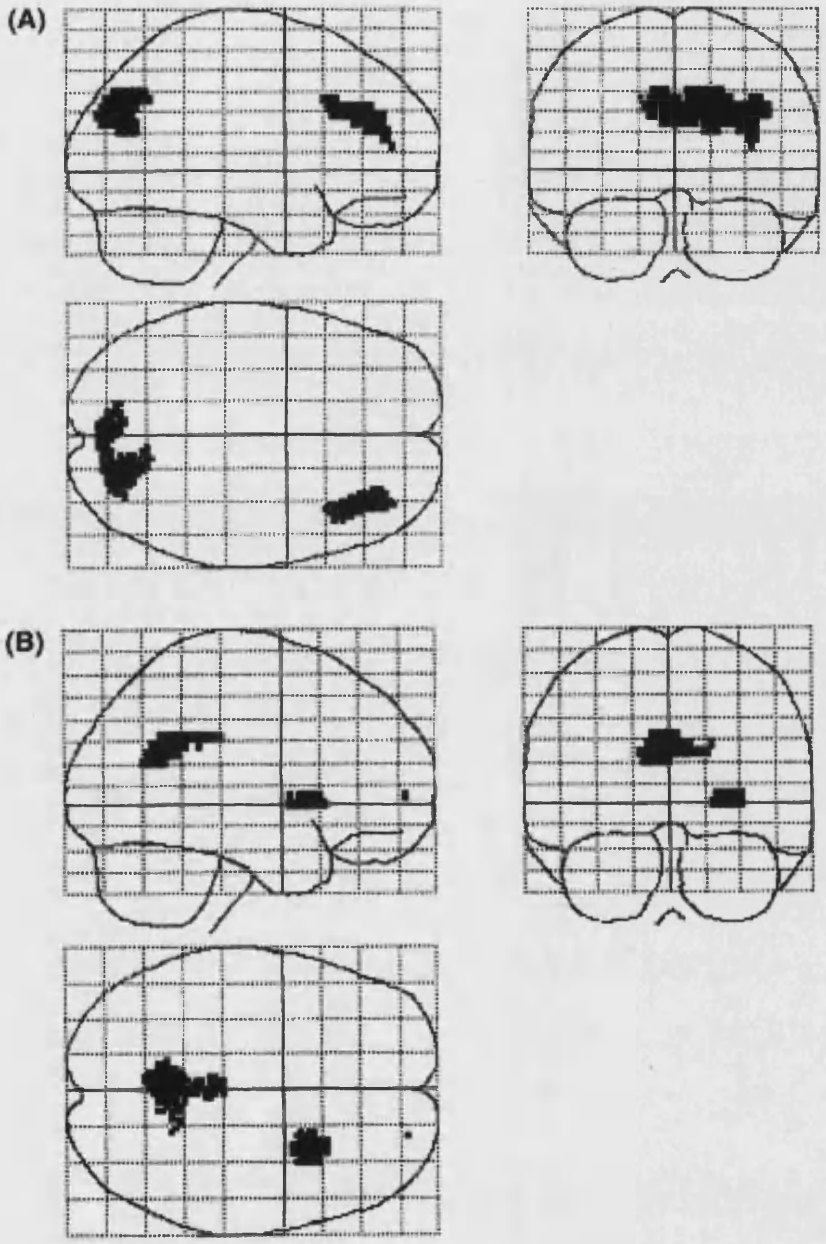

Figure 6.1 Retrieval-related activations.
SPMs showing direct comparisons between the *Retrieval 1* and *Retrieval 2* conditions. The activations are shown as 'glass brain' images. In both cases the analyses were constrained to the subset of voxels identifying a retrieval system in experiment 2 (chapter 3). The contrast identifying this system was thresholded at $P < 0.001$ (uncorrected) and the contrasts between *Retrieval 1* (internally cued) and *Retrieval 2* (externally cued) were set at $P < 0.01$ (uncorrected). **(A)** shows regions significantly more active in *Retrieval 1*: right DLPFC and the posterior superior region of the medial parietal cortex are seen. **(B)** shows regions significantly more active in *Retrieval 2*: insula/VLPFC and the posterior cingulate/anterio-inferior region of medial parietal cortex are seen.

In addition to the regional dissociation in right PFC activations, the other region widely implicated in memory retrieval, a medial posterior parietal region (Brodmann's area 7/31) also showed activation differences as a function of whether retrieval was internally or externally cued. In association with *Retrieval 1*, there was significantly greater activity in a more dorsal and posterior region. The *Retrieval 2* condition showed significantly greater activity in a more antero-ventral region, at the transition between the part of the medial parietal area (referred to as precuneus) and the posterior cingulate cortex.

In order to show this double dissociation between dorsal and ventral PFC regions more clearly, rCBF equivalents from each are plotted in figure 6.2

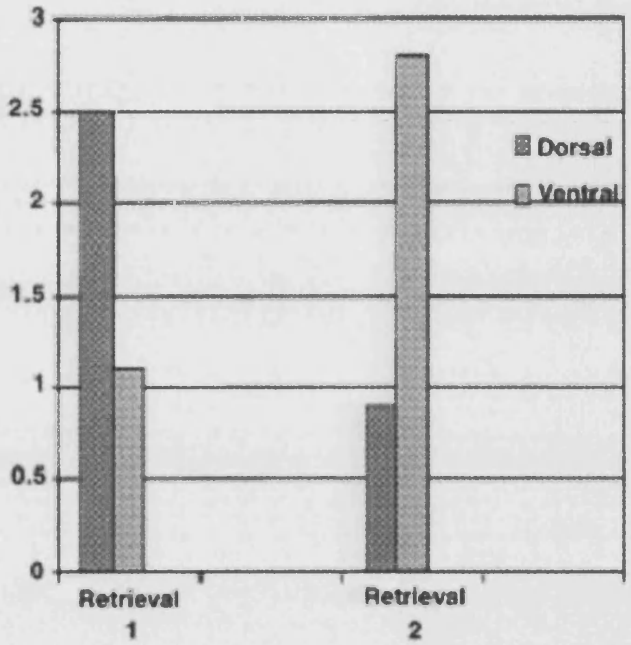

Figure 6.2 Plots of activation in right dorsal and ventral frontal regions.

Data from the two frontal regions (coordinates x, y, z = 36, 36, 32 for the more dorsal region; 30, 12, 0 for insula/ventral PFC region) when the *Retrieval 1* and *Retrieval 2* conditions are compared separately with their respective control tasks. As can be seen, both are activated compared to the control tasks, the more dorsal region showing relatively (and significantly) greater activation in *Retrieval 1* and the more ventral region showing significantly greater activation in *Retrieval 2*. (Units on the y axis are ml/dl/min rCBF).

With respect to the unmasked comparisons (see table 6.2), *Retrieval 1* compared to *Retrieval 2* produced no activations outside the mask area. For the reverse contrast, additional activations were seen in medial and superior temporal gyri extending into parietal lobes bilaterally, and in medial ventral PFC. These regions have been implicated in previous studies of memory (Grasby et al, 1993; Grasby et al, 1994; Fletcher et al, 1995), where they have shown relative deactivations compared to

baseline condition. Indeed, in a fuller analysis of the data from experiment 2 the same relative "deactivation" was found (reported in (Fletcher et al, 1995)). It may therefore be the case that, for this contrast, these additional activations reflect a greater deactivation in *Retrieval 1* rather than an activation in *Retrieval 2*. Interpretation of the behavioural implications of these activations must be highly speculative since the functional significance of relative deactivations is unclear. The discussion will consequently focus on those regional activations constrained by the masking since, in these cases, one can be confident that, relative to baseline, there is a true activation.

6.1.8 Summary of results.

Compared to their control tasks, both cued paired associate retrieval and uncued, structured free recall were associated with activation in right PFC and in medial parietal cortex. This replicates the results seen in experiment 2. The right PFC activation consisted of two foci, a more dorsal one, found to be significantly more activated during the free recall condition and a more ventral one, found to be more active during cued paired associate recall. Both regions fall within the overall system activated in the initial episodic retrieval experiment in chapter 3.

6.2 Discussion

These findings provide further support for the hypothesis that right PFC activation observed at memory retrieval reflects executive processing optimising memory function at this stage. As discussed in association with experiment 3, the creation of an organisational structure at encoding emphasises the abstractions of the semantic attribution of studied items. At retieval, such abstraction is not required: the emphasis is upon the use of this previously learned structure to guide retrieval. These findings suggest that a slightly more dorsal focus of right PFC is sensitive to such a demand. This is consistent with the finding of a greater level of activation of this region in association with *Retrieval 1* compared to *Retrieval 2* (in which retrieval specifications, for each of the previously studied items, were provided by the experimenter).

Activation of right DLPFand VLPFC/insula were seen when both retrieval conditions were compared with baseline, repetition tasks. There have been suggestions from the neuropsychological literature that retrieval emphasising organisational processes make more demands upon left than right PFC (Incisa Della Rochetta and Milner, 1993). However, this evidence must be viewed in light of the limited capacity of the lesion approach to differentiate effects acting at encoding from those at retrieval.

The behavioural data, acquired during scanning, indicates that subjects were using the pre-learned list structure during retrieval in that the number of category shifts was much less than would be expected if subjects were not using such a structure.All subjects reported that they engaged in what might be described as "monitoring" of their list recall, checking backwards and forwards to avoid omissions and repetitions.

An unexpected finding in experiment 6, however, was of the double dissociation between activation of right DLPFC and right VLPFC/insula regions. Previous PET studies (Tulving et al, 1994b; Kapur et al, 1995; Haxby et al, 1996), including experiment 2 above, have not shown a ventral-dorsal dissociation, the majority indicating activation of both regions . This is unsurprising given that these studies did not seek to fractionate retrieval into possible component sub-processes. A study of the influence of monitoring demands upon a spatial working memory task, however, has shown evidence for regional specificity within PFC (Owen et al, 1996a), the greatest degree of monitoring being associated with a dorsolateral activation. In the current experiment, both areas showed significant activation when each of the memory tasks was compared with its control. However, in the direct comparison of the two types of retrieval, *Retrieval 1* was associated with significantly greater right DLPFC activation and *Retrieval 2* with significantly greater right VLPFC activation. *Retrieval 2*, unlike *Retrieval 1*, did not require that subjects refer to items than had already been retrieved or were yet to be retrieved. Why might this condition show significantly greater insula/VLPFC activity . One possible explanation is that retrieval specifications (determined by the cue that provides the subject with the memory search description) (Burgess and Shallice, 1996a) change more frequently and often in *Retrieval 2* and it is this that is reflected in the ventral activation. I shall return to this possibility in the concluding chapter.

While caution is necessary in comparing findings in human verbal memory with animal data, I suggest also that the observation in experiment 6 is consistent with theoretical perspectives derived from monkey experiments, where it has been suggested that VLPFC is concerned with acting directly upon the products of memory retrieval, particularly in relation to contextual operations (e.g. salience, temporal sequence). It

has been argued that the deficits in mnemonic tasks produced by ventrolateral legions arises because of disrupted judgement of mnemonic information (Petrides, 1994; Petrides, 1995). The dorsolateral region, on the other hand, is suggested to be required for "complex, high-level planning" of intended acts and for the monitoring of the retrieved information within working memory (Petrides, 1994). Thus, a lesion to DLPFC in monkeys produces profound deficits in tasks requiring that animals monitor their previous responses in order to guide their current response, but does not affect performance on simple delayed response and delayed alternation tasks (Petrides, 1995).

The findings from this study (especially when viewed in conjunction with the complementary encoding experiment – experiment 3) suggest that PFC has multiple roles in memory and that these roles may be reflected at the neuronal level with certain processes reflected in left PFC activation and certain ones in right PFC activation. Moreover, tasks emphasising different types of processing at retrieval are associated with anatomically separable activations within right PFC.

Note: Data from this chapter have been presented in the following publication
Fletcher PC, Shallice T, Frith CD, Frackowiak RSJ, Dolan RJ. The functional roles of prefrontal cortex in episodic memory. II Retrieval. Brain 1998 121: 1249-1256

Chapter 7

The roles of lateral PFC in episodic encoding and retrieval: a synthesis.

Introduction

The application of the functional neuroimaging techniques to human long-term memory has helped to motivate interest in the nature of frontal lobe contribution to these processes. The almost ubiquitous activation of lateral prefrontal cortex in association with memory encoding and retrieval tasks is a little surprising given the fact that prior neuropsychological studies have emphasised the importance of medial temporal cortex and diencephalic structures (Squire and Cohen, 1984). The importance of the frontal lobes in memory, while acknowledged, has been seen as subsidiary. It is difficult to equate this position with that emerging from functional neuroimaging. Clearly the two approaches have different strengths. Neuroimaging is more likely to be sensitive to the transient processes involved in encoding and retrieval. Accordingly, it appears likely that control processes accompanying these stages will be emphasised. The frequent prefrontal activation in functional neuroimaging studies is thus likely to reflect the nature of the technique, rather than any fundamental disagreement with the neuropsychological literature. In any case, one must bear in mind that different observations across different techniques are not necessarily incompatible.

With a growing body of work implicating frontal cortex in memory encoding and retrieval, the challenge is to understand frontal activations in terms of the underlying cognitive processes. The precise nature of these processes is unclear however and, since a brain activation is only meaningful with respect to the process manipulation that engendered it, interpretations of such studies is not straightforward. In view of the uncertainty surrounding the precise nature of the cognitive processes upheld by PFC, this consideration of the literature and the attempt to synthesise the findings reported in the preceding chapters will be articulated in terms of tasks used rather than through a strict adherence to a particular cognitive framework.

Nevertheless, an attempt will be made, in closing, to consider emergent patterns, from both memory encoding and retrieval studies in terms of broad regional parcellation of function and to discuss this parcellation in terms of existing models. Since the experiments carried out were all related primarily to verbal material, I shall confine my discussion of the broader literature to experiments using verbal stimuli (although some consideration will be given to likely effects of different types of material, particularly with reference to the lateralisation of frontal activations)

This chapter is divided into three parts. The first and second parts consider existing encoding and retrieval studies respectively. The third attempts to draw together findings from both stages and to consider the extent to which common or analogous processes are associated with overlapping frontal activations. Overall, the chapter will suggest that the experiments reported here, viewed in conjunction with the literature, provides insights into the function of two lateral frontal regions: VLPFC and DLPFC. These are the regions most commonly activated in memory-related tasks.

DLPFC consists of the area lying superior to the inferior frontal gyrus and VLPFC to the area below it, that is, the inferior frontal gyrus. The distinctions are slightly blurred by imperfect spatial resolution of the imaging techniques and the enormous inter-subject anatomical variability. Moreover, I do not consider this distinction to be in any way final: it is most likely that these areas will themselves be shown to be functionally sub-divided. The distinction is made with a view to finding a balance between problems posed by the limited spatial information provided by group studies (particularly with PET) and problems that would arise from treating clearly separate regional responses as undifferentiated ''frontal'' activations. Thus, I concede that, in several of the experiments reported here (and, indeed, in the functional

neuroimaging literature, generally) one cannot be sure whether an activation lies above or below the inferior frontal sulcus. The sub-division settled upon here is based on existing functional imaging data, rather than micro-structural findings. Of course, the macro-anatomical features may be considered to provide some clues to underlying anatomy. VLPFC corresponds loosely to Brodmann's areas 44, 45 and 47, DLPFC to areas 9 and 46. I wish, however, to avoid relying upon the uncertain and inconsistent relationship between macroscopic sulcal/gyral features (onto which the PET and fMRI activations are mapped) and Brodmann's areal boundaries (Roland et al, 1997; Zilles et al, 1997; Amunts et al, 1999). Since functional neuroimaging provides macro-anatomical information and since this macro-micro anatomical relationship is uncertain and variable, I shall avoid the use of Brodmann's nomenclature. The chosen sub-divisions are likely to reflect differences in patterns of connectivity, too (Passingham, 1993; Fuster, 1997). As one cannot be certain,of the precise relationship between connectivity and macro-anatomical landmarks, I shall also refrain from further speculation in this regard. Finally, in considering the literature emerging in this field I shall confine myself to studies of groups of young, healthy individuals performing auditory-verbal episodic memory tasks.

In many ways, a review of the dorsal-ventral distinction in human PFC is incomplete when confined to episodic memory since much interesting work has been done in the setting of working memory tasks. Furthermore, it seems most likely that the processes considered to be supported by lateral PFC will transcend the distinction between long-term and working memory. However, for reasons of space I will not consider the vast working memory literature but point to an expanded discussion of this area (Fletcher and Henson, 2001).

Separating encoding from retrieval processes

Most neuroimaging experiments of long-term memory consist, like those in the experiments reported here, of two phases: a study phase, in which multiple stimuli are presented (with or without explicit instructions to remember the stimuli) and a test phase, during which those stimuli must be recalled, or recognised from amongst other stimuli. A clear methodological advantage of functional neuroimaging over neuropsychology is in the possibility of dissociating the encoding and retrieval stages of episodic memory, given that it is difficult to attribute a patient's anterograde memory deficit specifically to either an encoding or a retrieval problem. Neuroimaging attempts to dissociate encoding and retrieval are rarely straightforward however since the two stages may share a number of sub-processes. For example, both are likely to involve searches of semantic memory, firstly to produce a rich memory trace of the encoding episode, and later to generate cues that aid access to that trace. Furthermore, an attempt to retrieve a word from episodic memory may result in a train of associative thought that can then become the substrate of a further encoding episode. Thus the encoding-retrieval distinction is driven more by the format of the typical episodic memory task than by consideration of the executive processes involved. Nonetheless, one goal of functional imaging researchers over the last few years has been to isolate more specifically the cognitive processes that differentiate encoding and retrieval and this attempt has been the main theme of my initial experiments. The encoding-retrieval distinction provides a useful means of organising my review of the experiments reported here and of neuroimaging research in general.

7.1 PFC function in episodic memory encoding.

Bearing in mind the difficulties discussed in chapter 1 (1.1.4), with respect to defining what, precisely, constitutes encoding, I refer to it here it in operational terms as

the process(es) associated with subsequent explicit (conscious) memory retrieval. Experiment 1, examining memory encoding, showed evidence for engagement of left PFC. This is a functional lateralisation that has been observed and commented upon, forming part of the influential HERA model (Hemispheric Encoding Retrieval Asymmetry), which associates greater left than right PFC activation with episodic encoding, and greater right than left PFC activation with episodic retrieval (Tulving et al, 1994a). Furthermore, the left PFC activation during encoding is found whether or not subjects are aware that their recall will be tested later, that is, when encoding is "incidental" to task demands. The evidence for left PFC activation in incidental encoding comes from studies that manipulate the degree of semantic processing of verbal material (a ''depth of processing`` manipulation (Craik and Lockhart, 1972)) Kapur et al. (Kapur et al, 1994), for example, showed left VLPFC activation in association with a deep encoding task (judging whether words referred to living or non-living entities) compared with a shallow encoding task (judging whether words contained the letter 'a'). In this study, subjects were unaware that their memory would be tested subsequently.

In experiment 1 (chapter 3) a similar observation was made to that of Kapur and colleagues. In this case, paired associates were intentionally encoded. The observed left VLPFC activation was attenuated when learning occurred in the presence of a distracting motor task. The fact that this distraction was associated with impairment in subsequent cued recall is perhaps suggestive of a further attribute of encoding-related left VLPFC activation: an intimate relationship with subsequent retrieval success. Subsequent evidence appears to confirm this. For example, using an event-related or trial-specific experimental design, (Wagner et al, 1998c) showed that activity in left posterior VLPFC was higher during presentation of words that were subsequently

remembered confidently than those forgotten. Given that the study task remained constant, this is more direct evidence that left PFC region is related specifically to successful encoding. (Brewer et al, 1998) showed *right* PFC activity associated with encoding success when material was visuo-spatial. This difference in lateralisation, which may be material-dependent, will be discussed later.

7.1.1 Theories of PFC contribution to encoding.

I suggested in chapter 5 that a number of positions have been taken up with regard to the possible role of left VLPFC in association with semantic processing and episodic memory encoding. I shall review these more fully here, particularly with respect to the question of whether my encoding studies offer insights. It has been suggested that VLPFC is important to: (i) the *Generation/Retrieval* of semantic attributes and associates of a word (Tulving et al, 1994a), (ii) the *Maintenance* (in "semantic working memory") of those attributes and associates (Gabrieli et al, 1998), (iii) the *Selection* of task-appropriate attributes or associates from among those associated with the word (Thompson-Schill et al, 1997), (iv) The *Control*of semantic retrieval (Wagner et al, 2001) and, finally, (v) the *Organisation* of multiple words or associates on the basis of these semantic attributes. (The latter position is the one that drives experiment 3). I shall refer to these positions as the *Generation, Maintenance, Selection, Control* and *Organisation* views of the left PFC contribution to encoding.

It is difficult to differentiate fully between these positions, either descriptively or experimentally as they seem to form a hierarchy: Semantic information cannot be maintained on-line until it is first generated, and cannot provide the basis for selection without on-line maintenance. Furthermore, control of retrieval requires an iterative movement through all of these more basic processes. Finally, effective organisation of

multiple items is unlikely to proceed unless appropriate attributes have been retrieved, maintained and selected. This makes the picture very complex and I do not think that conclusions can be drawn on the basis of existing literature. However, I shall now consider these positions in more detail and attempt to reframe my own encoding experiments in terms of the relevant ones.

7.1.1a Semantic Generation

Clearly, left PFC, particularly VLPFC, is involved in semantic processing of verbal material (Petersen et al, 1988; Raichle et al, 1994; Binder et al, 1997; Gabrieli et al, 1998). This effect may generalise to pictorial material (Vandenberghe et al, 1996; Wiggs et al, 1999). Furthermore, it seems unlikely that this frontal activation simply reflects the fact that semantic processing tasks are simply more 'difficult' (e.g., more demanding of attentional resources) than their control tasks since Demb and colleagues showed that left posterior VLPFC is more active during a deep than shallow encoding task, but this activation was insensitive to task difficulty (Demb et al, 1995). Moreover, it is often the case that shallow tasks are chosen to take longer and be subjectively more difficult than deep tasks (Otten et al, 2001). Since semantic processing is normally associated with better subsequent memory, Tulving and colleagues (Tulving et al, 1994a) suggested that the left PFC activation is related to successful encoding. Indirect evidence for this comes from the observation that the left frontal activation associated with verb generation is stronger when subjects were performing the task initially and it attenuates with practice (Raichle et al, 1994). A similar pattern of left PFC response is seen when subjects make repeated semantic decisions (Demb et al, 1995). Kopelman and colleagues have linked this effect more directly to memory function (Kopelman et al, 1998). They showed that the more learning that occurred (in a verbal learning task), the greater the level of activation in left DLPFC. Activation of left VLPFC was

associated with novel compared to repeated words. These findings are consistent with the encoding into episodic memory only occurring for novel processing of the study material and accord also with those reported in chapter 5: experiments 5a (indirectly) and 5b (directly) indicate that left PFC shows a reduction in activity as material is learned but that this attenuation disappears when subjects must attend to novel semantic attributes of the same material.

Tulving and colleagues suggest, therefore, that the left VLPFC activation, associated with incidental and intentional verbal encoding tasks, and with tasks engaging semantic processing (in the absence of any direct reference to episodic memory), is associated with the generation/retrieval of semantic material: a critical feature of episodic memory encoding.

7.1.1b Semantic Maintenance

Gabrieli and colleagues have suggested a modified view of VLPFC function in semantic processing: a role in "domain-specific semantic working memory" (Gabrieli et al, 1998). This relates to a broader view (Goldman-Rakic, 1998) that PFC may be sub-divided on the basis of the domains over which working memory processes operate. This would be consistent with observations made in studies of semantic generation cited above. Gabrieli and colleagues sought to test this by comparing brain responses to two types of word stem completion. In the first type, the word stem could be completed in many ways (e.g. ''STA...''). In the second, they used word stems that could form the beginning of only a limited number of words (e.g. ''PSA...''). Subjects were instructed to complete each stem with the first word that came to mind. In this way they tried to dissociate the effort or search required in generating a response (maximised when word stems allowed few possible completions) from the amount of material that

subjects produce in making their response (maximal when the stems had many completions). They found greater left PFC activation in association with word stems offering many rather than few possibilities, and concluded that this activation reflected the increased amount of material that was maintained in semantic WM. The precise location of this activation appeared to be more dorsal than that reported by Kapur and colleagues (Kapur et al, 1994) and that found in experiment 1. However, in experiments 3, 4(chapter 4) and 5a and 5b (chapter 5) activations were seen in a more dorsal part of VLPFC in association with a series of tasks manipulating semantic processing within an encoding task. These activations are close to those reported by Gabrieli and colleagues (although it is difficult to be precise since no coordinates are available in their experiment).

However, while intriguing, the experimental manipulation devised by Gabrieli and colleagues does not differentiate maintenance of semantic information from processes associated with the selection of one response from a set of possibilities (since selection is likely to be more demanding when there are more possibilities). Gabrieli et al. acknowledge this and ponder whether ''the amount and selection of information are inevitably intertwined or whether those two processing dimensions can be dissociated``. Attempts to achieve this and to address the question of whether the core function of left PFC lies in *selection* is addressed in the next section.

7.1.1c Selection

Thompson-Schill and colleagues provide two pieces of evidence to support their assertion that left VLPFC activation reflects the selection of semantic attributes from competing alternatives (Thompson-Schill et al, 1997; Thompson-Schill et al, 1999). In an initial study, they manipulated selection demands within three types of task:

Generation of an appropriate response, *Classification* of a stimulus, and *Comparison* of two or more stimuli. Each task was performed at two levels: *high selection* and *low selection.* Their prediction of increased left PFC activation in high selection compared to low selection conditions was borne out in each of the three tasks. Interestingly, the focus of common activation appeared to be in more posterior and dorsal regions of VLPFC and, indeed, for two of the tasks, Classification and Comparison, localises to DLPFC in that appears to lies above the inferior frontal sulcus. Their design may be criticised in that it is not absolutely clear that they have produced pure manipulations of selection in each of the tasks. For example, in the case of the *Generation* and *Classification* tasks, the High selection condition was likely to involve the retrieval of a greater number of stimulus features than the low selection condition. In the *Comparison* task they were more confident of a purer *selection* manipulation since, in the high selection condition, subjects made a decision on the basis of a pre-specified dimension (colour, function or shape), whereas, in the low selection condition, a comparison judgement was based upon global features. If anything, they argued, more semantic features were likely to be produced in the latter task than the former task.

Their second study manipulates selection processes through the introduction of competing responses (Thompson-Schill et al, 1999). Subjects were scanned while generating colours or actions appropriate to cue words. Scanning occurred on the second presentation of these cues, and two conditions were compared. In the "high competition" condition, an action had to be generated to a cue word previously generating a colour (or vice versa). In the "low competition" condition, the same task (action or colour generation) was performed on a cue word during its first and second presentation. The high competition condition produced greater left posterior VLPFC activation, as predicted, consistent with increased selection demands (by assuming that

the semantic attributions produced by the first presentation compete with those produced during the second presentation).

The finding from experiments 5a and 5b (chapter 5) provide support for the selection hypothesis. In both experiments, activity in left DLPFC was greater during encoding of word paired-associates that had already been presented in different pairings than when they were novel. In experiment 5b, the use of fMRI allowed scanning throughout this cycle so that changes in PFC could be observed as pairs became increasingly familiar and then when they were rearranged to emphasise a different semantic relationship. Left VLPFC/inferior frontal sulcus was activated when initial learning was compared to the baseline task. In keeping with previous observations (Raichle et al, 1994; Demb et al, 1995), repeated learning of the same pairs was associated with reducing levels of activity in this region. When the words were re-paired, this activation increased again. Furthermore, this activation was significantly greater than when a completely novel set of words was presented. The latter suggests that it is not word novelty *per se,* but novelty of the semantic processes performed on those words, an observation consistent with an association between left PFC and a requirement to select from among semantic attributes. The question of whether it was DLPFC or VLPFC that was sensitive to these experimental manipulations is a difficult one. For the most part, the activations lie in or just above the inferior frontal sulcus, close to the macro-anatomical border that demarcates the two regions. Strictly speaking, the activations should probably be localised to DLPFC (the same is true for some of the activations reported by Thompson-Schill and colleagues).

7.1.1d Control

Wagner and colleagues have also considered the role of left VLPFC in terms of retrieval of material from semantic memory. However, they propose that its specific role lies in *Control* of retrieval irrespective of whether selection from among competing items is required (Wagner, 2001). Such control processes would be called into play when the cue that provokes the recovery of semantic information does not strongly specify what, precisely, should be recovered. In contrast, when the cue has a good deal of semantic overlap with the required response, it may be sufficient to facilitate retrieval without a need for the top-down control putatively associated with left VLPFC.

They tested this hypothesis in an event-related fMRI study. Strength of relatedness between cue and targets was taken as an inverse measure of the degree to which control processes would be invoked. Subjects were required to judge which of two words were most closely associated with a cue. In "low control" tasks, the correct response was associated strongly with the cue (e.g. cue – CANDLE; target choice FLAME and BALD). In the task designed to require a high degree of retrieval control, the correct response was only weakly related (choice: EXIST or HALO). In addition, they varied the number of possible targets, from which to choose, between two and four. Left VLPFC activation was seen when contrasting weak with strong cue-target relatedness and four item with two items. They argue that this finding is compatible with a role in the control of retrieval and that, since there is no reason to suppose that selection demands would change across these tasks, that this position is untenable.

7.1.1e Organisation

It is clear from behavioural experiments that divided attention at study impairs subsequent memory (Baddeley et al, 1984), and organisation of study material aids subsequent memory (Segal and Mandler, 1967). In experiment 3, I manipulated both

the level of attention and degree of organisation of study material. Left DLPFC activity was maximal when organisational demands were greatest and this organisation-related activation was vulnerable to (i.e. was attenuated by) the distracting motor task. Subsequent retrieval was also correspondingly impaired. I concluded that the left DLPFC activation reflected the organisation of study material, and that the distractor task disrupted this process. This evidence in favour of left PFC contribution to organisational processes at encoding is not necessarily incompatible with the other views (discussed above), partly, because organisational processes would demand the processes already referred to (semantic retrieval, maintenance and selection). In addition a more dorsal activation probably reflects a functional specialisation that differs from that of ventral regions more commonly reported in perhaps less demanding tasks.

More recent evidence in favour of the Organisation position comes from a study by Savage et al who showed that left VLPFC and DLPFC (the latter with a focus at identical coordinates to those reported in experiment 3) were active in response to an increasing tendency to cluster words, according to semantic attributes, in an encoding task (Savage et al, 2001). Additionally, Wagner and colleagues, using fMRI, presented subjects with three words that they either had to maintain in the same order for a short period (using sub-vocal rehearsal), or to reorder along some abstract semantic dimension (e.g. pleasantness) (Wagner, 1999). Both tasks activated left VLPFC, but the reordering task produced greater additional activation of left DLPFC. The reordering task led to better subsequent memory, also implicating this region in encoding. This result is consistent with an association between organisation, encoding and DLPFC as suggested by experiment 3.

Finally, with regard to the functional significance of left PFC in episodic memory encoding, it is worth reconsidering the view proposed by Frith that activation of DLPFC reflects ''sculpting of the response space`` (Frith, 2000) (see chapter 5). With regard to the neuroanatomical correlates of such "sculpting" processes, Frith postulated DLPFC to be crucial. As described above, it is not entirely clear whether the majority of studies support this localisation since a number of them have emphasised the role of VLPFC. At present, one should be cautious with respect to this localisation, especially given that the border between ventral-most DLPFC and dorsal-most ventral PFC is not always clear. In the next section, however, I shall make some cautious attempts to draw interim conclusions on the basis of this review and of the experiments reported in preceding chapters.

7.1.2 Encoding: interim conclusions

The set of proposals outlined above may provide a useful heuristic within which to frame imaging studies and develop imaging paradigms. Attempts to distinguish between possible explanations of PFC contribution to memory have, however, met problems. The suggested processes are intimately related and, descriptively at least, hierarchically organised. At what point does semantic retrieval merge into semantic maintenance? How could we have selection without retrieval and maintenance and, if we wish to increase selection demands, how do we do so without making greater demands on retrieval/maintenance? How might we increase demands to control semantic retrieval or to organise studied items without increasing the demand to select the semantic features that form the basis for an organisation scheme? In short it may prove difficult to apply the standard imaging experimental design – in which groups of cognitive processes must be subtracted from each other, leaving the processes of interest – to address this multi-level model of processing. It certainly seems unlikely that any single experimental manipulation could perform this function satisfactorily. Moreover, we must remind ourselves that this is a descriptive model whose validity at the neurobiological level is unproven. It may ultimately turn out that the patterns of imaging findings may be more parsimoniously interpreted with respect to another model.

Bearing in mind these caveats, it remains worthwhile to attempt a synthesis of the existing findings with respect to the processes reviewed. First, it is both compelling and consistent that tasks requiring basic semantic processing of stimuli are associated with activation of various regions of left VLPFC and, on occasions left DLPFC. Such processing optimises encoding (i.e. it improves levels of subsequent retrieval) but, for this to occur, subjects need not be actively trying to remember the material. Almost

invariably, the semantic processing requirements encompass semantic retrieval, maintenance and selection and the common region of frontal activation is in VLPFC. It has been suggested that the locus of semantic-related activation may lie in an anterior portion of VLPFC but this has not proved entirely consistent. Thus, while Poldrack et al provide convincing evidence that this is so (Poldrack et al, 1999), Thompson-Schill et al localise it to a posterior region of VLPFC, extending into DLPFC (Thompson-Schill et al, 1997; Thompson-Schill et al, 1999).

In addition to this localisation of the semantic processing requirement to VLPFC, Otten and colleagues have shown that, in the setting of both a semantic and a non-semantic task, a left VLPFC region shows activity that is predictive of subsequent memory (Otten et al, 2001). Moreover, there is, within subjects, overlap between the regions subserving semantic processing and those predicting subsequent memory, even when the task demands do not require semantic processing.

While imaging evidence therefore suggests that VLPFC activation is strongly related (though in a way that is yet to be fully ascertained) to memory encoding, there are also studies in which DLPFC activation is observed. The dissociation between ventral and dorsal activations is not complete but there may be a broad pattern emerging. More dorsal activation is seen when the task demands are greater than simple semantic processing. Thus, the requirement to reorder or to organise are associated with DLPFC activity (experiment 3, [Wagner, 1999 #39; (Savage et al, 2001)). Additionally, in tasks where stimuli were processed in conditions that contrasted with previous presentations of the same stimuli, dorsolateral activation was observed (experiment 5a, 5b (Thompson-Schill et al, 1999)) . Further, the explicit

manipulation of "selection" demands (Thompson-Schill et al, 1997) produces dorsolateral in addition to ventrolateral PFC activation.

There are thus grounds for making an initial distinction between ventrolaterally- and dorsolaterally-mediated processes: the latter occurring in response to demands to process stimuli with greater specificity and with respect to their relationship to other stimuli especially when this relationship forms the basis for a reordering or grouping. This is an inexact observation however and there are exceptions: for example, Petersen and colleagues found that DLPFC activation occurred during simple word processing without any apparent higher demands (Petersen et al, 1988). Intriguingly, too, Poldrack and colleagues showed that activity in dorsolateral PFC was higher for non-semantic (case and phonological) than for semantic judgements (Poldrack et al, 1999). However, notwithstanding the apparent inconsistencies, I believe that this is an observation that invites further consideration.

One further consideration concerns the lateralisation of encoding/semantic related PFC activations. The HERA (Hemispheric Encoding Retrieval Asymmetry) model of frontal contribution to episodic memory (Tulving et al, 1994a) was based on early observations that many semantic tasks and encoding tasks were associated with left PFC activation and many retrieval tasks were associated with right PFC activation. It has been influential in framing functional neuroimaging findings. It has subsequently been suggested, however, that lateralisation of activation reflects the material that has been used rather than the memory stage that was imaged. If this were so, we would expect to find that encoding of non-verbal material produces right-sided activation. Kelley and colleagues have confirmed this, showing that encoding of words is associated with left (dorsolateral) PFC activation, encoding of nameable objects with

bilateral PFC activation and encoding of unknown faces with right PFC activation (Kelley et al, 1998). Wagner and colleagues also demonstrated material-related lateralisation of PFC activation in an encoding task (Wagner et al, 1998b). Most convincing perhaps is Grady and colleagues' direct comparison showing that left VLPFC activity is significantly greater with encoding of words compared to pictures (Grady et al, 1998). In addition to these findings, we should bear in mind that some studies exploring the encoding of verbal material have produced right as well as left PFC activation (Thompson-Schill et al, 1997; Poldrack et al, 1999; Otten et al, 2001) . Furthermore, the lateralisation appears to be process-dependent (Fletcher et al, 2002).

(As I shall discuss, while the lateralisation of encoding activations may be explicable in terms of the almost invariable use of verbal material, the HERA model may not be dismissed easily in the face of the huge number of verbal retrieval studies that show right PFC activation. We should also bear in mind that the model was formulated to deal specifically with verbal (or verbalisable) material. Tulving and colleagues were clear that the same lateralisation may not apply to non-verbal encoding and retrieval).

7.2 PFC function in episodic memory retrieval.

The experiments reported in chapters 3 and 6 focussed upon the cognitive processes controlling retrieval. In considering the result of these studies, it is necessary to explore the nature of retrieval processes and the ways in which researchers have fractionated them and attempted to manipulate them. A number of possible retrieval processes and strategies have been put forward. These include the cueing and interrogation of an episodic memory ''store``, the re-entry of episodic information into working memory (''ecphory``, (Tulving, 1983)) and the evaluation or monitoring of this

information. Further, higher level functions, such as the development of retrieval strategies and metamemory reasoning, should also be considered since all contribute to the observed patterns of brain activation. Because psychological models of these retrieval processes are still under development, I shall, at the outset, review imaging studies in the terms in which they were formulated. I will consider them in terms of more basic, operational distinctions between, for example, retrieval attempt and retrieval success (Tulving et al, 1994b; Kapur et al, 1995; Nyberg et al, 1995; Rugg et al, 1996) rather than broad and incomplete models. I will also attempt to consider existing studies in association with the two retrieval studies reported here. I believe that, as with the section on encoding, some patterns, albeit inconsistent ones, are beginning to emerge.

7.2.1 The nature of the retrieval task

In attempting to make sense of the results that have emerged from functional neuroimaging studies of memory, there are a number of ways in which the literature may be organised. Here, I shall categorise retrieval studies into those exploring the effects of the retrieval task itself (effects dependent upon, for example, task instructions, or the nature of retrieval cues) and those manipulating the amount of information retrieved (such as the ratio of old to new items, or the depth with which the items were originally studied). This is not to say that studies that come under different sub-headings isolate distinct retrieval processes. Indeed, as I shall discuss, interactions between these two factors have been observed. Ultimately, I wish to formulate the results in terms of a specific retrieval model, based on that of Burgess & Shallice (Burgess and Shallice, 1996a).

As with the Encoding section, I focus primarily on imaging studies that, like those reported here, have used verbal material. In fact, these form the majority of episodic memory retrieval studies.

7.2.1a Intentional versus incidental retrieval

The feeling of a memory simply 'coming to mind', in the absence of any particular aim to recall it, is a familiar one. This contrasts with the intentional retrieval of previously studied items, which subjects may find effortful and attention-demanding and which they may attempt to achieve through controlled and strategic memory searches. Experiment 2 (chapter 3) explored the effects of cued retrieval compared to a low level baseline and a semantic retrieval task. Experiment 6 evaluated free recall compared to cued recall, and vice-versa. In both cases, therefore, I used tasks that may make explicit demands upon the retrieval system rather tasks that emphasised incidental memory recall. Furthermore, the tasks that I used (particularly in experiment 6) were deliberately chosen to characterise a demanding and strategic approach. The extent to which the results of these experiments are applicable to retrieval generally or are specific to instances of paired associate or free recall must therefore be a matter for speculation. However, I believe that the results of these two experiments can be integrated with the results of experiments that have used alternative methods of cueing retrieval and will attempt to discuss the entire field in this concluding chapter.

One of the earliest functional imaging studies of retrieval provided some clues as to the neurophysiological effects of both intentional and incidental retrieval. Squire and colleagues showed that, when subjects used word stems (e.g. GAR...) as the basis for retrieving previously presented words (e.g. GARAGE), activation in bilateral PFC was greater than when they were instructed merely to complete stems merely with the

first word that came to mind (Squire et al, 1992). The activation was located in right and left anterior PFC (APFC) and in right DLPFC. This latter activation was located anterior to the foci of activation seen in experiments 2 and 6. The authors suggested that it reflects the undertaking of a memory search, especially in view of the fact that the same APFC region did not appear sensitive to two different incidental conditions in which the word-stems did, or did not, happen to match studied words. This finding was subsequently replicated with respect to the right APFC activation (Buckner et al, 1995).

Subsequently, Rugg and colleagues used PET to replicate and extend this result. Their task study used a manipulation of two factors (intentional versus incidental recognition memory) and depth of prior encoding (deep versus shallow). In the intentional condition, subjects indicated whether or not they had seen each word in the previous study phase. In the incidental condition, subjects were aware that some of the words had previously been seen, but simply had to decide whether each word was animate or inanimate (i.e. this task required semantic but not episodic retrieval). They showed that several regions of PFC were more active during intentional than incidental recognition. In particular, consistent with experiments 2 and 6, they showed that right DLPFC is significantly more active during intentional recognition. They also showed a region of right APFC to be responsive to intentional recognition, with this effect occurring to a significantly greater extent when the words were more difficult to recognise because they had been studied under shallow encoding conditions (Rugg et al, 1997).

So, the studies reported here and those of Squire et al and Rugg et al, suggest that retrieval-related right PFC activations occur primarily during intentional memory search (or when the subject adopts a "retrieval mode", (Tulving, 1983)). The latter two

studies also provide evidence for involvement of a further frontal regions in retrieval, one not identified by either experiments 2 or 6: right APFC. Activation here seems to occur when memories are weak or difficult to retrieve (though this is not entirely consistent as will be discussed).

7.2.1b Paired Associate Cued Recall, Free Recall, Recognition and Source Memory.

Intentional memory retrieval may be tested in a number of ways. Generally, experimental manipulations of the degree to which subjects are prompted in their recall of an encoded event or stimulus are made. In tests of recognition, the prompt is most direct and complete ('copy cueing'). That is, subjects are prompted with, for example, an entire word and required to indicate whether or not it was among those that were studied. In tests of free recall, subjects are completely unprompted. In between these two extremes are varying degrees of prompting. For example, subjects may be presented with an associate (semantic or otherwise) of the item that was previously seen (paired associate cued recall), or they may see some portion of the item and use this to recall the whole. In the case of words, for example, the first two or three letters of the word may be presented (stem-cued recall) or perhaps only selected letters (fragment-cued recall). A source memory task is really defined by the nature of the information that must be retrieved. A subject is not merely required to specify whether an item was previously presented but also the context (or 'source') of that memory. To some extent source memory tasks may be considered as another variation on the type of cueing that is presented since the subject uses the retrieved item as a cue to provide the further information that is required. All of these manipulations, as I shall discuss, produce large effects on the position and magnitude of neurophysiological responses. I suggest that these effects are explicable in terms of subjects' strategic approaches to the task.

Experiment 2 shows that paired associate cueing, in comparison to a control task in which subjects were required merely to repeat stimuli aloud, was associated with activation in right DLPFC and a posterior region of right VLPFC. A condition in which free associates were generated in response to a new set of categories did not produce any right PFC activation when compared with the same control task, suggesting that right PFC activation reflected episodic rather than semantic retrieval. No APFC activation was associated with episodic retrieval in this study, unlike the intentional stem-cued and recognition tasks referred to above (Squire et al, 1992; Rugg et al, 1997). This may reflect stronger memories (that come to mind more easily) in the paired-associate task, particularly given the strong and relatively novel (for the subject) semantic relationship between the category and exemplar in any given pair.

I and colleagues carried out a follow on cued recall study (not included here) exploring the effects of a parametric variation in the strength of semantic relatedness between word pairs (Fletcher et al, 1996). Lists of word-pairs varied in designation from '5' (close semantic associations) to '0' (no clear semantic relationship, i.e. randomly paired words). To control for the ease with which the cue prompted the appropriate response during retrieval, randomly and weakly-related pairs received more study trials, so that overall performance at test was approximately balanced across the six levels of relatedness. PET scanning during retrieval revealed bilateral DLPFC and APFC activations that decreased as the semantic relatedness between cue and response decreased (i.e., from 5 to 1). However, for a right APFC region among others, this trend reversed: when moving from weakly-related to random pairs (i.e., from 1 to 0) activity here increased. Our speculation, highly conjectural, was that this U-shaped pattern of right APFC activation reflects different amounts of post-retrieval

"monitoring". When word-pairs are strongly related semantically, the response elicited by the cue during retrieval may require further processing to establish that it was not simply an automatically generated associate (i.e. to check that it came from episodic rather than semantic memory). When word-pairs are completely unrelated however, there is increased vulnerability to a different type of error: the production of an associate that was previously presented but paired with a different cue in the study list. Thus for the two extremes – strongly related and unrelated – post-retrieval monitoring would be maximised, with a resulting activation of right APFC. This monitoring hypothesis is also consistent with greater right APFC activation during intentional than incidental retrieval tasks (Squire et al, 1992), and when memories are weaker (Rugg et al, 1997), both situations where close monitoring of retrieved information is required.

In the study comparing paired associate cued recall with free recall (experiment 6) a double dissociation was seen between activation of right DLPFC and posterior VLPFC as a function of retrieval task. Right DLPFC activity was greater during free recall, whereas right VLPFC activity was greater during cued recall. DLPFC activation is perhaps attributable to the additional monitoring processes that are required during free recall in order, for example, to ensure that no items are repeated or omitted during recall. This conception of monitoring is related to, but possibly distinct from, the use of monitoring in checking response appropriateness in the study varying semantic relatedness (Fletcher et al, 1996). The greater VLPFC activation during cued recall may be attributed to the fact that each response was retrieved on the basis of a different, external, semantic cue. In other words, each cue defined a new search space within which to select a candidate response, and more such search spaces would be defined, on average, in the cued than free recall condition. This is consistent with the right VLPFC activation during paired associate recall (relative to simple repetition) reported in

experiment 2. However, in a study comparing cued and free recall, Petrides and colleagues found the opposite pattern of response in VLPFC (Petrides et al, 1995). This is perhaps explained by the fact that, in this study, items for cued recall were fewer and were well-practised. A further difference between experiment 6 and that of Petrides' group is that I used a free recall task that could be (and was) approached in a strategic manner by virtue of the semantic structure within the list. Perhaps this encouragement of a strategic search approach accounts for the DLPFC activation seen here.

Another inconsistency lies in the findings of Cabeza and colleagues who showed that neither VLPFC nor DLPFC differentiate between cued recall and recognition memory tasks (Cabeza et al, 1997a). This finding, too, may be at odds with the notion of DLPFC in the monitoring processes evoked when retrieval is less specified or more demanding. However, since performance was carefully matched across the two tasks, it is feasible that monitoring requirements did not differ. In another PET study, (Cabeza et al, 1997b) presented two words to subjects at test, and required either a two-alternative forced choice recognition between a studied and nonstudied word in one condition, or a judgement of recency between two old words in another condition. The only PFC difference between these two conditions was seen in a right DLPFC region that was more active during recency judgements than during forced choice recognition. This pattern is consistent with a role for DLPFC in "source monitoring", in which temporal or spatial context information is retrieved from the study episode in order to make the appropriate response. It is consistent, too, with a subsequent study of both temporal and spatial source retrieval (showing bilateral DLPFC sensitivity to both) (Henson et al, 1999c) but appears to be at odds with studies of Nyberg et al and of Rugg et al (Nyberg et al, 1995; Rugg et al, 1999). In both these studies comparisons were made between source and simple recognition memory. In the former, no PFC region

showed greater activation in source memory (indeed, right VLPFC activation was greater for the recognition memory task). In the latter, left APFC and VLPFC were relatively more active in a spatial source judgement task. It is therefore, difficult to equate the results of these latter two source memory tasks with the idea that DLPFC is important to some form of retrieval monitoring. It should be remembered however, that in Rugg et al's study, steps were taken to optimise source retrieval (by designing study tasks to optimise the encoding of source information). Such a manipulation may have had some effect upon the degree to which monitoring became necessary at the retrieval stage.

The study of Henson and colleagues (Henson et al, 1999c) is worth considering in more detail with respect to the findings from experiment 6. They presented study words either high or low on the screen, and in one of two lists. In the standard recognition task (the "Inclusion" condition), subjects had to respond "yes" to studied words, which were randomly intermixed with a set of new, unstudied words. In a second recognition condition (the "Exclusion" condition, based on Jacoby (Jacoby, 1996)), subjects responded "yes" only to words that were studied in a specific spatial or temporal context, i.e. either high or low on the screen, or in the first or the second of the two study lists. Direct comparison of the Exclusion versus Inclusion task revealed bilateral DLPFC activation. They attributed this activation to source monitoring, during which the feeling of familiarity associated with studied words had to be checked against explicit retrieval of the study context. Furthermore, though bilateral VLPFC regions were more active in the Inclusion condition than in a simple perceptual Control condition, the activity of these regions did not appear to differ between the Inclusion and Exclusion tasks. The latter is consistent with the suggestion above and in chapter 6 (on the basis of experiment 6), that VLPFC is involved in retrieval cueing since, in both

the inclusion and the exclusion conditions, each new cue would specify the conditions for the next memory search.

7.2.2 Amount of Information Retrieved

The memory searches referred to above are, usually, a prelude to the retrieval of information. This successful retrieval, together with the processes that then act upon its products, must have their own neuronal signatures. We must therefore consider the extent to which actual retrieval and its sequelae contribute to the frontal activations seen in episodic memory studies. This question has led to a number of studies exploring neuroimaging differences between 'retrieval attempt' and 'retrieval success' (Kapur et al, 1995; Nyberg et al, 1995; Rugg et al, 1996). Such a manipulation, particularly within the constraints of the blocked design demanded by PET, has proved difficult. One method of varying the probability of retrieval success in PET designs is to manipulate the ratio of studied to unstudied words during the scanning. With event-related designs, old and new words in a recognition task can be randomly intermixed, and, furthermore, responses to correct and incorrect decisions can be separated and compared.

While experiments 2 and 6 do not allow a separation of attempt- and success-related activations, they must nevertheless have produced activations evoked by, or contingent upon, successful retrieval. This makes a consideration of the studies that have attempted this dissociation potentially worthwhile. The following three sections attempt to do this. First, I consider attempt/success effects in recognition memory tasks (both block and event-related designs). Then, I consider an alternative approach to this question: the manipulation of pre-retrieval depth of encoding. Finally I draw attention to the likelihood that regions sensitive to retrieval success are most likely to be

dependent upon the nature of the retrieval task and vice-versa. In all cases, where relevant, I shall speculate upon the relevance of these studies to my findings.

7.2.2a Amount of information retrieved: Recognition.

One of the earliest studies of episodic memory retrieval entailed a comparison between a condition in which retrieval success was high and one in which it was low, by virtue of the fact that in the former, most material had been studied whereas in the latter it was unstudied (Tulving et al, 1994b). Retrieval success (predominantly studied items) was associated with right APFC and VLPFC activation, together with left APFC activation. Subsequent PET recognition studies, however, showed no differential right PFC activation as a function of the studied:unstudied ratio, from 3:20 to 17:20 (Kapur et al, 1995), or from 0:20 to 20:20 (Nyberg et al, 1995). Nonetheless, right VLPFC and DLPFC activation was found when both high and low studied:unstudied ratio conditions were contrasted with a control task (of animacy judgements and reading respectively), suggesting that these regions are engaged in retrieval attempt (or the adoption of a "retrieval mode"), rather than retrieval success. So, an apparent inconsistency arose at an early stage. The earliest work suggested a right PFC sensitivity to retrieval success but the later studies related these activations to retrieval attempt.

Later work produced evidence in favour of an activation in right PFC and success (Rugg et al, 1996; Rugg et al, 1998). The relationship was not a linear one however: activations in right DLPFC and bilateral APFC increased from a studied:unstudied ratio of 0:20 to 4:20 and from 0:20 to 16:20, but not from 4:20 to 16:20. Rugg and colleagues suggested that PFC activity associated with retrieval success, at least as measured in these blocked PET designs, quickly asymptotes as the studied:unstudied ratio increases. This might explain the presence of right PFC

activation in a 20:20 versus 0:20 comparison (Tulving et al, 1994b), and the failure to find right PFC activation in a comparison of 17:20 with 3:20 conditions (Kapur et al, 1995). The proposal does not, however, explain the absence of right PFC activation in comparison of the 100% and 0% target conditions in the study of Nyberg and colleagues. One possibility is that this finding may arise from the high false positive rate in this study (almost one in five items were incorrectly identified as old in the 0% condition). This suggests that right APFC activation also occurs in association with "false memories", i.e., incorrect recognition decisions, a suggestion that is consistent with two neuroimaging studies that have directly compared true recognition of old words with false recognition of semantic lures (Schacter et al, 1996b; Schacter et al, 1997). However, an alternative consideration is that the activations produced by such ratio manipulations are actually associated with the occurrence of relatively rare events occurring in a setting of commoner ones and with the ways in which this influences subjects' task performance. It has recently been shown that right DLPFC, at least, is sensitive to rare and 'surprising' events within the setting of a learning task (Fletcher et al, 2001). Wagner and colleagues showed, too, that right APFC and DLPFC activation is greater for blocks of words in which 91% are studied compared to blocks in which 9% were studied only when subjects were oriented towards the rarer items, i.e. unstudied words in the 91% block or studied words in the 9% block (Wagner et al, 1998a). Therefore, using such manipulations we must be careful that the activations seen do not reflect subjective biasing of attention to items dependent upon their rarity.

With respect to the experiments reported in preceding chapters, the question of the influence of retrieval success cannot directly be addressed. Nevertheless, it is worth considering the relevance of the findings to these studies, especially with reference to DLPFC activation. It may be the case that the DLPFC activation seen occurring in

association with (some) studies of retrieval success is associated with post-retrieval monitoring (an explanation that has previously been put forward (Rugg et al, 1996)). This would certainly fit with the interpretation of the right DLPFC activation seen occurring in association with free, as opposed to cued, retrieval in experiment 6 wherein it was insufficient merely to retrieve an item but to maintain and update an internal schema of which items had already been retrieved and which had yet to be retrieved, in order to avoid repetitions or omissions.

The earliest studies attempting to dissociate the neuronal correlates of successful retrieval from the retrieval attempt were forced, by the temporal limitations of the PET technique, to use blocked experimental designs. In all cases, there is a danger that subjects may quickly become aware of the rather artificial experimental design. That is, it may become quickly obvious that, in some blocks, words are old/studied and in others, words are new/unstudied. As a result, there is a danger that the subject will recognise the nature of a block at its outset and then, for the unstudied items, simply give up trying. If this happens, then the blocks will differ not just according to retrieval success but also according to retrieval attempt. Even if subject are not aware of the blocking of items it is possible that, in a run of predominantly old items, they may realise that they have been endorsing nearly all items as old, and may wonder whether they are being too lenient in their response criterion. In other words, any differences in brain activity between two blocks may reflect different response criteria (or different expectancies, strategies or mental sets), rather than retrieval success per se. There is direct evidence, from ERP work, that these worries are more than just theoretical. Johnson et al that found that the differential ERP between old target items and semantic lures itself depended on whether those targets and lures were blocked or intermixed (Johnson et al, 1997).

Thus, a more satisfactory dissociation of encoding and retrieval will require the use of the event-related design. Strangely, the earliest use of this approach found no difference between studied and unstudied items anywhere in the brain (Schacter et al, 1997; Buckner et al, 1998a). Subsequent event-related fMRI studies have found such differences. Saykin et al found greater right DLPFC activation for old than new words in a recognition task (Saykin et al, 1999). Henson and colleagues used the "Remember/Know (R/K)" approach (Tulving, 1985) in which subjects indicate not only whether a word was old or new, but also whether the word was accompanied by recollection of the specific episode in which it was studied ("remember"), or simply a feeling of familiarity in the absence of recollection ("know"). Both R and K judgments activated VLPFC and DLPFC relative to new words, although this was found solely on the left for R judgements. These results suggest that PFC is generally sensitive to retrieval success. Moreover, a direct comparison of correct R and K judgements revealed greater left APFC for R judgements, and greater right DLPFC activation for K judgements. Thus PFC is sensitive not only to retrieval success, but also to the type of information retrieved (as operationalised by the subjective experience accompanying retrieval). Left APFC activity was attributed to the retrieval of source information (forming the basis of an R judgement), and right DLPFC activity to monitoring processes that are particularly important for K judgements, when an item seems familiar in the absence of any recollection of its prior occurrence (akin to the notion of retrieval monitoring discussed earlier).

In a related event-related fMRI recognition study, Henson and colleagues used confidence judgements in order to characterise the subjective trial-to-trial experience of retrieval (Henson et al, 2000). Subjects in this study indicated whether each old-new

decision was made with high or low confidence. Greater monitoring for low than high confidence decisions was predicted, regardless of whether the word was old or new. As expected on the basis of previous findings, greater right DLPFC activation was found for low than high confidence decisions, consistent with the monitoring prediction. A comparison of old versus new words, regardless of confidence, activated left and right anterior PFC, consistent with the blocked studies of retrieval success reviewed above. This study provides important evidence explaining the apparent inconsistency in studied versus unstudied effects in recognition memory, discussed above. Whether such a comparison activates DLPFC may depend on whether the subject makes the chosen response with confidence or not. Once again, the picture that emerges most compellingly, though by no means entirely consistently, is that DLPFC activity in a retrieval task reflects the monitoring of retrieved information with respect to its likely veracity and to its appropriateness in meeting the demands of the task: a picture that is consistent with the finding of DLPFC activation during the free recall condition in experiment 6.

7.2.2b Amount of information retrieved: Depth of encoding at prior study

One other experimental approach to manipulating retrieval success lies in varying the depth with which words are studied, thus altering the likelihood with which they will later be recalled. Using word-stem cued recall, Schacter and colleagues identified bilateral APFC activation during more difficult retrieval, i.e. retrieval of shallowly encoded items (Schacter et al, 1996a). This finding, interpreted as suggestive that APFC activation reflects retrieval attempt rather than retrieval success, is consistent with the finding (discussed above) of greater right anterior activation during intentional than incidental recognition following shallow rather than deep encoding of words (Rugg et al, 1997). However, in a comparable study, using a recognition memory task, the

opposite pattern was found: greater right APFC activation during recognition of words previously studied deeply than of words previously studied shallowly (Buckner et al, 1998b). In this study, left DLPFC and bilateral VLPFC regions showed greater activation during recognition of shallowly compared to deeply studied words. The depth of encoding approach, therefore, also produces inconsistencies. Perhaps it is not a good way to tease apart retrieval attempt and retrieval success, in that the cue for a deeply studied word may not only affect the ease of retrieval, but also the type of information retrieved (e.g. conceptual versus perceptual). Indeed, the attempt-success dichotomy may not be such a useful distinction. Rather, the specific pattern of PFC activation may depend on the particular type of retrieval task (see below), and perhaps the overlap between the processes performed at encoding and the processes performed at retrieval (Morris et al, 1977).

7.2.3 Interactions between Retrieval Task and Amount of Information Retrieved

The findings described above (Schacter et al, 1996a; Buckner et al, 1998b) , are apparently inconsistent with each other and with other retrieval studies. They are, however, compatible with the observation by Rugg et al that retrieval success in the setting of a recognition memory task produces different PFC activations to those accompanying a cued retrieval task (Rugg et al, 1998). They showed that, while cued recall produced greater activation in bilateral APFC and left DLPFC during cued recall, high success during the recognition task was associated with greater right APFC activity while lower success in the cued retrieval task produced greater bilateral APFC activity. That is, in right APFC at least, there is an interaction between retrieval task and retrieval success. This set of observations suggests the possibility that some frontally mediated processes are engendered by recognition success and by stem-cued failure. What might such processes be? One clear difference between a failure to recognise an

item and a failure to generate a remembered word (in response to a word stem) is that, in the latter case, one is likely to continue to generate candidate responses in the hope that a remembered one may arise. This is unhelpful in a recognition task, where, if one does not recognise an item, there is little further to be done. Thus, a difference between recognition "failure" and stem-cued retrieval "failure" is that the latter invites further exploration, in the form of further search and monitoring and the repeated switching between these two processes, and the former does not. Perhaps this might account for one part of the interaction.

Why, though, should this APFC region show significantly greater activation for recognition success than for stem-cued retrieval success? With the same model in mind, one may speculate that, for old words in a recognition test, memory processes that are incidental to task demands, such as conscious recollection of source information, may follow automatically. These additional processes become redundant as soon as the next copy cue is presented and subjects must switch back to the task at hand (evaluating the next word). If this switching is minimal when a new (nontarget) word is presented, APFC activity will be higher on average for successful than unsuccessful recognition. Thus, the apparently inconsistent pattern of APFC response may be rationalised if we consider its function in terms of the control of switching between search and retrieval processes. This explanation may be applied to the retrieval success versus attempt studies described in preceding sections, including those of Schacter et al and of Buckner et al, suggesting that their results may be compatible with each other and with those of Rugg et al. It is, however, a highly speculative suggestion and there is no direct experimental evidence in its favour at present.

A related study explored the effects of retrieval success across two types of cued recall tasks (Allan et al., 2000). Word stem-cued and fragment-cued retrieval were explored in high and low success blocks. As with the experiments above, APFC (on the right) was activated for low success in the stem-cued retrieval. This effect was significantly greater than for low success in the fragment-cued condition, in which fewer completions were possible. This pattern is compatible with the idea of a role for right APFC in switching between search and monitoring processes since such switching will occur in cases where more (incorrect) candidate responses are generated, i.e., in this case, for stem-cued rather than fragment-cued retrieval. This study also produced results that may be inconsistent however: left APFC activity was greater for successful than unsuccessful stem-cued retrieval and right DLPFC activity was greater for successful than unsuccessful fragment-cued retrieval. How these findings may be resolved on the basis of the current models is unclear. Certainly, they suggest that strenuous attempts must be made to choose tasks that constrain, as far as possible, the processes engaged and, perhaps, more realistically, to recognise that many processes may be called upon to optimise retrieval and that the nature and extent to which given processes contribute to task performance will vary from subject to subject and will be highly dependent upon the type of task, the instructions issued and the context in which the task is carried out (for example, what control tasks are used and what subjects believe is expected of them).

One further study relevant to the search versus success question examined the "tip of the tongue" phenomenon (Maril et al., 2001). This is a common feeling: of knowing something but being unable to access and it predominantly concerns semantic knowledge. I mention it briefly here in view of the insights that it offers into retrieval processes. Maril et al elicited this phenomenon in healthy volunteers and showed that it

is associated with activation in right APFC and VLPFC. Activation was significantly greater than that associated with both correct responses and with "don't know" responses that were not accompanied by the 'tip of the tongue' phenomenon. This suggests that these regions reflect processes associated with a continuing memory search and particularly, with a search in which candidate responses may be produced but rejected – a characteristic of this phenomenon. My findings, and those reported above, might predict that this condition would engender monitoring requirements and should therefore activate DLPFC. Perhaps, the absence of this activation arises from the control tasks, which also involve memory retrieval. The presence of VLPFC activation is certainly consistent with the idea for a role in cue-specification proffered in chapter 6 since such processes are likely to be repeatedly engaged as one interrogate memory in order to overcome the memory 'block'. Furthermore, as successive candidate responses are generated and rejected, the switching processes referred to above are also likely to be engaged, accounting for the APFC activation.

7.2.4 Retrieval: conclusions.

The pattern to emerge from episodic memory retrieval studies is much less clear than from encoding studies. There are many inconsistencies that may be in part explained by technical and design limitations (see chapter 2 for discussion). Notwithstanding these inconsistencies, I think that it is possible to make sense of the findings and incorporate observations from experiments 2 and 6 into the broader literature. I shall do this in terms of a modification of an existing model of memory retrieval (Burgess, Shallice, 1996). This model includes two stages of the retrieval process, the first of which lies in the identification and the specification of search parameters. The second lies in the post-retrieval appraisal of the products of that memory search. An inclusion of a third component to this model – the additional

control processes that must be required to integrate and adjust the components of the search-monitor-verify process – allows me to account for the retrieval imaging data more fully. In brief, I suggest that the three main areas of lateral PFC activation that have been repeatedly found, in different combinations, across episodic memory retrieval studies may be usefully related to these three cognitive components of the retrieval process. More specifically, I suggest that VLPFC activation tends to reflect the initial specification of the search process, DLPFC reflects the post retrieval monitoring/verification processes and APFC activation reflects the higher order processes that are used in controlling and switching between specification, retrieval and monitoring, with such processes being sensitive to the "metamemory" processing pertaining to ongoing success and to any changes that may occur due to a lack of success or to the demands of the task. It must be conceded that the experimental support for this tentative model is weak and inconsistent and that direct experimental testing is required. It is worth, however, reiterating some of the existing evidence in its favour.

First, with respect to the idea that VLPFC is concerned with cue-related specification of search parameters, this initial stage is akin to the semantic generation processes referred to in the encoding section of this chapter, insofar as they are required to retrieve information from long-term semantic memory. The results of such a search also need to be maintained in working memory for the purposes of further monitoring and manipulation. Experiment 2 showed that VLPFC activity was associated with cued paired associate retrieval and experiment 6 that free recall produced a lesser activation in the same region. One clear difference between these two tasks was that, in the cued recall condition, the search space was repeatedly defined and re-defined on the basis of experimentally-provided cues. The particular sensitivity of VLPFC to this task is

therefore compatible with the model. Moreover, in an extreme case of memory searching, when something is on the 'tip of the tongue' VLPFC activity is provoked (Maril et al, 2001) and a similar explanation is feasible. An inconsistency of VLPFC activity associated with recognition memory tasks is perhaps unsurprising since, in many instances, there is no real search required – a copy cue is presented and defines precisely the response that is required (e.g. (Henson et al, 1999b)). Although both experiments 2 and 6 made explicit demands upon memory retrieval, the lack of activation in VLPFC when comparing intentional with incidental retrieval (Squire et al, 1992; Rugg et al, 1997) using word-stem completion suggests that this region may be insensitive to whether or not cue specification processes are occurring as part of an explicit memory task or not.

With respect to the role that DLPFC may play in monitoring and manipulation of the products of episodic retrieval, this suggestion is based upon the general pattern that activation here tends to occur when the task demands that retrieved material is further processed. Thus, for example, in experiment 6, any retrieved item would need to be incorporated into a pre-defined structure in order to prevent repetition or omission (more fully discussed in chapter 6). Further processing according to the source information (Cabeza et al, 1997b; Rugg et al, 1999) will also engender DLPFC activation, as will the requirement that retrieved material forms the basis for a confidence monitoring judgement (Henson et al, 1999a).

Although it was not a feature of the retrieval experiments that I carried out here, it is important to consider the possible roles of APFC. The activation of this region in retrieval, I suggest, reflects higher level controlling processes that are required under a number of circumstances. An early observation was that APFC activity is greater for

intentional than incidental retrieval and that more demanding retrieval tasks (e.g. when the preceding encoding task is a shallow rather than a deep one) tend to provoke greater activation here. These observations in themselves are suggestive that APFC may have such a controlling role but the picture is not an entirely consistent one. One factor that must be taken into account in considering the inconsistencies is that a memory retrieval task will, in different circumstances and subjects, comprise many different processes and strategies. In dealing with blocks of stimuli, subjects are likely to evaluate each component stimulus not only in isolation but also with respect to the overall design of the task and to their expectancy and changing strategies. The suggestion is that APFC may play a part in precisely this sort of evaluation and reappraisal. As a result, its activity may very from study to study in a way that is inconsistent with respect to task demands but that may be perfectly consistent when the subject's covert behaviour is considered more closely. This is a speculative but it does provide an explanation for some of the PFC activity patterns e.g. the task-by-success interaction (Rugg et al, 1998). In a meta-analysis by Duncan & Owen (Duncan and Owen, 2000), APFC was one region that did appear to dissociate from other mid-lateral PFC regions, being activated more often in episodic retrieval tasks than working memory tasks. However, I am assuming that this is nothing to do with retrieval per se, but rather with differences in the component processes of the working memory and retrieval tasks typically used.

With respect to the question of lateralisation of frontal contribution to episodic memory retrieval, according to the HERA model described above, retrieval of verbal (or verbalisable material) should be associated with right PFC activation. As with the left-sided activation that is seen at encoding, this may be a reflection of material rather than a reflection of differential processes that occur at these stages. Relevant to this, Wagner et al showed that retrieval of verbal material was associated with left and retrieval of

non-verbal material with bilateral VLPFC (Wagner et al, 1998b). In addition, the lateralisation of retrieval-related PFC activation is highly inconsistent (more so than in verbal encoding studies). In a recent review of encoding and retrieval studies separately, I and a colleague observed that out of twenty-two verbal encoding studies reviewed, seventeen contained encoding-related contrasts that were associated with PFC activation solely on the left side. Out of twenty-five verbal retrieval studies, only eleven showed a purely right-sided effect (Fletcher and Henson, 2001). This, of course, is a highly informal analysis but it serves to illustrate the point.

In summing up the position with respect to the HERA model, there have been two notable observations regarding left-right PFC differences. First the type of material influences the laterality of activation. Second, the nature of the verbal task: whether it involves mainly encoding into, or retrieval from, episodic memory also has an effect and this may be to some extent dissociable from the material effect. The two observations are perfectly compatible with each other. If retrieval processes tend to emphasise the sorts of processes associated with non-verbal material and these processes are lateralised to right PFC then we would expect such a lateralisation in retrieval tasks. Furthermore, if some retrieval tasks make extra demands – engaging processes more associated with verbal material – then retrieval-related left PFC activation would occur. Such would be the case in more complex retrieval tasks such as source retrieval or word stem/fragment cued recall. One test of this possibility would be to examine whether the lateralisation of PFC activation switched when non-verbal material is processed in a way that is similar to verbal material, and vice versa. This however is difficult (Fletcher et al, 2002).

7.3 General Conclusions.

7.3.1 Possible reasons for inconsistencies.

The results of experiments 1 to 6 are mutually compatible and consistent with findings that have emerged from the broader functional neuroimaging literature. However, it would be specious to treat the results as in any way complete or consistent. While many of the existing inconsistencies across studies may be reconciled, there are a number that cannot and possible reasons for this should be considered at the outset. The discrepancies across studies may arise at a number of levels: Foremost, we are applying the techniques to poorly defined cognitive processes: this will make our tasks inexact and introduce noise to the data. Second, there is likely to be inconsistency in the ways that different subjects approach tasks, particularly in view of the fact that the goals in frontally-mediated tasks may be achievable in more than one way. Since many of the earlier studies were based upon low subject numbers, differences in strategies and performance across the small subject samples could have produced relatively large effects. Third, as I discussed in the introduction to this chapter, the relationship between PFC macro- and micro-structure is highly variable such that activations in microstructurally similar regions across subjects may be localised to apparently different macrostructural regions, and vice-versa. Fourth, the question of whether or not a given activation is actually present (''significant``), is normally determined by pre-specified statistical thresholding. Any given activation, or absence of activation, is actually therefore rather arbitrarily defined, particularly within the setting of functional neuroimaging where classical statistical inference is beset by problems. The net result is that the presence of a significant activation in one region, but absence of significant activation in another, is only weak evidence for functional specialisation. More powerful evidence is the observation of significant double dissociation between regions and tasks (as was demonstrated in experiment 6). Finally, and more generally, we must

bear in mind that attempts to understand localised correlates of cognitive processes often fail to emphasise a more global picture of integrated systems in the brain. Despite clear evidence of functional specialisation in the brain, the widespread connections of PFC remind us that an over-emphasis on localisation of function may prove detrimental to an understanding of functional integration of PFC with other brain regions (Fuster, 1997).

7.3.2 A synthesis

So there are a number of reasons why inconsistencies might arise in the functional imaging literature. Nevertheless, I believe that the studies carried out here have produced insights into the functional attributes of two lateral PFC regions: DLPFC and VLPFC. The findings are compatible too with many existing studies. The body of evidence points towards these regions subserving two broadly distinct functions, each of which may be engaged, to a greater or lesser extent in encoding and retrieval. I refer to these processes as "updating and maintaining the contents of working memory" and "selecting, manipulating and monitoring the contents of working memory" and suggest that these functions map onto VLPFC and DLPFC respectively. Finally, although my own experiments are not directly relevant to them, I shall also consider a third set of possible processes: "selecting processes, goals and sub-goals", which I shall relate to APFC activation.

These ideas, relating to VLPFC-DLPFC distinctions, are not new and draw heavily upon existing models and anatomical theories (Petrides, 1994; Petrides, 1998; Shallice and Burgess, 1998).

7.3.2a Updating and maintaining the contents of working memory.

All of the tasks that I have used, and indeed, many of the tasks in the memory literature more generally, require subjects to examine the contents of working memory in order to make a decision. Therefore, as an initial step in task performance, candidate information must be brought into working memory (*updating*), and held on-line (*maintaining*) in the service of further processing of that material. In some cases, this information is externally provided, as was the case in the majority of the encoding studies (experiments 1, 3, 4 and 5). In other tasks, the information must be retrieved from long-term semantic or episodic memory, reflecting the reinstantiation of stored (passive) information into active working memory. This was the case with the cued paired associate retrieval tasks (experiments 2 and 6). With reference to the terminologies used in the descriptions of the individual experiments, this step corresponds to the *generation* (often of individual or shared semantic attributes) discussed in encoding tasks, and the cue *specification* discussed in retrieval tasks. In deep encoding tasks for example, subjects are required to retrieve information from long-term semantic memory into working memory in order to make a response. In paired associate cued retrieval tasks, the cue must be maintained in working memory, together with possible responses retrieved from long term episodic (and perhaps semantic) memory. One of the clearest pictures to emerge from the literature reviewed above is the activation of VLPFC in such cases, whether in the context of tasks considered as episodic memory encoding or retrieval.

7.3.2b Selecting, manipulating and monitoring the contents of working memory.

For most memory tasks, particularly in everyday life, simple updating and maintenance processes are necessary but insufficient. Often the maintenance of information is an initial step and is followed by the need to select from, and refine, this information. Additionally, with task demands in mind, the subject must engage in

periodic evaluation of the sufficiency of produced information in meeting the needs of the current task. Referring once more to the terminology used in describing the experiments, this function would correspond to *organisation* in encoding tasks (experiment 3) and to *monitoring* in retrieval tasks (experiment 6). The term *selection* is considered appropriate in this concluding formulation since it is frequently the case that tasks require not merely the rearrangement of material held on-line but also the selection of the most appropriate stimuli before a response can be made. I believe such selection processes to have been engaged in the tasks used in most of the reported encoding experiments, including the distant semantic pairing (experiment 4), the semantic interference condition (experiments 5a and 5b) and they would most likely have played a part in meeting the demands of the organisation condition in experiment 3. This use of the term *selection* is differs from that which may be applied to VLPFC; VLPFC is involved in selecting information from long-term memory (so that it is brought into working memory), whereas DLPFC is involved in selecting information that is already active in working memory.

Monitoring processes are loosely grouped with *selection and organisation* for two reasons. First, it is difficult to envisage successful selection and organisation processes being performed in the absence of continual monitoring of the appropriateness of the resulting changes. Second, while my studies have attempted to differentiate descriptively between these processes, most existing functional imaging tasks have used paradigms that do not. It is thus more parsimonious to group them loosely together and to observe that a most likely candidate for their anatomical implementation is DLPFC, activation of which is, for example, decreased by divided attention during demanding encoding tasks (experiment 3), increased when encoded material must be organised according to an evolving semantic structure (experiment 6)

and increased when retrieved information must provide the basis for further retrieval (as in source memory tasks) or assessment (in confidence judgements) or when it is inconclusive or uncertain.

7.3.2c Selecting processes, goals and sub-goals

The above two sections imply an interaction between VLPFC and DLPFC: the results of DLPFC-subserved monitoring and manipulation might lead to a reupdating of information held in VLPFC with this, itself, acting as the substrate for further processing requiring DLPFC, and so on. Thus, efficient interaction between DLPFC and VLPFC is likely to be necessary to meet the demands of tasks. The model would therefore be incomplete without the postulation of ''meta`` processes involved in setting goals and coordinating the DLPFC and VLPFC processes required to achieve these goals. This has been described in the concluding section on retrieval as being compatible possibly with the patterns of activation observed in APFC responses to retrieval tasks. In brief, more complex episodic memory retrieval tasks might also be expected to maximise the extent to which subjects must coordinate VLPFC and DLPFC functions, in the engagement of iterative search and monitoring processes (nonetheless, even what appear to be simple recognition tasks might engage complex metamemory or switching strategies, as discussed in the conclusion of the retrieval section). Intriguingly, there is hardly any evidence that APFC has been activated in episodic encoding tasks. The lack of APFC activation in typical ''encoding`` tasks probably reflects the fact that such tasks differ little in their requirement for selecting between different executive processes.

7.4 Closing comments.

Functional neuroimaging has, over the last decade, added fresh impetus to the cognitive neuroscience of memory. The early emphases that it placed upon frontal lobe contributions to memory encoding and retrieval have matured into a literature that is complex and difficult. I have tried to make some sense of this literature and to identify emerging patterns and to assess whether these are compatible with findings from the experiments reported in preceding chapters. I think that, generally, they are consistent with the model of functional segregation of DLPFC and VLPFC set out in this chapter.

Aside from this attempt to map function onto structure (a goal that, though useful, may ultimately prove a rather unambitious use of the techniques), I think that one may point to a number of areas in which functional neuroimaging is having an impact. First, the techniques have generated data that may be relevant to, and even act as a guiding influence upon, neuropsychological investigation of localised PFC lesions. Second, the results of imaging studies have prompted theorists to develop new terminologies with which to distinguish different executive functions (e.g., maintenance of information, selection between competing responses, monitoring of task relevance). Indeed, if one does assume a one-to-one mapping between function and anatomy, imaging results may even be used to further inform psychological models. For example, a model may be called into question if it makes the assumption that two tasks involve identical executive processes, but are found to activate different PFC regions or, alternatively, if two tasks are assumed to engage different executive processes but activate the same PFC regions. This is an exciting possibility: that functional neuroimaging introduces a new and highly sensitive "behavioural" measure that provides further leverage for prising apart, and testing, cognitive models. The possibility of rooting what will necessarily be a high level, and often metaphorical, terminology in objective measurements of brain activity is likely to prove valuable.

Note: Some of the theoretical viewpoints put forward in this chapter have been published in the following paper

Fletcher PC, Henson RNA Frontal lobes and human memory - insights from furnctional neuroimaging Brain 2001 124: 849-881

References

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B. and Zilles, K. (1999) Broca's region revisited: cytoarchitecture and intersubject variability. *Journal of Anatomy* 412(2): 319-341.

Baddeley, A., Vargha Khadem, F. and Mishkin, M. (2001) Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *Journal of Cognitive Neuroscience* 13(3): 357-69.

Baddeley, A. D. (1966) Short-term memory for word sequences as a function of accoustic, semantic and formal similarity. *Quarterly Journal of Experimental Psychology* 18: 302.

Baddeley, A. D. (1986) *Working Memory*. Oxford, Clarendon Press.

Baddeley, A. D. and Della Sala, S. (1998). Working memory and executive control. *The prefrontal cortex: executive and cognitive functions*. A. Roberts, T. W. Robbins and L. Weizkrantz. Oxford, Oxford University Press: 9-21.

Baddeley, A. D., Lewis, V., Eldridge, M. and Thompson, N. (1984) Attention and retrieval from long-term memory. *Journal of Experimental Psychology* 113: 518-540.

Baddeley, A. D. and Warrington, E. K. (1970) Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behaviour* 9: 176-189.

Battig, W. F. and Montague, W. E. (1969) Category norms for verbal items in 56 categories. *Journal of Experimental Psychology* 80(3): 1-46.

Benjamini, Y. and Hochberg, Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society B* 57(1): 289-300.

Benton, A. L. (1968) Differential behavioural effects in frontal lobe disease. *Neuropsychologia* 6: 53-60.

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M. and Prieto, T. (1997) Human brain language areas identified by functional magnetic resonance imaging. *Journal of Neuroscience* 17(1): 353-362.

Bland, J. M. and Laltman, D. G. (1995) Multiple significance tests: the Bonferroni method. *British Medical Journal* 310(6973): 170.

Bornstein, R. A. and Leason, M. L. (1985) Effects of localised lesions on the verbal concept attainment task. *Journal of clinical experimental neuropsychology* 7: 421-429.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H. and Gabrieli, J. D. (1998) Making memories: brain activity that predicts how well visual experience will be remembered. *Science* 281(5380): 1185-1187.

Brown, R. and Mcneill, D. (1966) The "tip-of-the-tongue" phenomenon. *Journal of Verbal Learning and Verbal Behavior* 5: 325-337.

Buchel, C. and Friston, K. J. (1997) Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cerebral Cortex* 7(8): 768-778.

Buckner, R. L. (1998) Event-related fMRI and the hemodynamic response. *Human Brain Mapping* 6(5-6): 373-377.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Dale, A. M., Rotte, M. and Rosen, B. R. (1998a) Functional-anatomic study of episodic retrieval. II. Selective averaging

of event-related fMRI trials to test the retrieval success hypothesis. *NeuroImage* 7(3): 163-175.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D. and Rosen, B. R. (1998b) Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. *NeuroImage* 7(3): 151-162.

Buckner, R. L., Petersen, S. E., Ojemann, J. G., Miezin, F. M., Squire, L. R. and Raichle, M. E. (1995) Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience* 15(1 Pt 1): 12-29.

Burgess, P. W. (1997). Theory and methodology in executive function research. *Methodology of frontal and executive function*. P. Rabbitt. Hove, Psychology Press: 81-116.

Burgess, P. W. and Shallice, T. (1996a) Confabulation and the control of recollection. *Memory* 4(2): 359-412.

Burgess, P. W. and Shallice, T. (1996b) Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia* 34: 263-276.

Cabeza, R., Kapur, S., Craik, F. I. M., Mcintosh, A. R., Houle, S. and Tulving, E. (1997a) Functional neuroanatomy of recall and recognition: a PET study of episodic memory. *Journal of Cognitive Neuroscience* 9: 254-265.

Cabeza, R., Mangels, J., Nyberg, L., Habib, R., Houle, S., Mcintosh, A. R. and Tulving, E. (1997b) Brain regions differentially involved in remembering what and when: a PET study. *Neuron* 19(4): 863-870.

Cocosco, C. A., Kollokian, V., Kwan, R. K. S. and Evans, A. C. (1997) Brainweb: online interface to a 3D MRI simulated brain database. *NeuroImage* 5: 425.

Conrad, R. and Hull, A. J. (1964) Information, acoustic confusion and memory span. *British Journal of Psychology* 55: 429-432.

Craik, F. I. and Lockhart, R. S. (1972) Levels of processing: a framework for memory research. *Journal of Verbal Learning and Verbal Behaviour* 11: 671-684.

Craik, F. I. M., Govoni, R., Naveh-Benjamin, M. and Anderson, N. D. (1996) The effects of divided attention on encoding and retrieval processes in human memory. *Journal of Experimental Psychology, General* 125: 159-180.

Craik, F. I. M., Morris, R. G. and Gick, M. L. (1990). Adult age differences in working memory. *Neuropsychological impairments of short term memory*. G. Vallar and T. Shallice. Cambridge, Cambridge University Press: 247-267.

Damasio, H. C. (1991). Neuroanatomy of frontal lobe in vivo: a comment on methodology. *Frontal lobe function and dysfunction*. H. S. Levin, H. M. Eisenberg and A. L. Benton. Oxford, Oxford University Press. *1*: 92-121.

Deese, J. (1959) On the prediction of occurrence of particular verbal intrusions in immediate recall. *Journal of Experimental Psychology* 58: 17-22.

Delbecq Derouesne, J., Beauvois, M. F. and Shallice, T. (1990) Preserved recall versus impaired recognition. A case study. *Brain* 113(Pt 4): 1045-74.

Delbecq-Derouesne, J., Beauvois, M. F. and Shallice, T. (1990) Preserved recall versus impaired recognition: a case study. *Brain* 113: 1045-1074.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H. and Gabrieli, J. D. (1995) Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process-specificity. *Journal of Neuroscience* 15(9): 5870-5878.

Duncan, J. and Owen, A. M. (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in the Neurosciences* 23: 475-483.

Eslinger, P. J. and Grattan, L. M. (1994) Altered serial position learning after frontal lobe lesion. *Neuropsychologia* 32(6): 729-39.

Fletcher, P. C. (2000). The functional neuroimaging of memory disorders. *Brain Mapping: The Disorders*. R. S. J. Frackowiak, J. Mazziota and A. Toga. San Diego, Academic Press.

Fletcher, P. C., Anderson, J. M., Shanks, D. R., Honey, R., Carpenter, T. A., Donovan, T., Papadakis, N. and Bullmore, E. T. (2001) Responses of human frontal cortex to surprising events are predicted by formal associative learning theory. *Nature Neuroscience* 4(10): 1043-8.

Fletcher, P. C., Buchel, C., Josephs, O., Friston, K. J. and Dolan, R. J. (1999) Learning-related neuronal responses in prefrontal cortex studied with functional neuroimaging. *Cerebral Cortex* 9(2): 168-178.

Fletcher, P. C., Frith, C. D., Grasby, P. M., Shallice, T., Frackowiak, R. S. and Dolan, R. J. (1995) Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain* 118(Pt 2): 401-16.

Fletcher, P. C., Frith, C. D. and Rugg, M. D. (1997) The functional neuroanatomy of episodic memory. *Trends in the Neurosciences* 20(5): 213-218.

Fletcher, P. C. and Henson, R. N. (2001) Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124(Pt 5): 849-81.

Fletcher, P. C., Palomero-Gallagher, N., Zafiris, O., Fink, G. R., Tyler, L. K. and Zilles, K. (2002) The influence of explicit instructions and stimulus material on lateral frontal responses to an encoding task. *Neuroimage* 17(2): 780-91.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. and Dolan, R. J. (1996) Brain activity during memory retrieval. The influence of imagery and semantic cueing. *Brain* 119(Pt 5): 1587-1596.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D. and Frackowiak, R. S. J. (1995a) Spatial registration and normalisation of images. *Human Brain Mapping* 2: 165-189.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D. and Turner, R. (1998) Event-related fMRI: characterizing differential responses. *NeuroImage* 7(1): 30-40.

Friston, K. J., Glaser, D. E., Henson, R. N. A., Kiebel, S., Phillips, C. and Ashburner, J. (2002a) Classical and Bayesian inference in neuroimaging: applications. *Neuroimage* 16(2): 484-512.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-B., Frith, C. D. and Frackowiak, R. S. J. (1995b) Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* 2: 189-210.

Friston, K. J., Penny, W., Phillips, C., Kiebel, S., Hinton, G. and Ashburner, J. (2002b) Classical and Bayesian inference in neuroimaging: theory. *Neuroimage* 16(2): 465-83.

Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S. and Dolan, R. J. (1996) The trouble with cognitive subtraction. *NeuroImage* 4(2): 97-104.

Frith, C. D. (2000) The role of the dorsolateral prefrontal cortex in the selection of action. *Attention and Perception*.

Fuster, J. M. (1997) *The prefrontal cortex. Anatomy, physiology and neuropsychology of the frontal lobe.* Philadelphia, Lippincott-Raven.

Gabrieli, J. D., Poldrack, R. A. and Desmond, J. E. (1998) The role of left prefrontal cortex in language and memory. *Proceedings of the National Academy of Science, USA* 95(3): 906-913.

Gardiner, J. M. and Richardson-Klavehn, A. (2000). Remembering and Knowing. *The Oxford Handbook of Memory*. E. Tulving and F. I. M. Craik. Oxford, Oxford University Press: 229-244.

Genovese, C. R., Lazar, N. A. and Nichols, T. E. (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage* 15: 772-786.

Gershberg, F. B. and Shimamura, A. P. (1995) Impaired use of organisational strategies in free recall following frontal lobe damage. *Neuropsychologia* 33: 1305-1333.

Goldman-Rakic, P. S. (1998). The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *The prefrontal cortex: executive and cognitive functions*. A. Roberts, T. W. Robbins and L. Weizkrantz. Oxford, Oxford University Press: 87-102.

Grady, C. L., Mcintosh, A. R., Rajah, M. N. and Craik, F. I. (1998) Neural correlates of the episodic encoding of pictures and words. *Proceedings of the National Academy of Science, USA* 95(5): 2703-8.

Graham, K. S. and Hodges, J. R. (1997) Differentiating the roles of the hippocampal complex and the neocortex in long term memory storage: evidence from the study of semantic dementia. *Neuropsychology* 11: 77-89.

Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S. and Dolan, R. J. (1993) Functional mapping of brain areas implicated in auditory--verbal memory function. *Brain* 116(Pt 1): 1-20.

Grasby, P. M., Frith, C. D., Friston, K. J., Simpson, J., Fletcher, P. C., Frackowiak, R. S. and Dolan, R. J. (1994) A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. *Brain* 117(Pt 6): 1271-1282.

Green, R. E. and Shanks, D. R. (1993) On the existence of independent explicit and implicit learning systems: an examination of some evidence. *Memory and Cognition* 21(3): 304-317.

Haxby, J. V., Ungerleider, L. G., Horwitz, B., Maisog, J. M., Rapoport, S. I. and Grady, C. L. (1996) Face encoding and recognition in the human brain. *Proceedings of the National Academy of Science, USA* 93(2): 922-927.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O. and Dolan, R. J. (1999a) Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience* 19(10): 3962-72.

Henson, R. N. A., Rugg, M. D., Shallice, T. and Dolan, R. J. (2000) Confidence in recognition memory for words: dissociating right prefrontal roles in episodic retrieval. *Journal of Cognitive Neuroscience*.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O. and Dolan, R. J. (1999b) Recognition and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience* 19(10): 3962-3972.

Henson, R. N. A., Shallice, T. and Dolan, R. J. (1999c) Right prefrontal cortex and epsiodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain* 122: 1367-1381.

Hodges, J. R. and Graham, K. S. (1998) A reversal of the temporal gradient for famous person knowledge in semantic dementia: implications for the neural organisation of long-term memory. *Neuropsychologia* 36: 803-825.

Hunter, J. E. (1997) Needed: a ban on significance testing. *Psychological science* 8(1): 3-7.

Incisa Della Rochetta, A. and Milner, B. (1993) Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia* 31: 503-524.

Jacoby, L. J. (1996) Dissociating automatically and consciously controlled effects of study/test compatibility. *Journal of Memory and Language* 35: 32-52.

Jacoby, L. J., Ste-Marie, J. and Toth, J. P. (1993). Redefining automacity: Unconscious influences, awareness and control. *Attention: Selection, awareness and control*. A. D. Baddeley and L. Weizkrantz. Oxford, Oxford University Press.

Janowsky, J. S., Shimamura, A. P. and Squire, L. R. (1989a) Memory and metamemory: comparisons between frontal lobe lesions and amnesic patients. *Psychobiology* 17: 3-11.

Janowsky, J. S., Shimamura, A. P. and Squire, L. R. (1989b) Source memory impairments in patients with frontal lobe lesions. *Neuropsychologia* 27: 1043-1056.

Johnson, M. K., Nolde, S. F., Mather, M., Kounios, J., Schacter, D. L. and Curran, T. (1997) Test format can affect the similarity of brain activity associated with true and false recognition memory. *Psychological Science* 8: 250-257.

Josephs, O. and Henson, R. N. A. (1999) Event-related functional magnetic resonance imaging: modelling, inference and optimisation. *Philosophical Transactions of the Royal Society of London* 354: 1215-1228.

Josephs, O., Turner, R. and Friston, K. (1997) Event-related fMRI. *Human Brain Mapping* 5: 243-248.

Kapur, S., Craik, F. I., Jones, C., Brown, G. M., Houle, S. and Tulving, E. (1995) Functional role of the prefrontal cortex in retrieval of memories: a PET study. *NeuroReport* 6(14): 1880-1884.

Kapur, S., Craik, F. I., Tulving, E., Wilson, A. A., Houle, S. and Brown, G. M. (1994) Neuroanatomical correlates of encoding in episodic memory: levels of processing effect [see comments]. *Proceedings of the National Academy of Science, USA* 91(6): 2008-2011.

Kelley, W. M., Miezin, F. M., Mcdermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., Ollinger, J. M., Akbudak, E., Conturo, T. E., Snyder, A. Z. and

Petersen, S. E. (1998) Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 20(5): 927-36.

Kirchhoff, B. A., Wagner, A. D., Maril, A. and Stern, C. E. (2000) Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *Journal of Neuroscience* 20(16): 6173-6180.

Kopelman, M. D. (1987) Two types of confabulation. *Journal of Neurology, Neurosurgery and Psychiatry* 50: 1482-1487.

Kopelman, M. D. (2002) Disorders of Memory. *Brain* 125: 2152-2190.

Kopelman, M. D., Stanhope, N. and Kingsley, D. (1997) Temporal and spatial context memory in patients with focal frontal, temporal lobe and diencephalic lesions. *Neuropsychologia* 35: 1533-1545.

Kopelman, M. D., Stevens, T. G., Foli, S. and Grasby, P. (1998) PET activation of the medial temporal lobe in learning. *Brain* 121(Pt 5): 875-887.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. and Oeltermann, A. (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412: 150-157.

Maril, A., Wagner, A. D. and Schacter, D. L. (2001) On the tip of the tongue: an event-related fMRI study of semantic retrieval failure and cognitive conflict. *Neuron* 31: 653-660.

Mayes, A. R. (2000). Selective Memory Disorders. *The Oxford Handbook of Memory*. E. Tulving and F. I. M. Craik. Oxford, Oxford University Press: 427-440.

Mccarthy, R. A. and Warrington, E. K. (1990) *Cognitive Neuropsychology*. San Diego, Academic Press.

Mcintosh, A. R. and Gonzales-Lima, F. (1994) Structural equation modelling and its application to network analysis in functional brain imaging. *Human Brain Mapping* 2: 2-22.

Mcintyre, J. S. and Craik, F. I. M. (1987) Age differences in memory for item and source information. *Canadian Journal of Psychology* 42: 175-192.

Metcalfe, J. (2000). Metamemory: theory and data. *The Oxford Handbook of Memory*. E. Tulving and F. I. M. Craik. Oxford, Oxford University Press: 197-211.

Milner, B. (1966). Amnesia following operation on the temporal lobes. *Amnesia*. C. W. M. Whitty and O. L. Zangwill. London, Butterworths: 109-133.

Mishkin, M., Suzuki, W. A., Gadian, D. G. and Vargha Khadem, F. (1997) Hierarchical organization of cognitive memory. *Philosophical Transactions of the Royal Society of London, B Biological Sciences* 352(1360): 1461-7.

Morris, C. D., Bransford, J. D. and Franks, J. J. (1977) Levels of processing versus transfer appropriate processing. *Journal of Verbal Learning and Verbal Behaviour* 16: 519-533.

Moscovitch, M. (1989). Confabulation and the frontal systems: strategic versus associative retrieval in neuropsychological theories of memory. *Varieties of memory and consciousness: essays in honour of Endel Tulving*. H. L. Roediger and F. I. M. Craik. Hillsdale, NJ, Lawrence Erlbaum: 133-160.

Moscovitch, M. (1994) Cognitive resources and dual-task interference effects in normal people: the role of the frontal lobes and medial temporal cortex. *Neuropsychology* 8: 524-534.

Nolde, S. F., Johnson, M. K. and Raye, C. L. (1997) The role of prefrontal cortex during tests of episodic memory. *Trends in Cognitive Sciences* 2(10): 399-406.

Norman, D. A. and Bobrow, D. G. (1979) Descriptions: an intermediate stage in memory retrieval. *Cognitive Psychology* 11: 107-123.

Norman, D. A. and Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. *Consciousness and self-regulation*. G. E. Schwartz and D. Shapiro. New York, Plenum Press.

Nyberg, L., Mcintosh, A. R., Cabeza, R., Habib, R., Houle, S. and Tulving, E. (1996) General and specific brain regions involved in encoding and retrieval of events: What, where and when. *Proceedings of the National Academy of Science, USA* 93: 11280-11285.

Nyberg, L., Tulving, E., Habib, R., Nilsson, L. G., Kapur, S., Houle, S., Cabeza, R. and Mcintosh, A. R. (1995) Functional brain maps of retrieval mode and recovery of episodic information [see comments]. *NeuroReport* 7(1): 249-252.

Otten, L. J., Henson, R. N. and Rugg, M. D. (2001) Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. *Brain* 124(Pt 2): 399-412.

Owen, A. M., Evans, A. C. and Petrides, M. (1996a) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cerebral Cortex* 6(1): 31-38.

Owen, A. M., Milner, B., Petrides, M. and Evans, A. C. (1996b) Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. *Proceedings of the National Academy of Science, USA* 93(17): 9212-9217.

Parkin, A. J., Bindschaedler, C., Harsent, L. and Metzler, C. (1996) Pathological false alarm rates following damage to the left frontal cortex. *Brain and Cognition* 32(1): 14-27.

Parkin, A. J. and Walter, B. M. (1992) Recollective experience, normal aging and frontal dysfunction. *Psychology and Aging* 7: 290-298.

Passingham, R. (1993) *The frontal lobes and voluntary action*. Oxford, Oxford University Press.

Passingham, R. E., Toni, I. and Rushworth, M. S. F. (2000) Specialization within the prefrontal cortex: the ventral prefrontal cortex and associative learning. *Experimental Brain Research* 133: 103-113.

Patterson, K. and Hodges, J. R. (1995). Disorders of semantic memory. *Handbook of memory disorders*. A. D. Baddeley, B. A. Wilson and F. N. Watts. Chichester, John Wiley: 167-186.

Perneger, T. V. (1998) What's wrong with Bonferroni adjustments? *British Medical Journal* 316: 1236-1238.

Petersen, S. E. and Fiez, J. A. (1993) The processing of single words studied with positron emission tomography. *Annual Review of Neuroscience* 16: 509-530.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M. and Raichle, M. E. (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331(6157): 585-589.

Petersen, S. E., Fox, P. T., Snyder, A. Z. and Raichle, M. E. (1990) Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* 249(4972): 1041-1044.

Petrides, M. (1994). Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. *Handbook of Neuropsychology*. F. Boller and J. Grafman. Amsterdam, Elsevier: 59-82.

Petrides, M. (1995) Impairments on non-spatial self-ordered and externally ordered working memory tasks after lesions to the mid-dorsal part of the lateral frontal cortex in the monkey. *Journal of Neuroscience* 15: 359-375.

Petrides, M. (1998). Specialised systems for the processing of mnemonic information within the primate frontal cortex. *The prefrontal cortex: executive and cognitive*

functions. A. Roberts, T. W. Robbins and L. Weizkrantz. Oxford, Oxford University Press: 103-116.

Petrides, M., Alivisatos, B. and Evans, A. C. (1995) Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proceedings of the National Academy of Science, USA* 92(13): 5803-5807.

Petrides, M., Alivisatos, B., Evans, A. C. and Meyer, E. (1993a) Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Science, USA* 90(3): 873-877.

Petrides, M., Alivisatos, B., Meyer, E. and Evans, A. C. (1993b) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Science, USA* 90(3): 878-882.

Petrides, M. and Milner, B. (1982) Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* 20: 249-262.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H. and Gabrieli, J. D. (1999) Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10(1): 15-35.

Preuss, T. M. and Goldman-Rakic, P. S. (1991) Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate Galago and anthropoid primate Macaca. *Journal of Comparative Neurology* 310: 429-474.

Price, C. J. and Friston, K. J. (1997) Cognitive conjunction: a new approach to brain activation experiments. *NeuroImage* 5(4 Pt 1): 261-270.

Price, C. J., Mummery, C., Moore, C., Frackowiak, R. S. J. and Friston, K. J. (1999) Delineating necessary and sufficient neural systems: functional imaging studies

of neuropsychological patients. *Journal of Cognitive Neuroscience* 11(4): 371-382.

Raichle, M. E., Fiez, J. A., Videen, T. O., Macleod, A. M., Pardo, J. V., Fox, P. T. and Petersen, S. E. (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex* 4(1): 8-26.

Ricci, P. T., Zelkowicz, B. J., Nebes, R. D., Meltzer, C. C., Mintun, M. A. and Becker, J. T. (1999) Functional neuroanatomy of semantic memory: recognition of semantic associations. *NeuroImage* 9(1): 88-96.

Roland, P. E., Geyer, S., Amunts, K., Schormann, T., Schleicher, A., Malikovic, A. and Zilles, K. (1997) Cytoarchitectural maps of the human brain in standard anatomical space. *Human Brain Mapping* 5: 222-227.

Rugg, M. D., Fletcher, P. C., Allan, K., Frith, C. D., Frackowiak, R. S. and Dolan, R. J. (1998) Neural correlates of memory retrieval during recognition memory and cued recall. *NeuroImage* 8(3): 262-273.

Rugg, M. D., Fletcher, P. C., Chua, P. M. and Dolan, R. J. (1999) The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. *Neuroimage* 10(5): 520-9.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S. and Dolan, R. J. (1996) Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* 119(Pt 6): 2073-2083.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S. and Dolan, R. J. (1997) Brain regions supporting intentional and incidental memory: a PET study. 8(5): 1283-1287.

Savage, C. R., Deckersbach, T., Heckers, S., Wagner, A. D., Schacter, D. L., Alpert, N. M., Fischman, A. J. and Rauch, S. L. (2001) Prefrontal regions supporting

spontaneous and directed application of verbal learning strategies - Evidence from PET. *Brain* 124: 219-231.

Saykin, A. J., Johnson, S. C., Flashman, L. A., Mcallister, T. W., Sparling, M. and Darcey, T. M. (1999) Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. *Brain* 122: 1963-1971.

Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L. and Albert, M. S. (1996a) Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proceedings of the National Academy of Science, USA* 93(1): 321-325.

Schacter, D. L., Buckner, R. L., Koutstaal, W., Dale, A. M. and Rosen, B. R. (1997) Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. *NeuroImage* 6(4): 259-269.

Schacter, D. L., Curran, T., Galluccio, L., Millberg, W. P. and Bates, J. F. (1996b) False recognition and the right frontal lobe: a case study. *Neuropsychologia* 34: 793-808.

Schacter, D. L. and Tulving, E. (1994) *Memory Systems*. Massachussetts, MIT Press.

Scoville, W. B. and Milner, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry* 20: 11-21.

Segal, M. A. and Mandler, G. (1967) Directionality and organisational processes in paired-associate learning. *Journal of Experimental Psychology* 74: 305-312.

Shallice, T. (1988) *From neuropsychology to mental structure*. Cambridge, Cambridge University Press.

Shallice, T. and Burgess, P. (1998). The domain of supervisory processes and the temporal organisation of behaviour. *The prefrontal cortex: executive and*

cognitive functions. A. Roberts, T. W. Robbins and L. Weizkrantz. Oxford, Oxford University Press: 22-35.

Shallice, T., Mcleod, P. and Lewis, K. (1985) Isolating cognitive modules with the dual-task paradigm: are speech perception and production separate processes? *Quarterly Journal of Experimental Psychology* 37(4): 507-532.

Shallice, T. and Warrington, E. K. (1970) Independent functioning of verbal memory stores: a neuropsychological study. *Quarterly Journal of Experimental Psychology* 22: 261-273.

Shimamura, A. P., Jurica, P. J., Mangels, J. A., Gershberg, F. B. and Knight, R. T. (1995) Susceptibility of memory interference effects following frontal lobe damage: findings from tests of paired-associate learning. *Journal of Cognitive Neuroscience* 7: 144-152.

Squire, L. R. (1987) *Memory and Brain*. Oxford, Oxford University Press.

Squire, L. R. and Alvarez, P. (1995) Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology* 5: 169-177.

Squire, L. R. and Cohen, N. J. (1984). Human memory and amnesia. *The neurobiology of learning and memory*. J. L. McGaugh, G. Lynch and N. M. Weinberger. New York, Guildford Press: 3-64.

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O. and Raichle, M. E. (1992) Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proceedings of the National Academy of Science, USA* 89(5): 1837-1841.

Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L. and Pogue, J. (1994) Organisational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 8: 355-373.

Sussman, G. J. (1975) *A computational model of skill acquisition*. New York, American Elsevier.

Talairach, J. and Tournoux, P. (1988) *Co-planar stereotaxic atlas of the human brain*. Stuttgart, Thieme-Verlag.

Teuber, H.-L. (1964). The riddle of frontal lobe function in man. *The frontal granular cortex and behaviour*. J. M. Warren and K. Akert. New York, McGraw-Hill: 410-444.

Thompson-Schill, S. L., D'esposito, M., Aguirre, G. K. and Farah, M. J. (1997) Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a re-evaluation. *Proceedings of the National Academy of Science, USA* 94: 14792-14797.

Thompson-Schill, S. L., D'esposito, M. and Kan, I. P. (1999) Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron* 23: 513-522.

Tononi, G., Sporns, O. and Edelman, G. M. (1992) Reentry and the problem of integrating multiple cortical areas: simulation of dynamic integration in the visual system. *Cerebral Cortex* 2: 310-335.

Tulving, E. (1983) *Elements of episodic memory*. Oxford, Clarendon.

Tulving, E. (1985) Memory and consciousness. *Canadian Psychologist* 26: 1-12.

Tulving, E., Kapur, S., Craik, F. I., Moscovitch, M. and Houle, S. (1994a) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proceedings of the National Academy of Science, USA* 91(6): 2016-2020.

Tulving, E., Kapur, S., Markowitsch, H. J., Craik, F. I., Habib, R. and Houle, S. (1994b) Neuroanatomical correlates of retrieval in episodic memory: auditory sentence

recognition. *Proceedings of the National Academy of Science, USA* 91(6): 2012-5.

Turkheimer, F., Pettigrew, K., Sokoloff, L., Smith, C. B. and Schmidt, K. (2000) Selection of an adaptive test statistic for use with multiple comparison analyses of neuroimaging data. *Neuroimage* 12(2): 219-29.

Vandenberghe, R., Price, C., Wise, R., Josephs, O. and Frackowiak, R. S. (1996) Functional anatomy of a common semantic system for words and pictures. *Nature* 383(6597): 254-256.

Vargha Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W. and Mishkin, M. (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277(5324): 376-80.

Verfaellie, M., Bauer, R. M. and Bowers, D. (1991) Autonomic and behavioural evidence of implicit memory in amnesia. *Brain and Cognition* 15: 10-25.

Verfaellie, M., Koseff, P. and Alexander, M. P. (2000) Acquisition of novel semantic information in amnesia: effects of lesion location. *Neuropsychologia* 38(4): 484-92.

Wagner, A. D. (1999) Working memory contributions to human learning and remembering. *Neuron* 22: 19-22.

Wagner, A. D. (2001). Cognitive control and episodic memory: contributions from prefrontal cortex. *Neuropsychology of Memory*. L. R. Squire and D. L. Schacter. New York, Guildford Press. *3*.

Wagner, A. D., Desmond, J. E., Glover, G. H. and Gabrieli, J. D. E. (1998a) Prefrontal cortex and recognition memory: functional-MRI evidence for context-dependent retrieval processes. *Brain* 121: 1985-2002.

Wagner, A. D., Pare-Blaegov, E. J., Clark, J. and Poldrack, R. A. (2001) Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron* 31: 329-338.

Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H. and Gabrieli, J. D. (1998b) Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport* 9(16): 3711-7.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R. and Buckner, R. L. (1998c) Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science.* 281(5380): 1188-1191.

Wheeler, M. A. (2000). Episodic memory and autonoietic awareness. *The Oxford Handbook of Memory*. E. Tulving and F. I. M. Craik. Oxford, Oxford University Press: 597-608.

Wheeler, M. A., Stuss, D. T. and Tulving, E. (1997) Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychological Bulletin* 121(3): 331-354.

Wiggs, C. L., Weisberg, J. and Martin, A. (1999) Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia* 37: 103-118.

Zattore, R. J. and Mcentee, W. (1983) Semantic encoding deficits in a case of traumatic amnesia. *Brain and Cognition* 2: 331-345.

Zilles, K. (1990). Cortex. *The Human Nervous System*. G. Paxinos. San Diego, Academic Press.

Zilles, K., Armstrong, E., Schleicher, A. and Kretschmann, H. J. (1988) The human pattern of gyrification in the cerebral cortex. *Anatomy and Embryology* 179(2): 173-179.

Zilles, K., Schleicher, A., Langemann, C., Amunts, K., Morosan, P., Palomero-Gallagher, N., Schormann, T., Mohlberg, H., Burgel, U., Steinmetz, H., Schlang, G. and Roland, P. E. (1997) Quantitative analysis of sulci in the human cerebral cortex: development, regional heterogeneity, gender difference, asymmetry, intersubject variability and cortical architecture. *Human Brain Mapping* 5: 218-221.