The role of the prefrontal cortex in episodic memory: PET studies in normal subjects.

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A thesis submitted in conformity with the requirements for
the Degree of Philosophy
in the Institute of Medical Sciences
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Abstract

This thesis documents the findings of a series of positron emission tomography (PET) experiments undertaken to elucidate the neural correlates of episodic memory - in particular, to understand the functional contributions of the prefrontal cortex to episodic memory. Healthy young adults were scanned using [$^{15}$O]-H$_2$O-PET imaging as they carried out encoding and retrieval tasks. The data were analyzed using the cognitive subtraction paradigm and Statistical Parametric Mapping technique of image analysis.

The results clearly document a differential involvement of the left and right prefrontal cortex in encoding and retrieval respectively. The thesis further suggests that the left prefrontal activation is invoked by the task requirement of "working with meaning" of the stimulus. The results are supportive of a role for the left prefrontal cortex in facilitating the formation of a retrievable engram, regardless of the subject's intention.

The right prefrontal cortex is invoked equally in recall and recognition tasks when these tasks are equated for difficulty. The role of the right prefrontal cortex in retrieval, as revealed by PET, is consistent with the concept of "retrieval attempt" and is distinguishable for the concept of "ecphory" which may be a medial temporal or posterior association cortex based process.

The results are discussed in concert with neuropsychological findings and it is concluded that the prefrontal cortex facilitates memory encoding and retrieval processes - though it may not be the site where the engram resides. The discrepancy with established neuropsychological findings is discussed and directions for future research are outlined.
I must first acknowledge my gratitude to the late Dr. Cleghorn - to work with whom I returned to Canada. His absence is still felt - but would have been felt even more had it not been for the guidance and mentorship of my supervisor - Dr. Greg Brown. I owe a special debt to Dr. Brown for shepherding me through the pitfalls and fallow periods which befall a doctoral pursuit. To Profs. F.I.M Craik and Endel Tulving for inviting me to study the ‘science of the mind’ and teaching me about memory - and making it a most memorable experience. To Dr. Robert Zipursky for encouraging me to undertake this journey in learning - at a time when many interesting clinical questions in schizophrenia stood waiting. And to Dr. Sylvain Houle for showing me how one can do wonderful things with a few detectors, mathematics and computers. To this group of talented and supportive mentors - a special thanks.

As I have tried to synthesize the work done over the last three years, establishing the exact parentage of each idea is not possible. Therefore, whenever I refer to our experiments and published papers I use the term “we” - for these papers and their underlying experiments reflect our efforts as a group. Thoughts which are being expressed for the first time in the PET-memory context in this thesis are owned with an “T” - though I am indebted to my committee, and particularly Professor Craik, for help in articulating them.

Thanks to my friends in the trenches - Douglas Hussey, Corey Jones, Stephen Dobbin, Terry Bell, Randi Rose, Kevin Cheung and Drs. Alan Wilson and Jean DaSilva. Through a myriad of kind and intelligent acts they helped me first in getting the work done, and then goaded me on in the seemingly endless task of writing this thesis.

Thanks to two outstanding Institutions - The Clarke Institute of Psychiatry and the Rotman Research Institute - for providing the support and the atmosphere without which work such as this can never be done.

I have thanked but a few, of the many, who have contributed in ways too numerous to make note of here. I have been fortunate to have your help and support. I hope this work meets your expectations.

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Outline of the research and organization of the thesis

The thesis is organized in five chapters. The first chapter provides a review of the relevant literature. It focuses on the concept of memory systems and memory processes as seen from a cognitive perspective. The chapter also reviews the role of different brain regions as revealed by classic neuropsychological studies. The second chapter focuses on the general experimental methods. It outlines the methods of subject recruitment, image acquisition and data analysis that were followed in these studies. It also reviews the assumptions and caveats related to the use of regional cerebral blood flow (rCBF) imaging and to the use of the cognitive subtraction paradigm. In addition, some of the original work done by our group to clarify the use of rCBF imaging is described.

Chapter three is a compilation of articles (three published, two in press) describing the results of the studies that we have done to investigate the role of the prefrontal cortex in episodic memory. Articles #1-3 report studies of encoding, Articles #4-5 report on studies of retrieval.

Chapter four attempts to synthesize the findings of the individual articles. The first section of this chapter highlights the hemispheric asymmetry in the involvement of the prefrontal cortex in encoding vs. retrieval (Hemispheric Encoding Retrieval Asymmetry). The second section shows how this thesis contributes towards a better understanding of HERA by clarifying the functional role of the left prefrontal cortex in encoding and the right prefrontal cortex in retrieval. PET studies have, for the most part, failed to observe activations in the medial temporal region - the possible causes and implications of this are discussed under the heading ‘Where’s the Hippocampus’. The next section entitled “A
rudimentary neurocognitive model of episodic memory” attempts to weave together PET and neuropsychological findings into a speculative, but testable, model of human episodic memory. The last section, “Contributions and Future Research”, points to the salient contributions of this work and to the pertinent questions which deserve further investigation.

The appendix contains abstracts of other studies involving PET imaging of memory in which I have been involved during my doctoral work and the Bibliography lists the citations.
Chapter 1

Introduction

This chapter introduces the theoretical framework that has guided the studies which follow. In particular, this chapter shows how the human ability of 'memory' comprises several different memory systems, each of which is distinguished by the processes which underlie it and the brain systems which subserve it. The chapter outlines what was investigated (the difference between encoding and retrieval in episodic memory) and distinguishes it from what was not studied (short-term and non-declarative memory). The chapter then reviews what is known about the neural correlates of episodic memory from cognitive and neuropsychological studies with a special focus on studies relating to the prefrontal cortex.

Memory Processes and Memory Systems

The scientific study of memory as we currently know it can be traced back to Ebbinghaus and his treatise Über das Gedächtnis, 1885, which launched what is termed the 'verbal learning' tradition in memory research (Tulving 1995). The emphasis of the verbal learning school was on experiments which used word-lists and manipulated the conditions under which verbal learning took place. The results from these experiments were usually interpreted in terms of the strength of the associations between pairs of words. Learning was seen as the formation of strong associations, remembering as the report of those associations (Tulving 1995). This tradition was dominant until the
introduction of the information processing framework in the 1960s (Ellis and Hunt 1993; Tulving 1995).

One contribution of ‘information processing’ approach to the study of memory was the division of memory into short-term memory (also called primary or working memory) and long-term memory (secondary memory) (Brown 1958; Peterson and Peterson 1959; Atkinson and Shiffrin 1968). Soon afterwards concepts such as levels of processing, encoding specificity and encoding/retrieval interactions suggested that long term memory was subserved by an interaction of different cognitive processes (Craik and Lockhart 1972; Tulving and Thomson 1973; Craik and Tulving 1975). Thus the understanding of memory evolved from the concept of ‘strength’ of associations to different types of memory (short-term vs. long-term), each subserved by discrete yet interdependent memory processes (encoding, consolidation and retrieval). These distinctions between encoding and retrieval, and short and long-term memory form the framework for the design of the experiments in this thesis and are discussed under the heading of memory processes and memory systems respectively.

Memory Processes

An important influence of information processing theories was that memory came to be seen as an interaction of dynamic processes rather than as a static entity with ‘storage bins’ and fixed ‘association strength’ (Ellis and Hunt 1993). Memory was seen as the result of an act that begins with the subject’s first interaction with the test-material and ends with the last retrieval of that memory (Tulving 1983). This process of learning changes the brain - the change or the imprint is referred to as the ‘engram’ - and the
process which leads to the formation of an engram is called encoding. This engram provides the basis for subsequent reconstruction of the event as a ‘memory’. Memory, thus, is the outcome of a dynamic interaction between the conditions at encoding and the conditions at retrieval, mediated by an intervening engram which connects the former event to the latter (Craik and Tulving 1975; Tulving 1983). Therefore, any comprehensive account of memory within this scheme will have to explain both encoding and retrieval, as well as the interaction between them.

Another impact of information processing was the realization that encoding and retrieval were not unitary processes. They were more accurately understood as a combination of several discrete, potentially separable, processes (Tulving 1983). Moreover, even the engram was not a static entity. Studies of interference showed that between encoding and retrieval the engram is susceptible to the effects of ongoing information processing. To accommodate this finding, Tulving (1983) proposed that the engram first laid down at encoding, gets continually recoded due to the effects of the intervening events, and even the process of retrieval recodes the engram.

The studies in this thesis conform to this view of memory. Encoding and retrieval are understood to be distinct and separate processes, albeit intimately inter-related. Therefore, in our studies we have made a special effort to separate the two. In fact, functional neuroimaging in uniquely suited to separate the neural correlates of encoding from those of retrieval. With traditional cognitive and neuropsychological methods it is difficult to distinguish the brain regions involved in encoding from those involved in retrieval. If a subject fails to retrieve a particular memory, it is difficult if not impossible, to ascertain whether that reflects a failure of encoding, a failure of retrieval or an improper
interaction between the two (Buckner and Tulving 1995). Fortunately, encoding and retrieval are separated in time. Therefore, one can use functional imaging to study encoding as distinct from retrieval. This distinction between encoding and retrieval formed one of the driving forces for this thesis and is reflected in the design of the experiments: Article #1, 2 and 3 report studies of encoding and Article #4 and 5 report studies of retrieval.

Memory Systems

The last two decades have seen the confluence of cognitive psychology and neuropsychology, which has reinforced the understanding that memory (defined as the ability to utilize past experiences to modify present and future thoughts and action) is not a unitary system. It is now customary to think of memory as being served by different memory systems, each served by a distinguishable network of brain regions (Tulving 1995). At present, there are two dominant taxonomies of memory systems which guide research. In their present version, these two taxonomies, proposed by Squire (Squire and Knowlton 1995) and Tulving (Tulving 1995), are more striking in their similarities than in their differences. The taxonomies are shown in Figure I-1.
Figure 1-1. Displays the two taxonomies (Squire '95 and Tulving '95) which show the relationship and hierarchy of the different memory systems. The major difference between the two taxonomies concerns the status of Semantic Memory. Squire considers it an instance of explicit memory, while Tulving considers it an instance of implicit memory and groups it with Procedural and PRS. The Skills and Habits in Squire's model corresponds directly with Procedural in Tulving's; and the Priming corresponds to PRS. There is no clear equivalent of Conditioning and Non-Associative learning in Tulving's model.
Memory systems can be separated along various dimensions as shown in Figure I-1. Perhaps the most important dimension along which these memory systems can be differentiated is the duration between encoding and retrieval. Almost a century ago William James introduced the concept of primary vs. secondary memory. In his view primary memory is comprised of the contents of which a person is consciously aware at a given moment. It is bounded by the limited capacity of consciousness which can apprehend only a few concepts at given time, and is restricted to short durations since the contents of consciousness are usually fleeting. In contrast, secondary memory comprises the bank of knowledge that is potentially accessible to conscious awareness. Therefore, primary memory, as it was then understood, is a time-limited and capacity-limited subset of memory which holds the sway of consciousness in the present; while long-term memory is the time and capacity unlimited store of knowledge about facts and events that are potentially available for retrieval (Ellis and Hunt 1993).

With the dawn of information processing theory, and Atkinson and Shiffrin’s ‘modal’ model of memory, the distinction between short and long-term memory was recast (Atkinson and Shiffrin 1968). While the notion of limited capacity and short-duration were retained, short-term memory now became the workspace for “rehearsing, coding, retrieving” (Ellis and Hunt 1993). Added to this was the notion that contents of short-term memory followed different principles of forgetting than those obeyed by contents in long-term memory (Brown 1958; Peterson and Peterson 1959); and that the coding of information in short-term memory more directly reflected the modality in which information was presented, while long-term memory coding seemed to be largely amodal (Baddeley 1966a; Baddeley 1966b; Ellis and Hunt 1993). This distinction between short
and long-term memory gained a strong hold in the neurologically oriented theories of memory as it was noted that amnesia, a disorder which has singularly shaped our understanding of the neural basis of memory, impairs long-term memory in the presence of preserved short-term memory (Baddeley and Warrington 1970). Thus from a psychological, information processing and neuropsychological perspective there are strong grounds for considering short and long-term memory as being different systems.

The concept of short-term memory, as distinct from long-term, has now been studied in primates (where it is often referred to as working memory) (Goldman-Rakic 1994) and elaborate models have been developed to define its components and sub-components in humans (Baddeley 1992). PET has also contributed to this distinction by clearly demonstrating that short and long-term memory are subserved by different structures, though there may be some overlap (Moscovitch et al. 1995). A particularly counter-intuitive, but compelling demonstration has been that retrieval from long-term memory of episodic information stored for one-minute and that stored for one week involved very similar neural regions. Andreasen et al. (1995a) had subjects learn a word list one week prior to, and a similar list one minute prior to a recognition test (during which they were scanned). The comparison of the brain regions invoked during the tasks showed that recognition of short and longer-interval material both invoked similar regions (the right prefrontal cortex, anterior cingulate and the cerebellum). These studies show that it is not tenable to consider short-term or working memory as a “short-duration” subset of long-term memory, but that these two types of memory are implemented via different processes which in turn are subserved by different neural substrates.
This distinction, between short-term and long-term, is observed both by Squire and by Tulving in their taxonomies (Figure I-1). This thesis primarily addresses long-term memory.

Long-term memory can be operationalised as the system that stores information longer than short-term memory, encompassing durations from a few minutes to a lifetime. As shown in Figure I-1, both Squire and Tulving postulate four different long-term memory systems: Episodic, Semantic, Priming/PRS and Skills and Habits/Procedural. Squire also refers to classical conditioning and non-associative learning, but those are not directly relevant to our work and therefore will not be discussed further.

The four long-term memory systems can be further classified into two groups. The episodic and semantic memory systems can be seen as propositional/declarative memory. The terms derive from the fact that subjects declare the results of the operation of these memory systems as propositions. This is in contrast to Priming/PRS and Skills and Habits/Procedural which are non-declarative. The subject does not declare the results of these memory systems. The operation of these systems has to be inferred from the changes in performance - be it the increased frequency of a certain completion of a word-stem, increased speed of identifying perceptually degraded stimuli, or increased proficiency at reading mirror-image writing (Graf and Schacter 1985; Schacter 1992).

Several overlapping words are used in the description of long-term memory. Two dichotomies frequently used to classify long-term memory are: declarative vs. non-declarative and explicit vs. implicit. Explicit-implicit derive from the types of experiments which are conventionally done to test the operations of these memory systems. Memories which can be declared as propositions can be tested explicitly by asking the subjects
"have you seen this before?" or "have you heard this before?" Thus declarative, propositional and explicit are often used interchangeably. Memories, which are not available to conscious awareness, cannot be declared as a direct proposition. They are inferred implicitly by monitoring the subject’s performance on a test which measures some aspect of behaviour which indirectly reflects the operation of the memory system. Thus, non-declarative and implicit are used interchangeably. Declarative and non-declarative will be used in this thesis for the sake of uniformity.

The non-declarative memory systems are not the subject of this thesis. They will be discussed only insofar as they impact on the interpretation of the results of the episodic memory system.

The two declarative forms of memory are semantic and episodic (Tulving 1972; Tulving 1983). Semantic memory refers to general knowledge of the world while episodic memory corresponds to autobiographical memories. The semantic memory system contains facts, ideas and concepts as opposed to the episodic memory system which retains personal episodes. Semantic knowledge is organized in an impersonal and conceptual fashion while the contents of episodic memory are organized in a spatio-temporal context with reference to the self.

The distinction between these two memories can be illustrated in a simple example. When a subject is asked: "What is the capital of France?" The subject should declare: "Paris." The answer to this question requires recourse to semantic memory. This answer is not usually accompanied by an awareness of the time and the situation when this fact was learned. This impersonal general knowledge is an instance of semantic memory. On the other hand, if the question was: "Do you remember your last visit to Paris?" This
question can only be answered with reference to the time and place of one's visit to Paris - a memory of Paris as an episode in one's life.

It should be noted here that while the above noted questions would typically invoke semantic and episodic memory respectively, there can be exceptions. For instance, one can remember that Paris is the capital of France only because one so informed just the day before. Conversely, one may have no personal memory of a long-forgotten visit to Paris, but may infer it from a souvenir that was bought on the trip; a process of inference which requires no 'personal' knowledge. Therefore, what distinguishes these two systems is not only the questions asked to elicit them, but also the nature of the information that helps in answering the questions. Information, devoid of any conscious connection to one's own past derives from semantic memory even though it may be used to answer personal questions. Personal information with a spatio-temporal awareness derives from episodic memory even when used to answer questions of general knowledge.

As is shown in Figure I-1 both Squire and Tulving support a distinction between episodic and semantic memory systems. The difference lies in how they classify semantic memory. For Squire, semantic memory is explicit. For Tulving it is implicit. For Squire, explicit implies those memory systems which declare their contents explicitly as propositions. Since one declares the answer to the question "What is the capital of France" as an explicit proposition, it is an explicit form of memory. For Tulving, tests are explicit only when the subject is "consciously aware of [the memory] as a personal experience" (Tulving 1995). Since semantic recollections (the capital of France) are rarely accompanied by the spatiotemporal correlates of when they were learned, semantic memories are implicit in Tulving's scheme. Both taxonomies acknowledge semantic
memory as a declarative, propositional memory system which stores impersonal facts and
general knowledge, the retrieval of which is devoid of any conscious awareness of where
and when the fact was acquired. Beyond just the use of different terms Tulving and Squire
differ on one important fundamental point. According to Squire, both the semantic and
episodic memory systems are declarative, and all declarative memories are encoded with
the involvement of the medial temporal system. This is supported by Squire’s assertion
that patients with medial temporal lesions do not learn new factual information (Squire
and Knowlton 1995). Tulving acknowledges that semantic learning is not totally preserved
in episodic amnesics, but has demonstrated that they can remember some new semantic
information independent of the episodic and non-declarative systems, and thus argues for a
separation of the episodic and semantic (Tulving et al. 1991).

Whether episodic and semantic memory reflect two distinct systems has been a
favorite issue of debate in cognitive psychology. In Tulving’s view episodic and semantic
systems carry different kinds of information, process the information differently and are
subserved by different neuronal systems (Tulving 1983; Tulving 1984). Opponents of this
approach concede that episodic and semantic memories differ in their informational
content, are not convinced that this difference alone is sufficient to classify them as
different systems. They suggest that the episodic/semantic distinction could be better
accommodated as differential functioning of a unitary memory system (McKoon and
Ratcliff 1986; Wilson and Baddeley 1988; Squire and Knowlton 1995); that semantic
memories reflect episodic memories shorn of their spatio-temporal context (McKoon and
Ratcliff 1986); that it is better to classify material depending upon the time since the
material was learnt (i.e. new learning vs. overlearned) rather then resort to
semantic/episodic (Baddeley 1984). The controversy still continues. Tulving wrote in 1983, before the advent of modern functional neuroimaging, "If neuroanatomical and neurophysiological correlates of episodic and semantic memory systems could be identified, the issue of the functional difference between the two systems would become redundant." The results of this thesis provide evidence for a neurophysiological distinction between episodic and semantic memory - perhaps, the kind of neurophysiological information that Tulving was seeking in 1983. However, one has to be cautious not to interpret neurophysiological differences between two tasks as sufficient evidence for two memory systems.

In this research there were several reasons for conforming to the episodic/semantic distinction in designing our experiments: i) The two taxonomies in current usage (Figure I-1), in cognitive psychology (Tulving) and in neuropsychology (Squire), treat episodic and semantic memory systems as neurologically differentiable systems; ii) the dichotomy is supported by experimental double-dissociations which show that it is possible to manipulate the operations of semantic memory, without an effect on episodic memory performance and vice versa. Several such examples are tabulated in Tulving's account (1983); iii) this dissociation is also supported in neuropsychological studies of patients who have lesion-associated amnesia (Weiskrantz 1982) and in patients with functional amnesia (Schacter et al. 1982). In both cases it has been shown that episodic memory is significantly impaired, with little or no changes in semantic memory. In fact patients with post-traumatic amnesia may acquire new semantic concepts, despite little or no ability to acquire episodic information (Tulving et al. 1988); iv) there is a wealth of literature that has used the episodic/semantic dichotomy to study long-term
declarative memory and by conforming to this framework we could relate our results to this body of literature; v) finally, while there may be debate over whether episodic/semantic constitute aspects of a single memory system or are two different memory systems, there is agreement on how to operationalise semantic and episodic memory in word-list tests and therefore the concept has important ‘heuristic’ value (Tulving 1983; Baddeleely 1984).

For the reasons cited above this thesis used the episodic-semantic distinction as a foundation for designing experiments to study of the neural correlates of long-term memory using PET. The central effort of this thesis is to understand the neural basis of episodic memory processes that reflect the encoding of information into long-term memory and the retrieval of information from it.

The Neural Basis of Memory Functions

One ought to know that on the one hand pleasure, joy, laughter and games; and on the other grief, sorrow, discontent and dissatisfaction arise only from the brain.

~ Hippocrates.

From the earliest times it has been known that the brain subserves memory. How it does so, has eluded satisfactory description. As early as the third century, Bishop Nemsios had enunciated that the brain consisted of three chambers. The anterior chamber registered perception, the middle chamber harbored reason and the posterior chamber stored
memories (Bruyn 1982). In the twelfth century this model was explicaded further by Guillaume de Conches who stated that only those things which were deeply considered were transferred from the site of reason to the site of memory (earliest mention of levels of processing perhaps!) (Bruyn 1982). In the late eighteenth century it gave way to the speculations of the phrenologists who published detailed accounts of where under the skull the faculties of memory reside (Peacock 1982). The more modern empirical studies to locate memory in the brain can be traced to reports of the experimental work by Lashley, who concluded in 1950 that “it is not possible to demonstrate the isolated localization of a memory trace anywhere in the nervous system” - just three years prior to the beginning of the modern era of study of amnestic patients.

The modern era can perhaps be traced to the work on the classic amnestic, HM, and the report by Scoville and Milner (1957) on the study of loss of long-term memory after bilateral hippocampal lesions. This was the beginning of modern neuropsychological lesion analysis with respect to memory. This, work led to two lines of related research. In humans, this led to the analysis of the memory consequences of regional brain injury and in animal experimentation it meant the induction of controlled and circumscribed lesions followed by an analysis of performance of the animals on tasks which were analogues of human memory. Most of what we know about the neural correlates of memory derives directly or indirectly from these two methods. The newest addition to this bank of knowledge are the data from functional neuroimaging.

When experiments for this thesis were being designed, there was only one published PET study of memory (Squire et al. 1992). As a result, there was no coherent body of PET literature to guide our work. Therefore, most of the original thinking was
guided by knowledge derived from neuropsychological studies of memory which are discussed in this chapter. Since 1992, however, several functional imaging studies of memory have been published. These studies appeared at different times during the course of this research and are introduced and discussed (in Articles #1-5) as they impacted on this research. Those functional neuroimaging studies which did not directly influence the individual studies, but are relevant nonetheless, will be mentioned in the final discussion of our findings.

Present neuropsychological research can be fairly summarized as pointing to the importance of three major brain regions: the medial temporal regions, the frontal regions, and elements of the limbic circuit apart from the medial temporal regions.

Medial temporal regions and their contributions to memory

Perhaps the earliest linkage of temporal lobes to memory can be traced to Bekhterev's report, in 1899, of a patient with profound memory impairment who on post-mortem analysis showed extensive bilateral medial temporal damage (Kolb and Whishaw 1990). However, the present acceptance for the role of the medial temporal lobes can be traced more directly to HM, who in 1953, had a bilateral resection of the medial temporal lobe in an attempt to treat his intractable refractory seizures (Scoville and Milner 1957). HM, single-handedly perhaps, has shaped our conceptions of what the hippocampus does for memory. On neuropsychological testing, HM has consistently showed severe deficits in long-term verbal and spatial memory - dense anterograde amnesia with temporally graded retrograde amnesia (Milner et al. 1968). This is in contrast to his performance on non-declarative procedural learning tasks, where he shows significant learning in tasks like the
Rotary Pursuit, Bimanual Tracking and the Tapping task (Corkin 1968), though without any recollection of ever having done these tasks. These memory deficits are noted in the face of preserved perception and general intellectual abilities and without any impairment in short-term memory (Milner et al. 1968).

A more recent case, RB, of selective hippocampal damage further confirms the role of hippocampus in declarative memory (Zola-Morgan et al. 1986). RB sustained an ischemic episode secondary to a coronary bypass graft, but recovered from the surgery to live another five years. During this period he showed dense anterograde amnesia, with a milder temporally-graded retrograde amnesia. This amnesia occurred in the face of otherwise preserved perceptual and cognitive abilities - similar in these regards to HM (Milner et al. 1968). RB's memory impairment was prospectively documented and a post-mortem study showed that RB had selective and specific bilateral damage to area CA1 of the Ammon's horn of the hippocampus (Zola-Morgan et al. 1986). Incidentally this region was noted by Sommers, in 1880, to be particularly sensitive to ischemic damage (Kolb and Whishaw 1990).

Both these cases, HM and RB, demonstrate the cardinal aspects of the amnestic syndrome that accompanies bilateral medial temporal and hippocampal damage: impaired recall of episodic memories acquired after the incident (anterograde amnesia) with a relatively preserved recall of episodic memories acquired prior to the injury/operation. They also exhibited relatively preserved abilities to acquire motor-skills and habits, although doing so in the absence of any episodic memory of the learning trials themselves. All of this in the face of preserved perception, preserved short-term memory and preserved general intellectual and reasoning abilities. This evidence has been interpreted to
signify a crucial role for the hippocampus in memory function, especially in the acquisition of new episodic memories.

The memory impairments associated with unilateral damage are more circumscribed and the contributions of the left hippocampal region can be dissociated from those of the right hippocampal region. In studies of unilateral hippocampal resections or related damage different authors have shown that maze learning (Corkin 1965), facial recognition (Milner 1968), spatial position and spatial association tasks (Petrides 1985; Kolb and Whishaw 1990) are specifically sensitive to right unilateral hippocampal damage. These functions are either unimpaired, or relatively spared after left hippocampal damage. On the other hand, tests requiring the learning of word lists and paired associates (Kolb and Whishaw 1990), non-spatial association (Petrides 1985) and self-ordered word recall (Petrides and Milner 1982) are sensitive to lesions of the left hippocampus.

These data suggest a functional dissociation between the role of the right hippocampal region (which mediates spatial/non-verbal memory) and that of the left hippocampal region (which mediates non-spatial/verbal memory). However, the deficits are material and not modality specific, and the pattern of deficits are similar whether the materials are presented aurally or visually (Kolb and Whishaw 1990). Despite robust evidence for functional asymmetry, patients do exhibit a limited capacity to store and access both types of material using either hemisphere (Jones-Gotman 1986).

Studies in patients are complemented by studies in primates with selective experimental lesions using simple behavioural tasks. Particularly useful have been the delayed non-matching-to-sample (DNMS) and a delayed discrimination task (DD) (Mishkin 1978; Mishkin and Appenzeller 1987). In the DNMS task the animal is presented
with two objects, one of these the animal has seen in a prior trial and the other is new. The animal is rewarded for identifying the new object. Since the animal must remember the old object after just a single trial this task has been considered analogous to the human episodic memory (Mishkin 1978; Mishkin and Appenzeller 1987). On the other hand in the DD, the animal is shown a single object, repeatedly paired with new objects and the animal is rewarded for identifying the old object which remains constant across trials. Since this task requires the learning of an association over several trials, similar to a ‘habit’, Mishkin considers this task an analogue of the procedural memory (Mishkin 1978; Mishkin and Appenzeller 1987).

Using these paradigms Mishkin has shown that performance on the DNMS, not the DD, is sensitive to the combined lesions of the hippocampus and the amygdala (Mishkin 1978; Malamut et al. 1984). It has now been shown that the same differential deficits are seen when pictures are used instead of objects (Overman et al. 1990) or when tactile learning tasks are used (Murray and Mishkin 1984). In Mishkin’s original view, both the amygdala and the hippocampus were equally important and performance deficits ensued only when both were damaged simultaneously (Mishkin 1978; Malamut et al. 1984).

However, Mishkin’s original view [which posits an equally important role for both the amygdala and the hippocampus] has now been contested. In a series of experiments in primates using the DNMS/DD distinction Zola-Morgan and Squire have clarified the respective contributions of the hippocampus and the amygdala. They demonstrated that selective hippocampal lesions led to deficits in DNMS (Zola-Morgan and Squire 1986) and further showed that Mishkin (1978) may not have observed DNMS deficits since their
monkeys had received extensive preoperative testing on the paradigm (Zola-Morgan and Squire 1986). More recently, using MRI guided, stereotaxic, highly selective radio-frequency lesions of the hippocampus have been shown to cause impairments in DNMS - confirming that hippocampal function is essential for normal functioning on monkey analogues of episodic-memory tasks (Alvarez et al. 1995). This view is supported by the report of RB [mentioned above] who shows dense anterograde amnesia with very specific lesions circumscribed to the CA1 region (Zola-Morgan et al. 1986).

Studies have also clarified the role of the amygdala. Mishkin's surgical approach to the amygdala lesioned the surrounding perirhinal cortex (Mishkin 1978; Zola-Morgan and Squire 1986). Stereotaxic lesions limited to the amygdala, which explicitly spare the perirhinal cortex, neither impair DNMS performance nor exacerbate the effects of hippocampal lesions on DNMS (Zola-Morgan et al. 1989a). The amygdala lesions do alter the emotional reactivity to the presented stimuli, suggesting a role in the affect modulation, but do not impair memory performance per se (Zola-Morgan et al. 1989a). On the other hand, the perirhinal cortex which was damaged as a byproduct of amygdala surgery in Mishkin's original experiments seems to have an independent role in DNMS tasks. Lesions of the perirhinal and parahippocampal cortex that spare the hippocampus and the amygdala caused profound memory impairment (Zola-Morgan et al. 1989b). These results are anatomically understandable since the perirhinal cortex and the parahippocampus are the source for 60% of the afferent input to the entorhinal cortex on its way to the hippocampus (Insausti et al. 1987). The perirhinal cortex has now been shown to exacerbate the effects of a hippocampal lesion, suggesting that it is not just a
conduit of information but may play an independent role in the mnemonic process (Zola-Morgan et al. 1993).

While it may seem that the role of the amygdala has been clarified in the DNMS task in monkeys, Markowitsch has drawn attention to cases with bilateral selective lesions to the amygdala, or to related basolateral limbic structures, who have notable memory deficits (Markowitsch 1995a). This raises the important issue of species differences in neuroanatomy, and cautions against a simple extrapolation from relatively mechanistic tests such as DNMS to the phenomenologically rich episodic memory (Markowitsch 1995a).

In summary, the human studies and animal data permit one to conclude with reasonable certainty that medial temporal structures are crucial for memory function. Episodic declarative memory is affected most of all, while working and procedural memory systems are spared. The usual consequence of injury involving hippocampus and its adjoining perirhinal and parahippocampal cortex is a transmodal anterograde amnesia, which is enduring, and which may be relatively material-specific depending upon the side of the lesion. The precise relative contributions of the perirhinal, parahippocampal, entorhinal and hippocampus proper to the mnemonic process are yet to be clarified.

Other Limbic and Diencephalic elements.

Delay and Brion, 1969, advanced the hypothesis that the hippocampus, the fornix and the mamillary bodies function as a single functional circuit and that damage anywhere along this circuit resulted in a similar memory impairment. The hypothesis received further support from Warrington and Weiskrantz (1982) who considered the fornix as an
essential connection between the frontal and the temporal cortices in the implementation of episodic memory. The advent of CT and MRI made it possible to localize fornicial lesions with accuracy and also made it possible to rule out concomitant involvement of other regions. In the last few years there have been several reports of patients with isolated, unilateral (Grafman et al. 1985; Gaffan et al. 1991; Hodges and Carpenter 1991), or bilateral fornicial lesions (D'Esposito et al. 1995), due to trauma or surgery, which resulted in dense anterograde amnesia, similar to that observed after hippocampal lesions. A review of this evidence led Grafman et al. (1985) to state that “fornix cerebri has a role in the maintenance of information accessibility to both encoding and recall during post-working memory processing and in the organization of verbal information during encoding and/or retrieval for declarative (recall) purposes”.

Striking support is obtained from a recent report of a right-handed 59-year-old female whose main complaint was that of memory loss (Araki et al. 1994). Clinical examination revealed dense anterograde amnesia, while semantic and procedural memory remained intact. Radiological procedures (CT scan and MRI) revealed a tumor of the septum pellucidum which involved regions from the lower part of the corpus callosum and the anterior parts of the bilateral fornices. Radiological and operative findings showed that the thalamus, the mamillary bodies, the hippocampus, and the basal forebrain were normal and uninvolved. The tumor was surgically removed and post-operatively the verbal and non-verbal memory impairments disappeared, presumably from the decompression of the fornices. Pre- and post-operatively, the patient had no aphasia, and her short-term memory, intelligence, and other frontal functions were intact (Araki et al. 1994). This case of a discrete fornicial lesion, which results in reversible memory impairment in the face of
few other cognitive impairments, is a rather convincing demonstration of the role of the fornix in memory function.

Studies in rats and primates have attempted to model the fornical deficits observed in humans. In both rats (Gaffan 1972; Aggleton et al. 1992) as well as primates (Gaffan 1977) it has been possible to demonstrate impairment in recognition tasks which are considered the analogues of human episodic memory. Gaffan (Gaffan and Harrison 1989; Gaffan 1993) has further tried to elucidate the specific contribution of the fornix to the process of visual recognition and has suggested that the fornix may have a crucial role in "scene learning" as opposed to just "place learning" - a concept that evolves from studies which show that animals with fornicial lesions have preserved ability to make simple spatial associations but show impairments in learning of complex naturalistic scenes. Gaffan asserts that what makes human memory 'episodic' is the ability to relate an observed stimulus to its spatio-temporal context, and the fornix with its unique role in "scene learning" may thus be a crucial mediator of human episodic memory, while not so involved in human semantic memory.

Another subcortical structure, the medial dorsal nucleus (MDN) of the thalamus has been associated with specific memory impairments in humans. These observations derive mostly from studies of patients with Wernicke-Korsakoff syndrome, especially those who exhibit Korsakoff's disease - a disorder, usually of alcoholic etiology, characterized by anterograde amnesia, retrograde amnesia and confabulation in the face of relatively preserved working memory and conscious awareness (Langlais 1992; Mair et al. 1992). Almost a century ago, neuropathologists had observed that the mamillary bodies (MB) and the median dorsal nucleus of the thalamus (MDN) are lesioned in patients with
Korsakoff’s disease. Since then the relative contributions of the two structures, MB and MDN, to memory has been a matter of debate. Different authorities have suggested that MB lesions alone are responsible for the noted amnesia (Mair et al. 1992), or, MDN lesions alone are sufficient for amnesia (Victor et al. 1989); while Mishkin (Mishkin 1982) has suggested that there are two independent pathways, a hippocampal-fornicial pathway that involves the MB and an amygdala-efferent pathway that projects to the MDN. A severe amnestic damage results only when both of these nuclei or their corresponding pathways are damaged.

Support for an independent role for the MDN is obtained from studies of patients with relatively circumscribed diencephalic tumors (Brown et al. 1989) and thalamic infarctions (Graff-Radford et al. 1985; von Cramon et al. 1985; Graff-Radford et al. 1990). Support is also obtained from lesion studies in monkeys who have selective lesions to the medial thalamic nuclei (Zola-Morgan and Squire 1985; Aggleton 1986).

However, the role of the MDN remains unclear for several reasons: first, most data pertaining to the MDN derives from Korsakoff’s patients of alcoholic etiology (Langlais 1992). Patients with alcoholic etiology have concomitant alterations in several brain regions and several biochemical systems; in particular lesions in the mamillary bodies, a region which has been shown to be linked to the hippocampus and important in memory systems. Second, patients with discrete thalamic lesions are few and far between (Mair et al. 1992). Finally, it is now appreciated that several cases of amnesia associated with discrete thalamic lesions, are actually associated with relatively widespread functional involvement (hypoperfusion or hypometabolism) of the prefrontal and medial temporal cortices (Kolb and Taylor 1990; Pepin and Auray-Pepin 1993; Terao et al. 1993; Clarke et
al. 1994). The last finding is particularly sobering as it suggests that even the best structural localization, using MRI and post-mortem techniques, may not reveal the widespread functional deficits in anatomical regions removed from the site of the structural lesion.

In summary, subcortical limbic structures (fornix and the mamillary bodies) along with diencephalic structures are crucial to memory. Evidence in animals suggests that the nature of deficits following lesions to these areas may be different, though it has not been possible to reliably separate the two types of deficits. More importantly, some of the early functional imaging data suggests that even after discrete structural lesions the functional deficit may be much more widespread. This obviously complicates any simple inferences regarding lesion localization derived from anatomical or structural data alone.

Role of the Prefrontal cortex in memory.

There is considerable difference in opinion regarding the involvement of the prefrontal cortex in memory: Shimamura et al. stated in 1990 that patients with frontal damage demonstrated "normal recall and recognition memory ... for words and facts" i.e. for episodic and semantic memory. A more conventional position has been that recall may be impaired in frontal patients but that recognition is spared. But, recently a study by Stuss et al. (1994) using a large sample concluded that "[while] the absence of recognition deficits [in the face of impaired recall] has been considered one of the defining criteria of frontal memory deficits ... We found significant recognition deficits." In light of these apparent contradictions two questions are pertinent: Is the prefrontal cortex involved in long-term episodic memory at all? If it is, what is the functional nature of the contribution.
that the prefrontal cortices makes to the processes of encoding, consolidation and retrieval? It was the intention of the thesis to address some of these issues.

Perhaps the earliest notions of a role of the prefrontal cortex in memory arose from the work by Jacobsen in the 1930s, where he noted impairment on tests such as delayed alteration and delayed response in primates who were selectively lesioned in the frontal cortex. Since the animals performed appropriately under conditions of no delay, certifying proper perceptual and motor functions, a logical interpretation of the findings was that frontal lesions led to “a loss of recent memory” (Stuss and Benson 1986). However, subsequent work has reinterpreted that finding. The delayed response and delayed alternation tests with short duration (10 to 15 seconds) are now seen more as tests of working memory and much of the earlier findings have been reconceptualised in terms of attention deficits (Stuss and Benson 1986).

This reconceptualisation is representative of the central debate regarding the role of the prefrontal cortex in memory. There is reasonable agreement that patients with prefrontal lesions do show some deficits in selected aspects of memory performance. It would also be fair to say that there is agreement that the severity and nature of these deficits is not the same as that observed with patients with hippocampal-thalamic amnesia. But there is disagreement whether these deficits should be labeled as “core” memory deficits or whether they are better understood as “impairment of attention” or “impaired strategy” or other such primary cognitive construct.

So, the important questions are: do frontal patients show evidence of impairment on “standard” tests of memory - viz. item recognition, cued-recall and free recall? And - are these deficits best understood as a primary deficit in memory or are they better
understood as the secondary consequence of disruption of some other primary cognitive capacity such as “attention”, “strategy”, “organization”, “inhibition” etc. The evidence that bears on these questions is reviewed here.

Prior to the 1980s there were several studies, mainly uncontrolled case reports, of studies on patients with frontal tumors, anterior communicating artery aneurysms and lesions, restricted frontal trauma and frontal leukotomies. Stuss and Benson (1986) reviewed this evidence and concluded “a preponderance of reported studies suggest that the frontal lobes have little, if any, role in the memory processes”. There were several drawbacks in most of the studies available then. Localization of lesions was perhaps the biggest problem. Since there was no neuroimaging corroboration most studies relied on indirect evidence to infer frontal lesions, except perhaps in the cases of surgical frontal lesions. Furthermore, many studies had not controlled for effects of proactive interference, aphasia and other factors we now understand could confound the conclusions.

Since Stuss and Benson’s conclusion several studies have looked systematically at memory deficits and the prefrontal cortex. These studies have used more homogeneous populations, have confirmed lesion localization using neuroimaging, and in several instances have controlled for confounding factors or corrected for them statistically. Most of this work comes from two centers: Shimamura, Janowsky and Squire (Shimamura and Squire 1987; Janowsky et al. 1989a; Janowsky et al. 1989b; Shimamura et al. 1990; Shimamura 1995; Squire and Knowlton 1995) from San Diego; and Milner, Smith and Petrides (Milner 1982; Milner and Petrides 1984; Smith and Milner 1984; Milner et al. 1985; Petrides 1985; Petrides 1989; Milner et al. 1991) from the Montreal Neurological Institute. While these studies confirm deficits in memory function with prefrontal lesions,
they also show that prefrontal deficits are not qualitatively similar to, nor as severe as, the deficits observed after temporal-diencephalic lesions.

Milner studied a series of individuals who had unilateral frontal resections for relief of focal epilepsy and observed that they had relatively preserved recognition, though patients with right frontal lesions made errors in monitoring the sequence of externally ordered events (Milner 1982). Smith and Milner (1984) further reported that these patients had little difficulty in immediate free-recall of spatial location of the objects though they did show impairments after intervals of 24 hr. and greater. Another observation of interest was that one such patient, with traumatic injury to the left prefrontal cortex showed particularly poor memory, associated with an inability to benefit from levels of processing, an observation that may now make sense in light of the findings to be presented in this thesis (Zatorre and McEntee 1983).

Significance of interval between learning and recall was also borne out in a study by Jetter and colleagues who studied patients with unilateral and bilateral frontal lesions and found that while performance on standard tests was not different at fifteen minutes, patients were significantly impaired in free recall after 24 hours (Jetter et al. 1986). In another cued-recall study Vogel (1987) reported that patients with frontal lesions were impaired on learned paired-associates, both immediately after learning and with a delayed recall, though the effect of the lesion was greater in delayed recall. In this study patients with frontal lesions were compared to those with medial temporal and diencephalic lesions and it was observed that the level of deficit in all tests of recall was greater in patients with medial temporal and diencephalic lesions. The study also found that only patients with frontal lesions were helped significantly when they were provided with opportunities to
engage in greater depth of processing. Patients with temporal-diencephalic lesions showed little benefits (Vogel et al. 1987). This suggests that the lesion-induced impairment in frontal functions is at least partially remediable with external provision of depth of processing at encoding and cues at retrieval.

Della Rocchetta (1986) reported that patients with frontal lesions were impaired in their ability to categorize and free-recall pictures, both after a short delay and after a two hour delay. This was complemented by findings by Milner (1991) who reported that patients with frontal lesions had normal item recognition, though they showed impairment in judgments of recency, with deficits being marked in patients with right frontal lesions, especially when they make decisions regarding recency on pictorial tests. These findings reinforce the position that frontal lobes are not essential for item-recognition _per se_, but may be important for other aspects of the episodic retrieval process (Milner et al. 1985).

The important role of the frontal cortex in judgment of temporal order was further borne out by studies of Janowsky (Janowsky et al. 1989a; Janowsky et al. 1989b) and Shimamura (Shimamura et al. 1990). They observed that patients with frontal lesions did not show significant impairment on test of item recognition and recall - and in this sense were not classical amnestic patients (Janowsky et al. 1989a; Janowsky et al. 1989b; Shimamura et al. 1990). This was in distinction to patients with medial temporal lesions and Korsakoff's patients who have diencephalic lesions. However, frontal patients did show impairments in recalling the correct temporal sequence of a word-list (Shimamura et al. 1990) and were also impaired in recalling the source from which this information was learnt (Janowsky et al. 1989b).
A recent article by Stuss et al. (1994), on the other hand, found impairment on both recognition and recall in thirty-two patients with frontal lesions. Recognition deficits were restricted to patients with left and bilateral frontal lesions and were observed in relation to the degree of aphasia or in patients whose lesions involved septal or cingulate regions. The authors speculate that the aphasia and the anoma seen in this subset of patients may have led to impaired encoding strategies, while the septal lesions may have impaired memory by injury to the septal nuclei which are limbic structures. Furthermore their study showed that there were different determinants of impaired recall in different patients - reflecting the disruption of one or more of processes of ordering, categorization and on-line monitoring that are used by normal controls in organizing encoding and retrieval (Stuss et al. 1994).

One is still left with the question: is “core” memory, as evident in recall, cued-recall and recognition, impaired after frontal lesions. Wheeler and colleagues (Wheeler et al. 1995) reviewed the available studies of recognition, cued-recall and free-recall in patients with focal frontal lesions. The authors analyzed the extant literature along two dimensions. One, they reviewed how many of the studies found a ‘statistically’ significant difference between the frontal and non-frontal group in the three tasks. Second, they analyzed the effect size differences between the frontal and non-frontal group in the three tasks regardless of whether the authors reported those differences ‘significant’ or not.

The authors analysed individual experiments available in a dozen different reports and found that 44% of these articles reported a statistically significant impairment in the “core” memory tests. The majority of the articles did not report a frontal-mediated memory impairment of those that did. Only 8% (1/12) of the articles showed frontal
impairment in recognition; 50% (5/10) showed a frontal deficit in cued recall, while 80% (8/10) showed a frontal deficit in free recall. These data explain the origin of the conventional wisdom that frontal patients are unimpaired in recognition but may be impaired in recall.

However, the second analysis by the authors questions the conventional interpretation. Instead of considering the statistical conclusions of the studies, the authors analyzed the experimental data in terms of the effect size of the difference in memory performance between the frontal and normal controls. In this analysis they find that greater than 80% of recognition studies (18/21) show frontal deficits (i.e. lower performance in frontal patients on recognition as compared to controls), as do studies of cued recall (25/27) and studies of free-recall (31/31). The difference across the three types of retrieval lies in the degree of impairment - the difference between patients and controls (expressed as the difference between the two groups) was on average 0.08 in recognition tests, 0.17 in cued recall and 0.16 in free recall. Wheeler et al. (1995) conclude, contrary to Stuss and Benson (1986), that “Contrary to conventional wisdom, there is strong evidence that frontal damage disrupts performance on all three types of tests, with the greatest impairment in free recall, and the smallest in recognition.” However, the statistical power of the comparisons to detect significant differences in the recognition tests is less than the power to detect the differences in tests of recall. Therefore, the prevalent view that recognition is spared, while recall impaired, may be an artifact of the limited power of the experiments to detect the differences. Wheeler and colleagues state: “We interpret the discrepancy between the conclusions drawn from individual studies and those arrived at
in our quasi-meta analysis as reflecting the lack of sufficient statistical power in single studies.”

This of course raises the question: is recall “more” impaired than recognition. At one level the answer is self-evident. Recall deficits have a larger effect size than recognition deficits, and in that sense recall is more impaired. However, this does not necessarily suggest that recall is more dependent upon the prefrontal cortex than recognition. Performance in recognition tests after a certain exposure is always higher than performance elicited using cued-recall or free recall after the same exposure (i.e. recognition tests conventionally used are easier than the cued recall and free-recall tests). Chapman and Chapman (1973) have pointed to an artifact (‘Chapman artifact’) that can result when two tests with different levels of difficulty are used to elicit a dissociation between two populations. Since recognition is easier it is conceivable that recognition performances are near ceiling in both the groups. Therefore, the fact that the effect size is smaller for recognition may not necessarily mean that that recognition is less impaired, but may reflect the different psychometric properties of the recognition tests conventionally used.

It is my conclusion that the present data do support a deficit in “core” memory performance after frontal lesions. The nature and the severity of these memory deficits is distinct from that observed after temporal-diencephalic lesions. Whether the disruption of the prefrontal functioning leads to equivalent impairment of different forms of retrieval, or whether there is a preferential impairment of recall over recognition is not as yet clear. In either case one still has to ask: what is the functional contribution of the prefrontal cortex to memory performance?
Several different, but complementary roles have been proposed for the prefrontal cortex. These roles essentially view the prefrontal cortex as a site of higher-order information processing. The prefrontal information processing is thought to follow the perceptual analyses of the stimulus and to aid the processes of encoding and retrieving information from memory. Several authors have proposed different versions of this theme. These views can be clustered under four major categories of roles accorded to the prefrontal cortex: i) working with memory; ii) temporal organization and source memory; iii) attention and inhibition of interference; and iv) autonoetic awareness.

Working with Memory

The most commonly espoused role for the prefrontal cortex is as a site which orchestrates the cognitive strategies crucial for encoding and retrieval. This role posits the prefrontal cortex as a gate-keeper of the flow of information from short-term memory to long-term memory. Broadly, this hypothesis suggests that the prefrontal cortex undertakes complex processing of incoming perceptual information which facilitates its transfer into long-term memory store at the time of encoding. At retrieval, the prefrontal cortex initiates the retrieval search and monitors and interprets the results of this search.

Several authors have expressed these ideas in their own words. A sampling is provided here. Luria, in 1973, suggested that the role of the frontal cortex is to “create stable motives of recall and maintain the active effort required for voluntary recall”. Warrington and Weiskrantz (1982) refer to these processes as ‘cognitive mediation’ of memory by the frontal lobes. These concepts encompasses terms such as “cognitive elaboration, use of imagery, embellishment, manipulation and organization”. A similar
conclusion was suggested by Stuss and Benson (1986) who saw frontal memory deficits as deficits of organization and suggested that "the frontal lobes are involved in the process of organizing methods of memorization and retrieval, and in comparing the results with the original intention".

Similar positions have also been developed by Baddeley (1992; 1995) who posits a role for a frontal "central executive" that selectively allocates working memory resources, an allocation which assists encoding and retrieval; and by Shallice (1988) who argues for a role of a frontally mediated "supervisory attentional system" which mediates the transfer of information from working memory to the long-term stores and vice versa. Perhaps the most elaborate and integrative version of these ideas is presented by Moscovitch (1992b; 1992a), in whose account memory is discussed in the context of consciousness and the role of prefrontal cortex is compatible with the above suggestions and is termed "working-with-memory," to distinguish it from the more commonly held role of the prefrontal cortex in working memory per se.

In Moscovitch's (1992b; 1992a) rendition of this theme, memory results as an interaction between the 'modular' hippocampal/medial temporal structures and the 'central' strategic frontal structures. In terms of flow of information, the frontal lobes receive information from the perceptual regions and are thought to be crucial in selecting and implementing encoding strategies which organize the input to the modular medial temporal structures. Any information that is processed by the frontal lobes, or consciously apprehended, is picked up by the medial temporal module. The role of the medial temporal module is to bind the neuronal events in the perceptual regions and the frontal cortex resulting in the engram or the memory trace. At retrieval, the frontal cortex processes the
cue and presents this information as a probe to the medial temporal structures. This presentation may reactivate the engram. The reactivation process is termed ecphory. It is proposed that the results of reactivation are returned to the frontal cortex which interprets the information in its correct temporal and spatial context. Thus, suggests Moscovitch (1992a), "the hippocampal circuit can be considered to consist of 'raw memory' structures, ... and the frontal lobes are 'working-with-memory' structures that operate on the input to the hippocampal component and the output from it". For the purposes of this thesis I will adopt Moscovitch's terms - 'working-with-memory' to refer to this class of roles for the prefrontal cortex.

Temporal Organization and Source Memory

Other ideas about the prefrontal cortex come from empirical studies of memory wherein specific attributes, such as temporal sequence or recency judgment, of an episodic memory were manipulated. One such important idea regarding the role of the prefrontal cortex comes from Milner and her colleagues from their neuropsychological analysis of frontal lesions in comparison to patients with medial temporal lesions (1971; 1984); and is buttressed by work in primates by Petrides (1989). In a series of tests [recency discrimination, frequency-of-occurrence judgments and self-ordered pointing] Milner and colleagues point to the important role of the prefrontal cortex, distinct from the contributions of the medial temporal lobe, in the temporal sequencing of information in long-term episodic memory (Milner and Petrides 1984).

Schacter (1987) argues for a specific role for the prefrontal cortex in encoding and retrieving the spatio-temporal attributes of an event; attributes which give a memory its
distinctly episodic character. Schacter reviews data by Milner and others, and distinguishes between memory for *where* and *when* an event happened (spatio-temporal context of a memory) and *what* occurred during that event (item recognition or item recall). His contention is that frontal dysfunction is related with a disproportionate impairment of the spatio-temporal context, as compared to item recognition and recall. This is buttressed by data from Squire’s study of Korsakoff’s patients and normal controls (Squire 1982). When the performance on item recognition was matched across the two groups by extending the learning-testing interval for normal controls, patients with Korsakoff’s still displayed a disproportionate impairment on temporal discrimination. Furthermore, there was a strong positive correlation between the degree of temporal-discrimination impairment and the impaired performance of these patients on frontal tasks such as Wisconsin Card Sort Test and Verbal Fluency (WCST and VF), facts which were subsequently confirmed in a larger group of patients (Shimamura et al. 1990).

Lewis (1989) contests Schacter’s conclusion that “spatial” context is impaired, and points out how most of the data from human studies only supports the notion of frontally mediated temporal-discrimination, and that spatial impairment can only be indirectly inferred from primate studies. Lewis further demonstrates that the *where* and *when* aspects of an episodic memory are functionally dissociable in normal subjects, thus suggesting that a temporal impairment need not necessarily be linked to spatial-context impairment.

Another way of conceptualizing the ‘spatio-temporal’ context is in terms of the source of the memory. Several authors have attempted to link “source amnesia” (memory for the experimentally presented information without recollection of its source) with frontal lesions. Schacter et al. studied a group of neurologically heterogeneous amnesiacs
on test of source memory (Schacter et al. 1984). These patients were told fictional statements from two experimental sources - and had to retrieve the statement as well as its intra-experimental source. Patients were matched to normal controls on item recall performance by manipulating learning-test interval. Patients still showed significant and disproportionate impairment in source recall. And, despite diverse etiologies, there was a significant positive correlation between impairment on frontal sensitive tasks (WCST and VF) and the degree of source memory impairment. This was more explicitly confirmed by Janowsky and colleagues in a more homogeneous group of frontal patients when they showed that as compared to age-matched controls, patients had a significant impairment in associating the correct source with a learned fact (Janowsky et al. 1989b). Janowsky also observed an age-effect on source memory, an effect that has also been noted by Craik and McIntyre and has been related to frontal dysfunction (McIntyre and Craik 1987; Craik et al. 1990).

These different views of Milner, Schacter, Shimamura and Janowsky show convergence. There is relative agreement that frontal lobes make a special contribution to the accurate temporal dating of memories, and are also important in the recollection of a source of a memory. Whether they have a special role in “spatial” context, in the three-dimensional physical sense of the word space, is as yet unclear.

**Attention and Inhibition of Interference**

The foregoing discussion shows how patients with frontal lesions may manifest impaired memory performance in several different ways: impairment in free recall, impairment in recognition, impairment in judgments regarding temporal sequence, recency
and source. Should one understand these manifestations as reflections of the manifold cognitive abilities of the frontal cortex or can these different manifestations be accommodated in some unitary basic function of the prefrontal cortex?

This question has led several authors to suggest that the role of the prefrontal cortex in memory function may involve, at the most elementary level, selection of appropriate materials and strategies for memory encoding. Similarly, attention to relevant aspects of the cue and the choice of appropriate retrieval strategies point to the central role of the prefrontal cortex in attention. Luria noted that while patients with brain-injury tended to be more susceptible to interference when carrying out memory tasks, patients with frontal lesions were particularly sensitive (Luria 1973) - exhibiting a difficulty in inhibiting distracting stimuli. Moscovitch observed that not only were frontal patients more susceptible to interference, they did not display the normal release from proactive interference that is observed in patients without frontal lesions (Moscovitch 1982).

In accordance with a special susceptibility to interference, Stuss and colleagues reported that frontal patients who were unimpaired in recalling paired-associates in the absence of interference, showed a greater susceptibility to interference as measured using the Brown-Peterson technique (Stuss and Benson 1986). Shimamura and colleagues have further confirmed this disproportionate susceptibility to interference in studies of frontal patients who were asked to learn two paired associate lists: a list pairing A with B, and a second list pairing A with a new association C. The frontal patients showed no impairment in learning the first list AB, but showed significant impairment in learning the second pairing, that of A to C (Shimamura 1995). This suggests that while frontal patients have no problems in acquiring the first association (A to B), the first association impaired their
ability to acquire a new association (A to C) - suggesting an inordinate susceptibility of the frontal patients to competing information.

Vogel et al. (1987) and McAndrews and Milner (1991) have shown that if frontal patients are given an opportunity to encode with sufficient distinction, be it via levels of processing or by manipulating the objects to be remembered, the patients are able to overcome their deficits. This suggests that at some level frontal deficits are related to impaired direction of attention and impaired inhibition of irrelevant information. Therefore when external instructions can control or remedy the interfering aspects of the learning and retrieving environment, memory performance of frontal patients can be improved (Shimamura 1995).

Shimamura has suggested that the manifold frontal manifestations of memory impairment may all result from the fact that “these patients do not seem to be able to control inadvertent information processing” (Shimamura 1995). In his view the frontal cortex is involved in a dynamic gating and filtering of information via inhibitory control of posterior cortical regions. The different prefrontal regions do not perform qualitatively different computations, but differ in the posterior cortical regions with which they connect and therefore the sensory information that they modulate. Shimamura’s view is attractive in its reductionism. However, one would be persuaded of its validity only if it could be shown that such a view permits predictions or interventions which are more effective than the multi-faceted view of frontal contributions to memory. Studies which directly contrast these two approaches to frontal memory have not as yet been done.
Autonoetic awareness

More recently Wheeler, Stuss and Tulving (1996) have suggested that the prefrontal cortex can be seen as the seat of the ‘autonoetic awareness’ which is a characteristic of human memory. According to this account what distinguishes episodic long-term memory from semantic long-term memory is the fact that episodic memory recollection is associated with a particular feeling of ‘having been there, at that time’ and is infused with an association of the event with the concept of ‘self’ in a way that impersonal general semantic knowledge is not. It is this quintessentially human feeling of the self-ness of long-term episodic memory that is its “autonoetic” quality. It is argued that one of the roles or consequences of prefrontal contribution to human memory is to imbue the phenomenological experience with a sense of autonoesis. While having obvious intuitive appeal, the concept of “autonoetic awareness” as a discrete psychological entity, and its prefrontal localization await empirical validation.

In summary, the prefrontal cortex plays an important role in the performance of episodic memory tasks, though its role is qualitatively different from that of medial temporal structures. While initial studies suggested that the prefrontal cortex is involved in recall and not recognition, more recent analysis suggests that the prefrontal cortex may be involved in both recall and recognition though the qualitative nature of the contribution may differ. As the above discussion shows, the precise functional role that the prefrontal cortex plays in long-term episodic memory is unclear. The field is rich with diverse, yet overlapping theories and frameworks. Most of the present evidence regarding its role derives from neuropsychological studies and is best captured as “working-with-memory”, though other explanations such as a special role in judging spatio-temporal context and
autonoetic awareness also remain valid. The studies in this thesis will bring PET evidence to bear upon this interesting question.

The neuroanatomy of memory

The above discussion proceeded in a region-by-region fashion. This piecemeal presentation is a more a reflection of how knowledge about memory has accumulated - rather than how the brain implements memory. The authors overall position is that information processing in the brain is subserved by widespread neural networks (Mesulam 1990; Markowitsch 1995a) - and memory is just one of the mental outcomes of this neural processing. The structures noted above do not work in isolation but represent the nodes that will have to be accommodated in any neuronal network model of memory. The unimodal and multimodal association cortices have input to the medial temporal regions. The parietal association cortices project to the parahippocampus while the infero-temporal regions project to the perirhinal cortex. Which in turn project to the entorhinal cortex, and via it, to several stages of information processing in the dentate gyrus, CA3 and CA1 of the hippocampus (Markowitsch 1995a).

Information processed in the medial temporal cortex is routed to frontal neocortical structures either directly or indirectly via diencephalic regions (subiculum → fornix → mamillary bodies → mamillothalamic tract → anterior nucleus of the thalamus → neocortical projections; and subiculum/perirhinal → mediodorsal nucleus of the thalamus → prefrontal cortex) (Zola-Morgan and Squire 1993). The prefrontal neocortical regions now considered important in memory also receive direct long association fibres
from the parietal multimodal association areas (Goldman-Rakic 1988). Thus forming, in a minimalist description, a reciprocal information processing system between the multimodal association cortices, the prefrontal cortex and the medial temporal/diencephalic regions. It will be the purpose of future research to specify how these regions share and process information, and why damage to discrete regions within this network leads to selective and specific deficits (Zola-Morgan and Squire 1993).

In closing, the purpose of this thesis was to use PET functional neuroimaging and the cognitive subtraction method to distinguish the role of the different brain regions, particularly the prefrontal cortex, in encoding and retrieval of verbal material in long-term episodic memory.
Introduction

The chapter provides an overview of the methods used for the studies. Details specific to each experiment are provided in each Article and an attempt is made to avoid duplication. This thesis rests on two crucial methods: the use of regional cerebral blood flow (rCBF) as an indicator of regional neuronal function and the use of the cognitive subtraction paradigm to relate rCBF to the cognitive processes of interest. This chapter outlines the assumptions inherent in the use of these methods and their consequences for interpretation of the results. Also presented are studies undertaken to test the residual effect of cognitive challenges on rCBF and to assess the statistical power of the current PET paradigms to detect small cognition-induced changes in rCBF.

Overview of the PET Methods

All studies presented here were done at the Vivian M Rakoff Brain Imaging Centre (PET Centre at the Clarke Institute of Psychiatry). The facility is equipped with a Scanditronix-MC-17 Cyclotron and a GEMS-2048-15B PET Camera and a network of Digital Equipment Corporation (DEC) and SUN-SPARC-10 workstations for image reconstruction and data analysis, respectively. The radiochemical synthesis of $[^{15}O] \cdot H_2O$ was undertaken by Stephen Dobbin, under the supervision of Drs. Alan Wilson and Jean DaSilva. The images were acquired by Douglas Hussey, David Wilson and Kevin Cheung, nuclear medicine technologists, under the supervision of Dr. Sylvain Houle, Director of the PET Centre. The PET cognitive tests were administered by myself, or by Randi Rose and Corey Jones, who were Research Assistants in the program.
Procedure for Subjects

Subjects for all the studies were healthy volunteers who responded to advertisements placed around the University of Toronto. Subjects were instructed to call a specified telephone number and approximately 50% of those who called agreed to come in for further participation. All subjects were given a "tour" of the PET experiment before they gave written consent. After consent was obtained, information regarding education, handedness, medical history, neurological history, as well as drug abuse and psychiatric history was recorded. Data for drug abuse and psychiatric history was obtained using an abbreviated version of the SCID for DSM-III-R (Spitzer et al. 1990). Fewer than half a dozen subjects were ever excluded on these grounds from the over fifty subjects that were screened for the studies. Most of these exclusions were for concurrent marijuana use. At this stage subjects would be given a date and time for their PET study. Usually 24 to 72 hours elapsed between a tour and the actual PET scanning. The PET scans were usually done either starting at 9 to 9:30 in the morning, 11 to 11:30 in the morning or 2 to 2:30 in the afternoon. Subjects came to the PET Centre about half an hour prior to scanning times and were met by me and introduced to the nuclear medicine technologists.

Subject Positioning

The subjects would be positioned on the scanning bed without any roll or yaw in their head position. Once the head was so positioned an intravenous line was inserted in the left arm. The left arm was chosen since it left their right arm free for manipulating the click-mouse. An individualized thermoplastic mask was made for each subject. A mark was made on the mask right next to the outer canthus, and a cantho-meatal (CM) line was drawn on the mask. The subject
was then moved in to the point such that the CM line was roughly in the line of the laser positioning-marker of the scanner. The camera was then tilted such that the laser markers were perfectly parallel to the CM line. The camera was then tilted an extra five degrees to bring the plane of the camera rings in parallel with the bicommissural (AC-PC) plane in the brain. After this positioning, the subject was moved about 12.5 cm up to capture maximal brain regions in the view of the scanner.

A transmission scan was obtained and the early frames were inspected to make sure that the subject was appropriately positioned. Since the nasal sinuses are easily found on the transmission scan it provided a check for adequate positioning in the camera.

The stimuli were all presented on a seventeen inch computer monitor which was suspended from the ceiling and permitted movement in all three axes. This allowed for accurate and individualized positioning of the monitor 60 to 70 centimeters in front of the subject. All word stimuli were presented in white on a black background using MEL software (Psychology Software Tools, Pittsburgh, PA, USA). The subjects responded using a mouse for the studies reported in Article # 1, 2 and 4 and vocally in studies reported in Article # 3 and 5. After a given scan was done the subject was informed that there would be a ten minute break before the next scan. During this break subjects had to do non-PET cognitive tasks as detailed in the respective studies. Subjects were never asked to do any specific learning or other cognitive activities in the two minutes prior to the beginning of the scan. When scanning for a session was over the thermoplastic mask was released. Subjects were debriefed about their experience, given their remuneration, thanked and dismissed.
PET data acquisition and image reconstruction

On each day of scanning, prior to the first PET data acquisition, a calibration scan was acquired using a $^{68}$Ge pin-source. This provided the correction used for inter-slice and day-to-day standardization. Once the subject was positioned appropriately, an attenuation scan was acquired with the subject’s head in position to obtain a subject-specific attenuation correction.

All PET emission scans were done with an intravenous injection of 40 mCi of $[^{15}\text{O}]-\text{H}_2\text{O}$. The subject was informed about the start of the scan two minutes prior to the injection. A minute prior to the injection the test administrator would go over the instructions with the subject and would check to make sure that the subject was still in alignment. The cognitive task started 15 to 20 seconds prior to the injection. The injection was administered as a bolus over five seconds. 20 seconds after the beginning of the injection and approximately 35 to 40 seconds after the beginning of a task, the radioactive counts in the brain crossed the scan-starting threshold and camera started a 60 second acquisition.

Once all the emission scans were completed, the raw counts from the scans were backed up on an optical disk, as was the corresponding standardisation scan and the attenuation measurements. The raw counts were reconstructed into an image by a system-dedicated software that accompanies PC-2048 15-B. The reconstruction for all our studies was done using a 5 mm FWHM Hanning filter.

The reconstructed image files were not directly compatible with Statistical Parametric Analysis (SPM) analysis. Therefore, these images were converted into an SPM compatible format and transferred to the SUN workstation for image analysis.

Region of Interest (ROI) versus Function of Interest (FOI) Analysis: There are two distinct
approaches to the analysis of $^{15}$O-H$_2$O PET data. The ROI approach is predicated on anatomy. The anatomical region of interest is identified first, on a co-registered structural image (e.g. MRI) or on the functional image itself. The level of ‘function’ is measured within this anatomically-defined ROI. This approach is suitable when there are a priori anatomical hypotheses, the anatomical regions can be defined with certainty, and the functional variable of interest conforms itself to the anatomically-defined regions (Andreasen et al. 1992; Arndt et al. 1995). While this approach is powerful in confirming predicted hypotheses, it is not very valuable in discerning new connections and new patterns of functional response. Furthermore, if a particular functional activation spreads itself over two predefined anatomical regions, the ROI approach may have a lesser sensitivity for detecting these changes.

In contrast the function of interest approach is exploratory. It makes no assumptions regarding anatomical constraints. Hence, it lends itself well to the exploration of the neural correlates of cognitive phenomena. There are several implementations of this approach (Fox and Mintun 1989; Friston et al. 1991a; Worsley et al. 1992; Andreasen et al. 1995a). Most widely used among these have been the SPM (Friston et al. 1991a) and the Montreal methods (Worsley et al. 1992). These methods differ in several important ways. The SPM method does not require a coregistered MRI to transform the PET data in the standard anatomical space, the Montreal method does. Second, the SPM method uses a pixel-based estimate of variance, the Montreal method uses a single estimate for variance across the brain space. Thirdly, the SPM method discards any pixel with missing data, the Montreal method uses data from the entire brain space after appropriate correction for the decrease in sample size.

Arndt et al. (1995) have compared these two methods by applying them to a standard set of thirty-three normal subjects who were engaged in a memory-PET experiment. They find that
the major conclusions one would draw (such as the enrolment of the right prefrontal cortex) are similar across both methods. However, there are significant differences too. One, the SPM method was more sensitive to the detection of peaks, and reported twenty discrete activations while the Montreal method reported seventeen. Fourteen of these were similar or identical. Second, by disposing of all pixels with any missing data the SPM method analyzed a much more limited brain space than the Montreal method. Thirdly, the Montreal method was more accurate in making judgements regarding the extent of activation. Finally, when the two methods did report an activation in the region, different nearby activation peaks in one method would appear as a plateau in the other. And, if discrete peaks are found with both methods they could differ in anatomical space by as much as 15 mm.

For the studies in this thesis we have applied the SPM as the FOI method. The choice of an FOI approach was determined by the fact that we were exploring the neural correlates of encoding and retrieval, for which there were few a priori hypothesis with respect to functional neuroimaging. In retrospect, this seems to have been a wise decision. Amongst the FOI methods, SPM was chosen since it had been validated by the time we started our studies, it was available in the public domain, it was compatible with our hardware capabilities, and it was finding widespread favour with other investigators.

**SPM Analysis**

The data were analyzed using SPM software from the Wellcome Dept. of Cognitive Neurology, London, UK; implemented in MATLAB (Mathworks Inc. Sherborn MA, USA). Statistical parametric maps are spatially extended statistical processes that are used to characterize regionally specific effects in imaging data. Statistical parametric mapping combines the general
linear model (to create the statistical map or SPM) and the theory of Gaussian fields to make statistical inferences about regional effects (Friston et al. 1991a; Friston et al. 1995b). The application of SPM requires three distinct steps: the spatial realignment of the images into the Talairach co-ordinates; the plastic transformation of the images to fit the average idealized PET image; the correction for differences in global means by using it as a co-variate and finally, the comparison, on a pixel-by-pixel basis for significant differences induced by one condition as compared to another.

Spatial realignment and normalization: The scans from each subject were realigned using the first scan as a reference. The six parameters of this rigid body transformation were estimated using a least squares approach (Friston et al. 1995a). This approach is based on an approximate linear relationship between the images and their partial derivatives with respect to parameters of the transformation. Following realignment all images were transformed into a standard space (Talairach and Tournoux 1988). This normalizing spatial transformation matches each scan (in a least squares sense) to a reference or template image that already conforms to the standard space. The procedure involves a 12 parameter affine (linear) and a 9 parameter quadratic (nonlinear) three-dimensional transformation. This is followed by a two-dimensional piece-wise (transverse slices) nonlinear matching, using a set of smooth basis functions that allow for normalization at a finer anatomical scale (Friston et al. 1995a). Again the parameters were estimated using standard least squares after linearizing the problem. As a final pre-processing step the images were smoothed using an isotropic Gaussian kernel.
Statistical analysis: After specifying the appropriate design matrix the condition, subject and covariate effects were estimated according to the general linear model at each and every voxel (Friston et al. 1995b). The design matrix included global activity as a confounding covariate and this analysis can therefore be regarded as an ANCOVA (Friston et al. 1990; Friston et al. 1991a; Friston et al. 1995b). To test hypotheses about regionally specific condition effects, the estimates were compared using linear compounds or contrasts. The resulting set of voxel values for each contrast constitute a statistical parametric map of the t-statistic, SPM(t).

For purposes of statistical inference the SPM(t) were transformed to the unit normal distribution SPM(Z). Since SPM involves multiple comparisons, a few voxels may reach the threshold of significance just by chance. To counter this possibility and to reduce the possibility of Type I error, two different approaches were used. First, using a univariate approach with multiple corrections, only those regions where the significance of the observed change corresponded to an uncorrected $p < 0.001$ ($Z > 3.09$) were considered. This cut-off level is defended since it has been empirically demonstrated to avoid false-positives (Bailey et al. 1991). However, more recently a theoretical approach for this problem has been offered based on the theory of Gaussian Fields (Friston et al. 1995b). As a first step, only those regions which show changes at a given threshold (usually an uncorrected $p < 0.001$ and a corresponding $Z > 3.09$) are considered. The regions identified by this cut-off are then characterized in terms of spatial extent ($k$) and peak height ($u$). The significance of each region was estimated using distributional approximations from the theory of Gaussian Fields. This characterization is expressed in terms of the probability that a region of the observed number of voxels (or bigger) could have occurred by chance [$P(n_{max} > k)$], or that the peak height observed (or higher) could have occurred by chance [$P(Z_{max} > u)$] over the entire volume analyzed (Friston et al. 1995b).
For Article #1 and #2 only the first approach was applied, whereas for Article #3, #4 and #5 the second approach was also implemented. It should be pointed out that a re-appraisal of the significance reported in Article #1 and Article #2 using the new criterion does not change any of the claims made in the original manuscripts mainly because the activations were very robust and were significant sufficiently beyond the threshold.

Assumptions and their implications

rCBF as an indicator of neuronal function.

The enterprise of using rCBF for functional neuroimaging rests on the premise that PET can accurately measure rCBF, and that changes in rCBF accurately reflect changes in regional neuronal function. In this set of experiments we used a single intravenous bolus of $[^{15}\text{O}]-\text{H}_2\text{O}$ followed by sixty seconds of PET imaging to provide a measure of rCBF. This method derives from the experiments by Herscovitch (1983) and Raichle (1983). In the these papers the authors describe the theoretical underpinnings of the single-injection intravenous $[^{15}\text{O}]-\text{H}_2\text{O}$ method of measuring rCBF with PET. They validate this method in baboons by directly measuring blood flow using the more established invasive monitoring techniques and correlating the results with PET derived estimations. Over the normal range of blood flow, the correlation between invasively measured rCBF and PET estimated rCBF was $> 0.96$ (Raichle et al. 1983). However, the method as reported by Herscovitch and Raichle required the intra-arterial monitoring of $^{15}\text{O}-\text{H}_2\text{O}$ input function, and was very sensitive to slight errors in the recording of this function in the first few seconds of the scan.

To simplify matters, Fox and colleagues (1989) have suggested a non-invasive modification of this technique. Fox et al. dispensed with the intra-arterial monitoring of the input
function, and used accumulated tissue-counts as an index of rCBF. They validated this simpler paradigm and demonstrated that the sensitivity and specificity of response detection and the accuracy of response localization were virtually identical for the two types of images (Fox and Mintun 1989). All our studies used the Herscovitch and Raichle technique with the Fox modification.

Several other methods have also been developed to measure regional cerebral blood flow. Important amongst them are the inhalation of $[^{15}\text{O}]$-oxygen (Frackowiak 1985) as well as the injection of $[^{15}\text{O}]$-butanol (Brooks et al. 1986; Roland et al. 1993). Of these methods $[^{15}\text{O}]$-H$_2$O is the most widely used method in cognitive activation studies. Its main benefit over the inhalation method is the ease and safety of administration, the reliability of uptake and its adaptability to multiple-scan single-session paradigm. $[^{15}\text{O}]$-butanol offers the advantage of a very rapid transfer across the blood brain barrier, and given its high lipophilicity, may provide a higher signal-noise ratio (Roland et al. 1993; Ingvar et al. 1994). However, this method was not available at our PET Centre, and is not widely used, except for the recent demonstrations of its usefulness by Roland's group (O'sullivan et al. 1994).

The fact that $[^{15}\text{O}]$-H$_2$O faithfully reflects rCBF is well established and non-controversial. The more important question is how faithfully changes in rCBF reflect changes in neuronal function. Since cognitive activity is implemented by information transfer between neurons, what is of fundamental interest to cognitive neuroscientists is neuronal activity, not rCBF. The main reason to measure rCBF is that task-induced rCBF changes reflect task-induced changes in neuronal activity (Raichle 1987; Roland 1993).

The relationship between rCBF and neuronal activity is logically evident, but it is not necessarily linear. Conduction of impulses across nerve cells involves electrical conduction along
the length of the nerve and chemical transduction at the synapse. This process of chemical transduction requires the transfer of Ca$^{2+}$, Na$^+$ and K$^+$ ions across the cell membranes, a process that requires metabolic energy to drive the ion pumps. It has been demonstrated that the major changes in metabolism consequent to stimulation take place in the neuropil at the axonal-dendritic synapse, and not at the level of the cell body (Raichle 1987). The important point here is that even though nerve cells conduct in a longitudinal fashion along their entire length, the major changes in energy consumption occur at the level of the terminal synapse. This has important implications for interpretation of the localization of the changes by rCBF. Local changes in rCBF may reflect changes in the firing rates of cell-bodies which lie remote from the observed change (Raichle 1987).

The other major issue is that both neuronal excitation (say excitation of neuron B by neuron A) and neuronal inhibition (inhibition of B by A) require active chemical transduction at the A-B axonal-dendritic synaptic junction. Both A-B excitation and inhibition require ion-transfer and would lead to hemodynamic activation. Therefore, the neuronal concepts of excitation and inhibition are not synonymous with the hemodynamic concept of activation or deactivation. If neuron B were linked to neuron C, then the excitation of B (by A) would lead to a hemodynamic activation at the A-B junction followed by another hemodynamic activation at the BC junction. Whereas, the inhibition of B (by A) would lead to a hemodynamic activation at the AB junction, but this would decrease the rate of firing of cell-body B and decrease the rate of synaptic transduction at BC, leading to a hemodynamic deactivation at BC. Thus, deactivations, may be second-order neuronal conduction effects, whereas activations may be first-order changes.

Whether deoxyglucose and rCBF PET differ in this regard is not clear. Even with deoxyglucose studies the major metabolic changes are at the level of the neuropil. Schwartz and
coiieagues (1979) osmotically loaded rats leading to stimulation of the hypothalamic (supraoptic nuclei) cell-bodies. Deoxyglucose reflected metabolic increase, in proportion to the degree of stimulation, was noted in the pituitary (i.e. the site of the axonal terminals of the above cell-bodies) and there was no detectable change in the hypothalamic cell bodies. Therefore, $^{18}$F-deoxyglucose PET may not be able differentiate neuronal excitation/inhibition any better than rCBF PET.

In this set of studies we used $^{15}$O-H$_2$O PET imaging, rather than $^{18}$F-deoxyglucose. The choice was simple. $^{18}$F-deoxyglucose studies reflect the brain metabolic activity over 15-30 minutes of uptake. It is not feasible for humans to sustain a temporally homogenous cognitive activity over that time interval. Practice-effects, learning, habituation, fatigue and head-movement will confound this interval. Second, most cognitive subtraction strategies required two if not more cognitive tasks. With $^{18}$F-DG it is not feasible to do more than two scans in a normal volunteer due to radiation dosimetry limitations, and even the two scans cannot be done on the same day. Thus, despite its limitations, rCBF PET imaging was the tool of choice for these studies.

For rCBF to serve as a reliable indicator of regional changes in neuronal activity several characteristics of the relationship need to be known. In particular, i) Is there a linear relationship between the degree of change in neuronal firing and degree of change in blood flow? (linearity). Is this relationship the same in all the regions of the brain? (uniformity). And finally, is there some minimal change in neuronal firing which does not induce a change in blood flow and is there a level of neuronal firing beyond which there is no change in blood flow? (floor and ceiling effects).

These characteristics, especially as they pertain to humans, are not available. The most compelling evidence is obtained from animal experiments (Sokoloff 1977; Sokoloff 1986; Raichle 1987). An increase in neural activity, as induced by electrical stimulation of the sciatic nerve,
olfactory stimulation and induced focal seizures, is related to a focal increase in metabolism. Similarly, decreased neuronal activity induced via auditory and visual deprivation is accompanied by a focal decrease in metabolic demand. These experiments establish, in principle, that changes in physiological activity in specific regions of the nervous system is associated with focal, synaptic changes in metabolic demand (Sokoloff 1977; Sokoloff 1986). However, there are little data in animals that systematically adress the three questions (linearity, uniformity, floor and ceiling effects) raised above.

Data in humans are even more limited. Most pertinent evidence comes from the study by Fox and colleagues (1988) who looked at the relationship between the task-induced change in glucose consumption, rCBF and oxygen consumption. If the change in blood flow merely reflected the change in oxygen consumption, which in turn merely supplied the increased oxygenation in response to increased energy demands of the firing neurons, one would expect that there would be a proportional relationship between the three. However, this assumption is probably an over simplification. Fox and colleagues showed that during a visual stimulation paradigm, as compared to a rest state, regional oxygenation consumption increased by 5%. But this was accompanied by an increase in regional cerebral blood flow of over 50%. Thus it seems that rCBF over-compensates when there is an acute change in the oxygenation demand. In other words, blood flow increased ten-fold more than would have been expected on the basis of change in regional oxygen consumption induced by an acute increase in neural activity. Why the body implements such a mechanism is not currently clear, but from the PET perspective there is a clear practical advantage: rCBF acts as a natural “amplifier” of changes in oxygen demand caused by changes in neuronal firing.
What about the fidelity of this amplifier? The data suggest that the picture is far from simple. In a series of experiments done on \textit{in vivo} preparations of rat sympathetic ganglia, stimulated at frequencies ranging from 0-20 Hz it was observed that peak increase in glucose consumption occurred at 15 Hz. The relationship between 1 and 15 Hz was not linear and after 15 Hz there was no further increase in metabolic demand (Sokoloff 1977; Raichle 1987). This suggests that, like most biological systems, the rCBF changes have a floor, a ceiling and a non-linear relationship in between the two.

In the only comparable report in humans, Fox (1984) and colleagues observed that as visual simulation was increased from 1-61 Hz there was a non-linear inverted-U type change in blood flow: the response was maximal at 7.8 Hz, the increase to 7.8 Hz was roughly linear, but above 7.8 Hz was a non-linear decrease in blood flow despite an increase the stimulation rate. Furthermore, Sabatini (1993) and MacKinnon (1995) have shown that within the motor system, as the rate of movement is increased, new areas are recruited and there is a variable relationship between rate and the level of activation. This has important implications for the design and interpretation of experiments. Because investigators often use different stimulus rates even when studying the same cognitive process, this may be the cause of some of the observed discrepancies between experiments (Petersen and Fiez 1993).

A review of the above rCBF-neuronal activity relationship has a sobering message. The few simple criteria that one would expect a reliable indicator to meet: linearity, uniformity and known floor and ceiling - are either not met by rCBF or not known at present. In light of this the relative uniformity of cognitive PET findings is reassuring. The lesson to take from these facts is that when one gets apparently paradoxical results, the cause may lie in the fact that rCBF-
neuronal activity relationship is semi-quantitative at best, is not linear or uniform and its floor and ceiling characteristics in the different brain regions are not as yet known.

Cognitive Subtraction: The other pillar on which the thesis rests is the concept of cognitive subtraction. The concept is illustrated in Figure II-1. The approach has come to hold the attention of functional neuroimaging researchers since its application to study the neural correlates of single word processing by Posner and colleagues (1988). The rationale and the operation of the method are illustrated in Figure II-1.

The application of the subtraction paradigm requires a series of implicit assumptions (Frackowiak 1994; Sergent 1994; Buckner and Tulving 1995). The major assumptions are as follows: i) cognitive processes are discrete and modular, specifiable and operationalisable in experiments, and additive in their operations; ii) information processing proceeds in a hierarchically organized manner and a given brain region performs a given cognitive process regardless of the experimental task in which the cognitive process is embedded; and iii) variations in cerebral blood flow are a valid index from which to infer changes in neuronal activity, over a range of cognitive operations, over a range of stimulus conditions and across different brain regions. The evidence regarding the third assumption has already been discussed. I now address the cognitive implications of the subtraction paradigm.
Figure II-2. The figure depicts the concepts of the cognitive subtraction paradigm. The use of this paradigm requires two tasks labeled ‘activation’ and ‘baseline.’ Further, it requires the enunciation of processes which are required to carry out each task - A and B for the baseline task, and A, B and X for the activation task. Brain scans are taken while the subject is carrying out the two tasks. The scans are compared and the difference in the activity of activation vs. the baseline scan is accorded to the process X, which is deemed to differ between the two tasks.
Figure II-2. The figure depicts the concepts of the cognitive subtraction paradigm. The use of this paradigm requires two tasks labeled ‘activation’ and ‘baseline.’ Further, it requires the enunciation of processes which are required to carry out each task - A and B for the baseline task, and A, B and X for the activation task. Brain scans are taken while the subject is carrying out the two tasks. The scans are compared and the difference in the activity of activation vs. the baseline scan is accorded to the process X, which is deemed to differ between the two tasks.
As Figure II-1 illustrates, to use the subtraction approach appropriately one has to specify the components of Task A and Task B a priori. This assumes that cognitive components of Task A and Task B are clearly and unambiguously specifiable, and therefore the interpretation of the differences between the two tasks is unequivocal. In practice, however, there is little agreement regarding the architecture of the mind. Descriptions about the component cognitive processes which subserve a task can be sought from different theoretical frameworks, which may be complementary at best, and non-overlapping at worst. This difference in interpretation is well illustrated in the debate between the researchers at Washington University (Petersen et al. 1988; Petersen and Fiez 1993) and the Hammersmith Hospital (Friston et al. 1991b; Frith et al. 1991b; Frith et al. 1991a) regarding the role of the left prefrontal cortex in verbal processing. Both groups used a semantic processing task and a lexical baseline task. Petersen et al. argue that the subtraction isolates “semantic processing,” while Frith et al. emphasize that the subtraction isolates the operations of “willed action.” This debate highlights how similar activations obtained from very similar tasks can be interpreted in two meaningful but non-overlapping contexts.

A similar example arises in the study of pain: several groups have undertaken studies in which subjects experienced noxious, but tolerable, painful stimuli while undergoing PET scanning. These studies were unanimous in their activation of the anterior cingulate and it has been claimed that the anterior cingulate is important for the representation of pain (Sergent 1994). However, others have suggested that the natural human impulse in the face of pain is to remove the hand from the source of pain, and that subjects were therefore inhibiting a reflex response, and that the activation of the anterior cingulate reflects that aspect of cognitive processing and not the representation of pain per se (Sergent 1994). These examples point out that the difference
between two tasks, A and B, is not always unambiguously specifiable and the interpretation of the experiments is only as compelling as the theoretical framework in which they are cast.

Even in cases where the difference between the two tasks A and B, process X, is clearly specifiable, the subtraction paradigm makes several assumptions about how the brain implements process X. It is assumed that all subjects perform all the specified cognitive operations and no other cognitive operations in undertaking the task (Frackowiak 1994; Sergent 1994), and that these operations are implemented by the brain in a hierarchical manner with each brain region, or ensemble of brain regions, being related to the processing of a single specified process. In essence, this implies that when one undertakes a cognitive task, say semantic processing, then regardless of the mode of input and output (whether the words were presented visually or aurally; and whether the response is via the spoken word or clicking a computer-mouse button) the same region of the brain is invoked. This “independence” assumption assumes a modular operation at the neural level, and runs counter to many notions of non-hierarchical and non-modular interactive parallel processing (Mesulam 1990).

We have recently obtained empirical evidence which contradicts this simple dictum. Janine Jennings in our group (personal communication) has recently studied twelve subjects who undertook semantic processing (living/non-living decision on words) and lexical processing (detect the presence of the letter “a” in the words) tasks - but conveyed their decisions in three different modalities. In all cases subjects saw words presented visually. However, in one pair of scans they gave their responses (to the semantic and the lexical condition) using a vocal response (yes/no); in another pair of scans they clicked a mouse button to indicate yes/no and in the third pair they made the decisions but were instructed not to give any external response. Their compliance with task instructions in the mind-only condition was confirmed with post-hoc tests.
The subtraction paradigm would suggest that the results of the respective subtractions (semantic minus lexical in each response modality) should be the same, since in each subtraction the perceptual input and the mode of output would get subtracted out, isolating the uncontaminated locus of semantic processing. However, that was not the case.

We had expected an activation of the left prefrontal cortex in all three subtractions - as has been obtained in previous uses of these tasks (Kapur et al. 1994a; Kapur et al. 1994c). Consistent with this expectation we did find an activation of the left prefrontal cortex in all three modes. But, the degree of activation of the left prefrontal cortex and the activation of other posterior regions differed across the three tasks. The mouse-click gave the most robust left prefrontal activation, followed by the vocal response and mind-only condition. Thus, the empirical test of the subtraction assumption is both a victory for the paradigm (the left prefrontal was robustly activated in each comparison) and a note of caution (there were several other equally (statistically) significant activations that were seen in one but not the other subtraction).

In summary, insofar as information processing by humans is related to neural transmission, and neural transmission requires energy expenditure which causes changes in rCBF, the subtraction approach applied using $^{15}$O-H$_2$O PET is theoretically defensible. However, the relationship between cognitive processing and neuronal recruitment is non-linear and the relationship between neuronal recruitment and blood flow is far from clear. Therefore, this method will yield results confounded by these factors. The venture of using rCBF based functional neuroimaging is exciting because it holds the promise of bridging the gap between the mind and the brain. However, since each of the spans of this bridge is tentative, the enterprise is hazardous. Mindful of these missing links I embarked on the application of PET to the study of episodic
memory in the hope of finding reliable empirical regularities and interpreting them in a theoretical framework provided by cognitive science and neuropsychology.

**Neurochemical modulation:** In our foregoing discussions we have assumed that the brain implements the mind like a static computational device, much like the electrical connections within a computer. This assumption disregards the fact that the brain is a biochemically implemented, and dynamically variable, computational device. The chemical transducers in the brain can be broadly classified into fast-neurotransmitters and slow-neurotransmitters. The fast neurotransmitters mediate the excitation (glutamate) and inhibition (GABA and glycine) that occurs in the order of milliseconds. The slow-neurotransmitters which include amine-neurotransmitters and peptides modulate the excitability of the synapses over which the fast-neurotransmitters act.

Most of the cognitive subtraction paradigms are concerned with differing fast-neurotransmission across two task. However, it has been convincingly demonstrated that the classic slow-modulators can exert profound changes in rCBF (Grasby et al. 1993a; Kapur et al. 1994b). Furthermore, changes caused by the administration of slow-neurotransmitter agents (apomorphine, buspirone and scopolamine) result in a functional interaction with cognitively-induced rCBF changes (Grasby et al. 1992; Grasby et al. 1995). Thus, cognition-induced fast-neurotransmission is perhaps interactively linked with neuromodulation and is an emerging subject of study (Friston et al. 1992). However, for the purposes of these experiments it was assumed, in the absence of any practical alternative, that the neuromodulatory influences were steady across the baseline and activation task conditions.
Methodological studies

Functional neuroimaging is in a state of continual development, and being a young science several stated and implicit assumptions mark its use. Two methodological questions bearing directly on cognitive PET imaging were addressed by the PET group, and I include them here as I had an important role in the conceptualization and implementation of the experiments. These studies investigated the following questions: i) How long after a cognitive task are the specific activations induced by the activity detectable under usual operating circumstances? (Residual Effect); and ii) What can one learn about the statistical power of $[^{15}\text{O}]-\text{H}_2\text{O}$ PET studies and how can that be used to guide future experimental design.

Residual Effect

(This work was led by Dr. Houle, and I was one of the major collaborators and a second-author on the resulting publication (Houle et al. 1994). See Appendix A)

In a typical experiment subjects undertake six to eight sequential scans during which they are asked to perform different tasks (Petersen and Fiez 1993; Kapur et al. 1994a). The scans obtained are compared statistically to delineate regions which show an increase in rCBF with a given cognitive task. The scans are typically separated by 10 to 12 minutes to allow the oxygen-15 (half-life 122 sec) to decay to negligible levels. This approach also assumes that the rCBF changes associated with a task subside quickly and return to baseline during the ten or twelve minute interscan interval. This assumption has been challenged by Momose and colleagues (1991a; 1991b). They reported that rCBF changes induced by a two-minute visual task could be detected as long as 15 minutes after the end of visual stimulation. Their observation has important implications. If the activated brain region does not reestablish resting
values within the interscan time, the subsequent scans would be contaminated with residual activation. Moreover, if mental tasks can have such long lasting effects on rCBF, activities that subjects undertake between scans would also influence what is recorded during the PET scan making clear interpretations nearly impossible.

This study was designed to test the claim of Momose and colleagues (1991a; 1991b). Six healthy right-handed subjects aged 19-42 (mean age 26) undertook six scans, ten minutes apart. Prior to the first scan, a twenty minute period of dark-adaptation allowed the subject to become accustomed to the ambient darkness of the scanning room. There were two experimental tasks: a baseline fixation task and a visuomotor activation task. The baseline task involved visual fixation on a small cross located at the Centre of a computer screen suspended 60 cm from the subject's eyes. For the visual and motor task, concrete nouns appeared on the computer screen at a rate of one word every second (average interstimulus interval 1000 ms, staggered ± 100 ms) and the subject was required to do a finger thumb pinch every time a word appeared on the screen. In previous PET experiments we have observed robust activation of the occipital cortex bilaterally for the visual task and of the contralateral primary motor cortex for the motor task. Scans 1 and Scan 2 were baseline scans for all subjects. Scan 6 was the activation scan during which the subjects carried out the visuomotor task while being scanned. Scans 3, 4 and 5 were residue scans. The subjects carried out the visual and motor task for 2.5 minutes prior to the scan and performed the baseline fixation task during the scan. The interval between the termination of the activation task and the start of the scan was one of the following three delays: 30 seconds, 3 or 6 minutes. The order of these delays was counter-balanced across the subjects. The PET images were subtracted to determine areas of activation (Scan 6 minus Scan 1 or Scan 2) and to identify significant residual effects (Scan 3, Scan 4 or Scan 5 subtracted from Scan 1 or Scan 2). The design is laid out in Figure II-2.
Legend for Figure II-2: The figure depicts the order of scans. The tasks marked with squares were carried out during the PET scans. Tasks shown below the timeline and marked with a circle were carried out in the interscan interval to assess their effect on the subsequent scan.

An SPM analysis of scan 6 (activation condition) minus the baseline conditions (scan 1 and scan 2) showed that the visuomotor task produced a significant activation (p<0.01) in the bilateral striate region, the extrastriate region, the left primary motor cortex, and a less significant (p<0.05) activation in the supplementary motor area. Similar SPM analyses of the residue scans (scan 3, 4, and 5) minus the baseline conditions showed no evidence of any significant residue in these regions at 30 seconds, 3 and 6 minutes after the termination of the activation task even when the statistical criterion were relaxed to obviate a Type-II error.

In summary, the experiment showed that with the usual scan sequence used in cognitive PET experiments there is no significant residual activation. The ten to twelve minute interscan time, which has been conventionally followed in PET experiments, is sufficient to allow for the return of the rCBF to an unstimulated level before the next scan. However, while this study confirms that the rCBF returns to baseline promptly, it does not rule out the possibility that the neural system may now be more or less
sensitive of activation. In other words while there is no main effect of prior cognitive tasks, there may still be an interaction effect.

**Power Analysis**

Most of the functional neuroimaging studies are done using a group design. The basic experimental design in most of these studies includes several subjects with six to twelve scans per subject, while the subjects undertake specified cognitive tasks during the different scans. The images obtained while subjects are involved in the specified cognitive tasks are compared for differences in regional cerebral blood flow (rCBF) using semi-automated software (Grasby et al. 1993b; Jonides et al. 1993; Petersen and Fiez 1993; Petrides et al. 1993b). Brain regions which show statistically significant difference in rCBF between the two tasks are considered to be especially involved in the cognitive processes which differentiate the two tasks (Posner et al. 1988). In the analysis of these studies the probability of false-positives (Type I error) i.e. the detection of an activation where none really exists is addressed by most authors (Grasby et al. 1993b; Jonides et al. 1993; Petersen and Fiez 1993; Petrides et al. 1993b). The issue of false negatives or Type II error, i.e. failing to detect a change that does indeed exist, has received much less attention. This study attempted to estimate the probability of Type II error in these experiments.

The power of a statistical test to reject a null hypothesis, or in this context to detect a change in rCBF, is determined by the magnitude of the change under study, the number of subjects, the probability of Type I error (designated by \( \alpha \)) and the variance in the dependent variable (Cohen 1988; Kraemer and Thiemann 1990; Rosner 1990; Keppel 1991). The number of subjects and \( \alpha \) are set by the investigator. The magnitude of change, which in cognitive PET studies is the change in the rCBF, depends on the cognitive tasks being compared. The baseline variance is determined by the physiological variation inherent in the measure and the variation introduced due to measurement error. The purpose of this study was to obtain an estimate of
baseline variance in PET cognitive experiments and to use the estimate to derive the probability of Type II error under usual experimental conditions.

An estimate of within-subject baseline variance requires test-retest of the subject under identical conditions. It has been suggested that an active-baseline task, as compared to passive-rest condition, decreases baseline variance (Duara et al. 1987; Cooper et al. 1991; Holcomb et al. 1993). While some authors disagree (Rottenberg et al. 1987; Ball et al. 1988), there is no evidence to suggest that an active-baseline task is less stable than a rest task. Therefore we used a continuous performance choice reaction-time task as an active baseline. Stimuli for this task were presented on a computer screen 60 cm. in front of the subject and perpendicular to their line-of-sight. The stimuli (developed using MEL-software, Psychology Software Tools, Pittsburgh, PA, USA) were horizontal arrows, white on black background, appearing in the center of the screen at the rate of one per second, lasting for 500 milliseconds and then replaced by a central fixation point. The subjects responded to the direction of the arrows by clicking one of the two buttons on a computer mouse held in the right hand. The subjects undertook a total of six consecutive scans doing exactly the same task. Absolute quantitation of regional cerebral blood flow from $^{15}$O-H$_2$O PET data requires arterial blood sampling, a feature which makes this technique more invasive. To avoid this, and in keeping with other recent PET cognitive activation studies (Grasby et al. 1993b; Pardo et al. 1993; Petrides et al. 1993a) we used integrated regional counts as an index of regional cerebral blood flow.

Estimates of baseline variance were obtained for 126 pixels, sampled in a stratified random manner from each of three different cortical regions - frontal cortex (Brodmann's areas 45, 46 &10); temporal cortex (Brodmann's areas 21 & 22) and the occipital cortex (Brodmann's areas 18 &19). For each pixel in the right hemisphere, a corresponding left hemisphere pixel was also selected. Estimates of within-subject baseline variance were obtained using values of rCBF at a given pixel across different scans. The power to detect a change depends on the statistical test being employed. In SPM analysis, the data analysis finally reduces to a paired t-test at a pixel by pixel level. In most exploratory PET cognitive studies, a clear directional hypothesis is not
formulated a priori and the number of subjects is usually less than 30. Under these conditions a two-tailed paired t-test is an appropriate test and power of such a test can be calculated utilizing the formula shown below (Rosner 1990):

$$t_{df=n-1;1-\beta} = \frac{\Delta \sqrt{n}}{s} - t_{df=n-1; 1-\alpha/2}$$

where $\beta$ is the probability of incurring a Type II error; $1 - \beta$ is the power of a two-tailed paired t-test to reject the null-hypothesis with a probability of Type I error of $\alpha$; $n$ is the number of subjects; $s$ is the estimated standard deviation while $\Delta$ is the change in rCBF in the smoothed images caused by the cognitive task. $t_{df=x;y}$ is the Student's t-value corresponding to $y$th percentile under $x$ degrees of freedom (Rosner 1990).

**Figure II-3.**

Legend Figure II-3. The power (y-axis) to detect a significant change at different levels of p-value (squares $p = 0.05$; circles $p = 0.01$; triangle $p = 0.001$) as a function of the magnitude of the increase to be detected (a, b, c) and the number of subjects (x-axis) in the experiment using a single trial of each task.
Figure II-4. The power (y-axis) to detect a significant change at different levels of p-value (squares p = 0.05; circles p = 0.01; triangle p = 0.001) as a function of the magnitude of the increase to be detected (a, b, c) and the number of subjects (x-axis) in the experiment using two trials of each task.

There was no significant change in task performance across the six practice runs and six experimental runs of the active baseline task (repeated measures ANOVA $F_{11,110} = 1.23$, Greenhouse-Geisser corrected $p = 0.34$). More specifically, there was no significant difference in response rate (mean ± standard deviation: 508±78 ms. vs. 507±75, paired $t_{df=0} = 0.147$, $p = 0.88$), or accuracy (mean ± standard deviation: 94.7%±3.6% vs. 93.9%±4.5%, paired $t_{df=0} = 0.54$, $p = 0.62$), in the two scans (scan 3 and scan 4) used for calculation of the baseline variance. The data attest to the stable nature of this active-baseline task. The coefficient of variation, in the smoothed data obtained from the active-baseline task was 2.4% in the single-task design and 1.7% in the repeat-task design. There were no significant difference in the estimate of the coefficient of variation in the three cortical regions ($F_{2,123} = 2.11; p = 0.12$), or across hemispheres ($F_{1,124} = 1.36; p = 0.24$).

Figure II-3 and II-4 demonstrate the expected tradeoff between statistical power and the probability of Type I error. For example, working with twelve subjects in a single-task design, the ability to detect a 2% increase may vary from a low of 7% ($p=0.001$), to a high of 72% ($p=0.05$)
depending upon the $\alpha$, the probability of Type I error accepted. This is not to recommend a lenient threshold, but to suggest that if a specific directional hypothesis can be postulated $a$ priori, one could use a one-tailed t-test, avoid multiple comparisons and justifiably use a lower value of $\alpha$ (resulting in a lower $t_{1-\alpha/2}$ in the power calculation) leading to a noticeable increase in power.

From the point of view of interpreting PET results, our results illustrate how the power to detect a given activation, say a 2% change at a $p=0.01$, may vary from an almost negligible power with 9 subjects and a single-task design, to a near 100% power when working with 15 subjects and a repeated-task design. This illustrates how in the usual operating range i.e. 9-15 subjects, two experiments using the same cognitive tasks, may lead to quite different neuroanatomical conclusions, only because of differences in their statistical power to detect change. It is possible that many discrepancies in the extant PET cognitive data may be artifacts of the differences in power between the studies.

In summary, our results emphasize the need to consider the probability of a Type II error, or the power of the experiment, while designing and interpreting cognitive activation studies using PET. The presented power curves should serve as a rough guideline for deciding upon the number of subjects in cognitive activation PET experiments. The curves also show how small differences in the number of subjects, and whether a task is repeated or not, can give rise to dramatic differences in power of the experiment and may lead to discrepant interpretation of similar raw data. It is suggested, therefore, that absence of an activation in a given region during a specific task should not be taken as conclusive evidence of non-involvement of that region. Such a conclusion is only warranted after consideration of the physiological, technical and statistical issues raised in the paper (Kapur et al. 1995c).
Chapter 3

Background and Rationale for the Experimental Plan

The experiments which constitute this thesis were conceived and carried out over a period of three years from 1992 to 1995. When we first started thinking about the problem in 1992 there were no published functional neuroimaging studies of memory. Today there are over two dozen, and close to a dozen of these are from the Rotman Research Institute-Clarke Institute of Psychiatry group. Given the expense and the constraints of this type of work several considerations went into each study in an attempt to maximize the scientific yield. As a result the experimental plan for the dissertation was modified in light of the emerging data from our work and from that of others. To help the reader comprehend the evolution of these studies, the strategic and the practical considerations which shaped this work are presented first. The formal justification for each article is presented in the introduction of each article.

As we were planning our first studies in the winter of 1992, Squire and colleagues published the first highly influential study of memory with PET. Squire and colleagues studied subjects while they were viewing word stems under baseline, priming and recall instructions. The Squire study established that PET scanning could be fruitfully applied to the study of memory and that regions beyond the hippocampus, particularly the prefrontal cortex, are activated when memory tasks are studied using PET. Soon a study appeared by Grasby and colleagues (1993b) from Hammersmith hospital that mapped the different brain regions that were involved in encoding and retrieval, without differentiating between the two.
Also at this time an important debate was underway regarding the role of the left prefrontal cortex between the researchers at Washington University (Petersen et al. 1988; Petersen and Fiez 1993) and the Hammersmith Hospital (Friston et al. 1991b; Frith et al. 1991b; Frith et al. 1991a). Both groups used a semantic processing task and a lexical baseline task. Petersen et al. argued that the subtraction isolates 'semantic processing,' while Frith et al. emphasized that the subtraction isolates the operations of 'willed action.'

These studies formed the background on which we planned our first experiment. From the point of view of memory, the studies above had not studied encoding (Squire et al. 1992), or had confounded it with retrieval (Grasby et al. 1993b). Given our orientation towards a memory processes framework we felt that further progress could be made by explicitly distinguishing encoding from retrieval. This was the first objective of the first experiment and led to Article #1.

On a second note we felt that the experiment could be designed in such a fashion so as to meaningfully contribute to the 'willed action' vs. 'semantic processing' debate. By 1993, most PET studies requiring a meaningful analysis of verbal material had shown a unilateral activation of the left dorsolateral prefrontal cortex (DLPFC) (Frith et al. 1991b; Frith et al. 1991a; Petersen and Fiez 1993). Explanations for this finding fell into two broad categories. One, proposed by Petersen and colleagues (1993) held that the DLPFC activity reflects a specific cognitive process, namely the use of the semantic information contained within the stimulus. The other, proposed by Frith and colleagues (1991b; 1991a), claimed that the activation, as observed in verbal processing tasks, is a specific instance of a more general strategy called 'willed action' (a task requires willed action when the response is "not completely specified by the stimulus", regardless of the nature
of the stimulus). In addition to these two explanations it had been argued that the left DLPFC activation in verbal processing tasks may be related to the requirement of producing an overt spoken response (Wise et al. 1991; McCarthy et al. 1993) and may be unique to the verb-generation paradigm only (Wise et al. 1991; Demonet et al. 1992).

Article #2 compares the different explanations for the DLPFC activation. First, to distinguish between semantic processing and willed action explanations we designed the tasks such that they differed in their semantic processing requirements, but did not differ along the willed-action dimension. Second, since most previous studies required a spoken response it had been suggested that the left DLPFC activation seen in the semantic task may be a response-modality dependent activation (Wise et al. 1991; Demonet et al. 1992; McCarthy et al. 1993). We used a hand-held mouse-click as a response mode to address the question. Third, to investigate whether the activation was unique to the specific task of verb-generation (Wise et al. 1991; Demonet et al. 1992) or was obtained from semantic processing in a wider context, our study used word categorization instead of verb-generation. The task requires semantic processing but is distinct from the verb-generation task. Fourth, in some of the previous studies the perceptual input was not identical across the comparison tasks (Frith et al. 1991b), or the rate of response generation varied across the two tasks (Frith et al. 1991a; Petersen and Fiez 1993). In our study the semantic and the non-semantic tasks were identical in terms of input-output characteristics.

The above work established a role for the left prefrontal cortex in encoding, and suggested that the involvement may reflect the "working with meaning" aspect of the prefrontal cortex.
As we completed the above study, Prof. Tulving was leading our group to study episodic retrieval using a related paradigm. The results of the first two studies [along with a study by Moscovitch et al. (1995)] made a very compelling case for a prominent role of the prefrontal cortex in memory operations and also showed that the two prefrontal hemispheres participated in encoding and retrieval differentially.

This led us to publish our encoding (Kapur et al. 1994a) and retrieval (Tulving et al. 1994b) findings together. At the same time Tulving et al. (1994a) published a review of the emerging studies and distilled from them the consensus that the left and the right prefrontal cortex are differentially involved in encoding and retrieval. Tulving et al. (1994a) focused on hemispheric asymmetry in the involvement of the left and right prefrontal cortex in encoding and retrieval (*Hemispheric Encoding Retrieval Asymmetry*).

The HERA model was an atheoretical empirical review of the data. Tulving et al. concluded that that left and right prefrontal cortex were differentially involved in encoding and retrieval, but what they did, at a functional level was unclear. Further experiments in this thesis were then aimed at specifying the role of the left and right prefrontal cortex in encoding and retrieval.

By the spring of 1994, close to a dozen different studies, some published, some abstracts and some anecdotal reports had shown that the right prefrontal cortex is preferentially involved in retrieval (Tulving et al. 1994a). However, no one had explicitly addressed what the right prefrontal cortex did in retrieval. A promising paradigm to understand the role of the right prefrontal cortex involved the study of retrieval attempt vs. ecphory. This paradigm derives from a view that the act of remembering is subserved by two sets of dissociable processes. Retrieval attempt refers to the processes that the
subject applies to a cue in an attempt to retrieve information. It is speculated that these processes are the same regardless of whether the cue refers to a previously learnt stimulus or not (i.e. it is involved both in correct-hits and in correct-rejections). On the other hand ephory refers to the reactivation of the memory trace, an event that happens only when the subjects remembers (i.e. in correct-hits and not in the case of ‘correct rejections’).

Furthermore, Moscovitch (1992b; 1992a) had clearly stated that the role of the prefrontal cortex is along the lines of retrieval attempt and not ephory, which is subserved by medial temporal and posterior structures.

Therefore Article #4 investigated whether the right prefrontal cortex was involved in the attempt to remember (retrieval attempt) or whether it was involved in the reactivation of the memory trace itself (ephory). The results of our study showed that the right prefrontal cortex was involved in retrieval attempt. This was in line with speculations from neuropsychology, it was consistent with the working with memory model and was replicated by two later studies, Schacter (1996) and Nyberg (1995).

By this time, we had studied encoding and retrieval in different experiments and our studies were yielding consistent results regarding the role of the left and the right prefrontal cortex in encoding and retrieval respectively. It became evident that we could start using these paradigms to study alterations in memory in the elderly and in other diffuse neurological disorders such as schizophrenia. However, we had only done encoding and retrieval across subjects, as had most others, and there was the need to develop an experiment that would tap encoding and retrieval in a single session.

Furthermore, one drawback of our encoding study (Article #1) was that it involved unintentional encoding. We did not ask the subjects to “learn”. We had manipulated the
task instructions which would ensure that they would encode differentially. While this type of learning is typical of what subjects do in real-life situations, it differed from the laboratory situations, wherein subjects are usually given instructions to “remember”. Therefore, the new experiment was designed to address the issue by including encoding under the usual learning instructions. Subjects would be asked to make an intentional “encoding attempt”; analogous to the retrieval attempt. This led to Article #3. The results of the study confirmed that left prefrontal cortex mediates encoding. But it does so via two distinct subregions. The anterior inferior prefrontal cortex facilitates encoding via semantic processing - it is involved in intentional and unintentional encoding. A more poster0 region, in the mid-dorsolateral prefrontal cortex, was also involved and we reason that it represents rote-rehearsal or verbal working memory.

At the time that we were planning Article #3, we were also struck by the fact that all studies which addressed retrieval, regardless of whether they used recognition (Tulving et al. 1994b; Kapur et al. 1995b; Moscovitch et al. 1995), cued-recall (Squire et al. 1992) or free recall (Grasby et al. 1993b) showed the involvement of the right prefrontal cortex. On the other hand, the statistical conclusion of most neuropsychological studies was that the prefrontal was more involved in recall that in recognition. Why then, were all the recognition studies also showing the activation of the right prefrontal cortex? Could it be that recall invoked the right prefrontal cortex to a greater degree than recognition? To our knowledge there was no study at that time, and there is no other study till this date, that had explicitly compared two different types of explicit retrieval using a within-subject design. This issue can be conclusively resolved only in a within-subject design. Therefore, we decided to compare recall and recognition, using verbal stimuli, using a within subject
design, after matching recall and recognition in terms of difficulty. This led to Article #5 which shows that there is no difference in the activation of the prefrontal cortex whether retrieval is achieved via cued recall or recognition.

In this account I have tried to explain the evolution of our reasoning and the winds and tides which influenced its course over three years of research.
Article # 3

Article # 4

Article # 5

This chapter synthesizes the results of Article #1 through Article #5 with an emphasis on
the role of the prefrontal cortex in episodic memory. The first section in this chapter highlights the
hemispheric asymmetry in the involvement of the prefrontal cortex in encoding versus retrieval
(HERA). The next sections discuss the functional contribution of the prefrontal cortex to the
processes of encoding and retrieval in episodic memory. The following section grapples with the
question of how the hemispheric asymmetry observed in HERA can be understood in the larger
context of asymmetric brain function. The chapter then deals with the question: Where's the
hippocampus? PET studies to date have not observed reliable activations in the medial temporal
region - the possible causes and implications of this are discussed. The section entitled ‘A
rudimentary neurocognitive model of episodic memory’ weaves together the PET findings into a
testable, though speculative, model of human episodic memory. The final section points to the
salient contributions as well as limitations of these studies and points out the questions which
merit further investigation.

Hemispheric Encoding Retrieval Asymmetry (HERA)

Functional neuroimaging makes it possible to differentiate cognitive processes which may
be difficult, if not impossible, to differentiate using traditional neuropsychological approaches
(Buckner and Tulving 1995). Encoding and retrieval are independent and interdependent
cognitive processes which subserve an act of memory. Using traditional neuropsychological
methods it has been difficult to separate the neural substrates of encoding from those of retrieval.
When a subject with a focal lesion is unable to recall recently learnt material, it is unclear if this
failure results from a deficit in encoding, a deficit in retrieval or from an interaction between the
two. While attempts have been made to differentiate encoding from retrieval through a study of
lesion effects on recent versus remote memory, or through an analysis of differential forgetting
rates, these methods permit only indirect inferences regarding the neuroanatomy of encoding and
retrieval. Therefore, the differentiation of encoding from retrieval, at a neural level, may be one of the most important contributions of PET data to the understanding of episodic memory.

That PET may offer a particularly unique means to investigate the difference between encoding and retrieval emerged from the observation of hemispheric asymmetry in the involvement of the prefrontal cortex in encoding and retrieval in the first three PET studies of memory that we had completed in 1994. These included the study of encoding reported as Article #1 (Kapur et al. 1994a), and studies of retrieval of episodic memories by Tulving et al. (1994b) and Moscovitch et al. (1995). These studies provided the seed for the conceptual development of HERA. A more elaborate case for HERA was developed by Tulving et al. (1994a) by reviewing the extant PET literature for studies of encoding. However, in 1994, with the exception of Article #1, there were no other PET studies of encoding per se. Therefore, the development of the HERA model required the reconceptualisation of the existing data as reflecting encoding; and validation of that reconceptualisation.

The key ideas which made HERA possible were: i) the assertion that explicit instructions to learn or memorize were not necessary for encoding to occur (Craik and Tulving 1975); ii) the consideration of semantic memory retrieval as a stimulus for episodic encoding (Tulving 1972).

Learning and encoding are terms that are often confused. In this thesis learning will denote the intentional cognitive processes that the subjects usually undertake when making an effort to commit to a fact to memory. Encoding denotes changes in the brain which support these processes. Learning is obviously important for encoding and therefore most studies ask the subject to “learn.” However, cognitive psychologists have known for a long time that what is vital for encoding is how the stimulus is processed, and not whether the subject has an explicit intention or instructions to “learn” (Craik and Lockhart 1972; Craik and Tulving 1975). Semantic processing of stimuli, that is the processing of stimuli with reference to their meaning, leads to strong encoding regardless of the subject’s intention. The subject’s intention to learn adds little to memory performance if the subject is already undertaking deep semantic processing (Craik and Tulving 1975).
Therefore PET studies wherein subjects were asked to undertake meaningful semantic processing of stimuli - verb-generation to nouns (Petersen et al. 1988) or category-exemplar generation (Frith et al. 1991a) - are all studies of encoding into episodic memory, regardless of whether the subjects were explicitly asked to learn or not.

This idea was validated in simple paper-pencil cognitive experiment using PET stimuli and PET instructions (Tulving et al. 1994a). Petersen and colleagues (1988) had completed a PET study of verb generation wherein subjects were asked to generate a verb to a provided noun (subjects hear the word ‘ladder’ and generate ‘climb’). When compared to a baseline task (subjects hear the word ‘ladder’ and repeat ‘ladder’) the verb-generate task showed a robust activation of the left prefrontal cortex (Petersen et al. 1988; Petersen and Fiez 1993). It was not the intention of Petersen et al. to study the memory consequences of the generate task. The verb-generation task requires semantic retrieval, in a fashion that the noun-repetition task does not. Therefore, Tulving et al. hypothesized that the verb-generation task, which had been demonstrated to be associated with left prefrontal cortex activation, would be associated with a superior encoding as ascertained by a higher memory performance.

To confirm this 82 undergraduates were exposed to four lists of 20 printed nouns each. In two of the lists the instructions were to write appropriate verbs in response to the nouns (analogous to the verb-generate task of Petersen et al.). In the other two lists the instructions were to copy the nouns (analogous to the repeat task of Petersen et al.). No mention was made of a later memory test. Five days later, the subjects were given an unexpected yes/no recognition test consisting of 80 original nouns and 80 new nouns, mixed randomly. The subjects were to decide whether they had seen these nouns in the exposure five days prior. The hit-rate for the generate-nouns was 0.50; for the repeat nouns was 0.26; the false-alarm rate was 0.11. These data correspond to a d’ of 1.23 for the words encoded in the generate condition and 0.58 for repeated-nouns (Tulving et al. 1994a).

This cognitive study demonstrated that semantic retrieval or semantic processing as Petersen et al. have described it, constitutes a robust stimulus for encoding of verbal stimuli. This
conceptual bridge between semantic retrieval and episodic encoding was essential because prior to Article # 1, there were no published PET studies focusing on encoding per se. Once semantic retrieval was seen as a stimulus for episodic encoding, it was plausible to consider the eight available PET studies of semantic processing as legitimate studies of encoding. All eight studies showed a left prefrontal activation. On the other hand, of the eight studies of retrieval, seven showed an exclusively right prefrontal and one a predominant right prefrontal activation (Tulving et al. 1994a).

This led Tulving et al. (1994a) to state that “encoding tasks engage the left prefrontal regions, in the absence of comparable right prefrontal activation, whereas retrieval tasks engage the right prefrontal areas, frequently in the absence of comparable left frontal activation.” The finding was named HERA, for Hemispheric Encoding Retrieval Asymmetry. The model asserts that regions of the prefrontal cortex are components of a widely distributed neuronal network which subserves episodic memory. Other components of this network include the medial temporal lobe, the diencephalic structures and posterior neocortical regions. The HERA model was largely atheoretical. It was the documentation of a remarkable empirical regularity but did not specify the differential contributions of the left and the right prefrontal cortex to the processes of encoding and retrieval. Furthermore, the prefrontal cortices are large and anatomically heterogeneous cortical structures (Stuss and Benson 1986) and even though HERA treated them as monolithic entities, it was expected that future work would provide more precise and specific delineation of function and interactions.

Since its enunciation in 1994, the number of PET studies which deal with encoding and retrieval have more than doubled. The current empirical support for HERA has recently been reviewed by Nyberg et al. (1996) and is summarized in Tables IV-1 and IV-2. Sixteen of the eighteen studies of intentional and unintentional encoding show activation of the prefrontal cortex, and all show activation only on the left. Twenty seven of twenty nine studies of retrieval show activation of the prefrontal cortex. Of these, nineteen show exclusively right prefrontal activation, six show predominantly right prefrontal activation and two show equal activity. No
study of encoding shows right prefrontal activity, and no study of retrieval shows predominantly left prefrontal activity.

*HERA is one of the most reliable finding in the functional neuroimaging of cognitive processes.*

A simple extrapolation of the HERA model would suggest that since the left prefrontal cortex is involved in semantic retrieval and episodic encoding, lesions of the left prefrontal cortex should lead to deficits on semantic memory retrieval and anterograde episodic amnesia as a result of lack of encoding. On the other hand, since the right prefrontal cortex is especially involved in episodic retrieval, lesions of this region should spare semantic memory retrieval and should result in retrograde as well as anterograde amnesia. While there is a body of literature supporting hemispheric asymmetry with respect to the material-specificity of the amnesia (Kolb and Whishaw 1990), support for neuropsychological asymmetry in terms of encoding versus retrieval is rather limited.

Several recent reports suggest that right-brain damage, in particular damage to the frontotemporal connections via the uncinate fasciculus lead to deficits in episodic retrieval, with relatively preserved semantic retrieval (Kapur et al. 1992; O'Connor et al. 1992; Markowitsch et al. 1993; Hodges and McCarthy 1995). Whereas damage of the left prefrontal cortex, left temporal cortex and left parietal cortex may lead to selective disruption of semantic memory and semantic retrieval, with relatively preserved episodic memory (De-Renzi et al. 1987; Grossi et al. 1988; Hodges and McCarthy 1995)

Furthermore, a recent case study, which included both functional neuroimaging as well as systematic memory testing, supports a differential role for the right prefrontal cortex in episodic memory (Baron et al. 1994). A 60 year old lady with a history of hypertension was studied during and after an episode of transient global amnesia. PET measurement of regional cerebral blood flow and regional glucose metabolism showed a significant (18%) reduction in perfusion and
metabolism in the right prefrontal cortex along with reductions in ipsilateral thalamus and lenticular nucleus, and a preserved perfusion and metabolism in the medial temporal areas. Three months later, the transient global amnesia had resolved, along with resolution of the right frontal perfusion and metabolic abnormalities.

Most of the above reports, however, involve single cases. Studies of groups of patients with frontal lesions have either not been studied, or do not support, the simple left-right dichotomy suggested above. A dozen of these studies have been reviewed in the introduction and none of them show a striking asymmetry along the lines of the simple extrapolation above. On the contrary, many studies of patients with frontal lesions do not find any episodic memory deficits when using standard tests of memory (recognition and recall) and conventional statistical analysis (Wheeler et al. 1995). Of the studies that do find deficits, differences between left and right are either not there, or do not conform to encoding/retrieval deficits predicted by HERA (Wheeler et al. 1995). While the case reported by Baron (1994) is remarkable, it is an outlier. Most neuropsychological reports associate transient global amnesia (TGA) with anterior medial temporal lesions, and two functional imaging studies associate TGA with changes in the medial temporal regions in the absence of evident frontal lesions (McCarthy and Warrington 1992; Lin et al. 1993).

Rather than a definitive theoretical model which reconciles data regarding the neural correlates of encoding and retrieval, HERA is a remarkable empirical regularity observed in functional neuroimaging that provides a reliable foothold for understanding the role of the prefrontal cortex in episodic memory (Tulving et al. 1994a). It clearly differentiates encoding from retrieval and distinguishes between the roles of the right and left prefrontal cortex in memory processes. A major objective of the experiments in this thesis, and of this synthesis, is to develop a theoretical understanding of the contributions of the left and the right prefrontal cortex to the processes of encoding and retrieval.
### Table IV -1. (Adapted from Nyberg et al. (1996))

**Activation of the Prefrontal Cortex Associated with Episodic Memory Encoding.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Task</th>
<th>Reference Task</th>
<th>Prefrontal Left</th>
<th>Prefrontal Right</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidental Encoding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Semantic Retrieval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen et al. (1988)</td>
<td>verb generation</td>
<td>noun repetition</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Petersen et al. (1990)</td>
<td>word reading</td>
<td>fixation</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Raichle et al. (1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1</td>
<td>verb generation</td>
<td>noun repetition</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Trial 9</td>
<td>verb generation</td>
<td>noun repetition</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wise et al. (1991)</td>
<td>verb generation</td>
<td>rest</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Frith et al. (1991a)</td>
<td>word generation</td>
<td>rest/count/lexical</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Frith et al. (1991b)</td>
<td>word generation</td>
<td>word repetition</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fletcher et al. (1995)</td>
<td>instance generation</td>
<td>category repetition</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Buckner et al. (1995a)</td>
<td>word-stem completion</td>
<td>fixation</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kapur et al. (1994a)</td>
<td>semantic decision</td>
<td>orthographic decision</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Demonet et al. (1993)</td>
<td>semantic decision</td>
<td>phonetic decision</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Demb et al. (1995)</td>
<td>semantic task</td>
<td>easy nonsemantic task</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Demb et al. (1995)</td>
<td>semantic task</td>
<td>difficult nonsemantic task</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Intentional Encoding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shallice et al. (1994)*</td>
<td>category-learning</td>
<td>number hearing</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fletcher et al. (1995)*</td>
<td>category-learning</td>
<td>number hearing</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kapur et al. (1996)</td>
<td>noun-pair learning</td>
<td>noun-pair reading</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Haxby et al. (in press)*</td>
<td>face learning</td>
<td>face matching</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Grady et al. (1995)</td>
<td>face learning</td>
<td>face matching</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by -. The * in adjacent studies indicate that they include overlapping data. f indicates fMRI studies.
Table IV -2. (Adapted from Nyberg et al. (1996))

Activations of the Prefrontal Cortex Associated with Episodic Memory Retrieval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Task</th>
<th>Reference Task</th>
<th>Prefrontal Left</th>
<th>Prefrontal Right</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squire et al. (1992)*</td>
<td>word-stem cued recall</td>
<td>word-stem completion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Buckner et al. (1995a)*</td>
<td>word-stem cued recall</td>
<td>word-stem completion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Different case</td>
<td>word-stem cued recall</td>
<td>word-stem completion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Auditory</td>
<td>word-stem cued recall</td>
<td>word-stem completion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Buckner et al. (1995a)*</td>
<td>cued-recall</td>
<td>word repetition</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Shallice et al. (1994)*</td>
<td>cued-recall</td>
<td>instance generation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fletcher et al. (1995)*</td>
<td>cued-recall</td>
<td>instance generation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Schacter et al. (1996)</td>
<td>word-stem cued recall</td>
<td>word-stem completion</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cabeza et al. (1996)</td>
<td>cued-recall</td>
<td>word-pair reading</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Petrides et al. (1995)</td>
<td>cued-recall</td>
<td>word repetition</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Petrides et al. (1995)</td>
<td>free recall</td>
<td>word repetition</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tulving et al. (1994b)</td>
<td>studied sentence Rn</td>
<td>nonstudied sentence Rn</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kapur et al. (1995b)</td>
<td>word Rn</td>
<td>semantic decision</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Andreasen et al. (1995a)</td>
<td>word Rn</td>
<td>word reading</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nyberg et al. (1995)</td>
<td>word Rn (shallow study)</td>
<td>word reading</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nyberg et al. (1995)</td>
<td>word Rn (deep study)</td>
<td>word reading</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nyberg et al. (1995)</td>
<td>nonstudied word Rn</td>
<td>word reading</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cabeza et al. (1996)</td>
<td>word-pair Rn</td>
<td>word-pair reading</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Nonverbal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haxby et al. (1993)*</td>
<td>face Rn</td>
<td>face matching</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Haxby et al. (in press)*</td>
<td>face Rn</td>
<td>face matching</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Grady et al. (1995)</td>
<td>face Rn</td>
<td>face matching</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>N. Kapur et al. (1995a)</td>
<td>face Rn</td>
<td>face gender decision</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tulving et al. (1994c)*</td>
<td>studied picture Rn</td>
<td>nonstudied picture Rn</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Roland et al. (1995)</td>
<td>visual pattern Rn</td>
<td>visual pattern learning</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Moscovitch (1995)</td>
<td>object identity Rn</td>
<td>object matching</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Moscovitch (1995)</td>
<td>object position Rn</td>
<td>object matching</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Schacter et al. (1995)</td>
<td>abstract object Rn</td>
<td>object perception</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Owen et al. (in press)</td>
<td>object-location Rn</td>
<td>object-location learning</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Owen et al. (in press)</td>
<td>location Rn</td>
<td>location learning</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by -. A smaller plus sign indicates prefrontal cortex with smaller or weaker activation, according to the authors. The * in adjacent studies indicate that they include overlapping data. Rn = recognition.
Left Prefrontal Cortex in Encoding

An act of remembering begins with the encoding of a stimulus and ends with the retrieval of it. To understand encoding, it is important to distinguish it from "learning". Learning encompasses cognitive tasks and strategies undertaken by the subject in an effort to encode; whereas encoding refers to the "neural process that converts (that perceptual) event into an engram" (Tulving 1983). The information stored in this engram (or memory trace) can then be used to guide subsequent retrieval activities. Encoding is the neural correlate of the subject's efforts to learn. However, as has been shown before (Craik and Tulving 1975) and has been replicated in the PET context in Kapur et al. (1994a), instructions to "learn" are not essential for encoding. Conversely, every attempt to learn does not necessarily lead to a retrievable trace.

When instructed to learn, subjects tend to use strategies which they believe will help in forming a better memory. Most subjects use a mix of two basic cognitive strategies - rote rehearsal which involves subvocal repetition, and semantic elaboration (Pressley and Levin 1977; Shaughnessy 1981; Geiselman et al. 1982). While semantic elaboration is clearly a more effective strategy for encoding, most subjects do not know this and tend to preferentially engage in rote rehearsal in an effort to learn (Shaughnessy 1981).

In contrast to laboratory experiments where subjects are often asked to learn, most real-life memories require no explicit instructions to learn. To develop a comprehensive understanding of the left prefrontal cortex in encoding we studied both the intentional and unintentional learning conditions.

Attributes of the left prefrontal contribution to encoding

The PET studies reported herein (Article #1, Article #2, Article #3) underscore a differential role of the left prefrontal cortex (as compared to the right prefrontal cortex) in encoding. This role is characterized by the following attributes:

i) The anterior inferior left prefrontal cortex activation is associated with superior encoding (Article #1).
ii) The anterior inferior left prefrontal cortex is associated with encoding, regardless of the intention to remember (Article #1, Article #2).

iii) The anterior inferior left prefrontal cortex activation can be best understood as reflecting semantic elaboration/semantic processing/semantic retrieval or as we have suggested "working with meaning." This is not attributable to a concept such as "willed action" and is not modality or material specific (Article #2).

iv) When subjects are asked to learn they have a tendency to rote-rehearse as well as attempt to make semantic associations. The act of rote-rehearsal may be associated with the activation of a region in the left posterior mid-frontal cortex (Article #3).

v) This posterior frontal region associated with rote rehearsal is not essential for encoding, and may not even enhance the efficiency of encoding (Article #1, Article #3).

Several authors have now presented results which are consistent with the above statements. This concordance is tabulated in Table IV-1 and commented on in Article #1 and Article #3. Until recently, all studies of encoding involved verbal materials. Therefore, a study of encoding using non-verbal materials was crucial to develop a more complete picture. This has recently been provided by Grady et al. (1995) who showed that when asked to learn faces (a non-verbal stimulus which shows asymmetric right sided perceptual processing) young subjects displayed an activation of the left (not right) prefrontal cortex. Similarly, Owen et al. (1996) showed a left preference for object-feature and object-location encoding, even though visuo-spatial processing is usually considered a right-lateralised phenomenon.

Left prefrontal facilitates encoding but is not essential for it

What does the left prefrontal cortex do in the process of encoding? The available evidence permits one to speculate that the role of the left prefrontal cortex in encoding is to facilitate the laying down of the engram - it is not the only site of the engram.

Several findings support this position. First, PET studies of encoding have usually compared a high-encoding condition to a verbal baseline condition. These baseline conditions do
show some encoding, i.e. the level of subsequent memory is above chance though the performance is not as good as the high encoding condition (Petersen et al. 1988; Petersen and Fiez 1993; Kapur et al. 1994a; Kapur et al. 1996). Petersen et al. have compared these conditions to a still more elementary baseline - just a passive visual fixation. However, when the verbal baselines are compared to the passive visual fixation there is no robust evidence of a left prefrontal activation. This suggests that some level of encoding, albeit small, is possible without a PET-detectable involvement of the left prefrontal cortex. Second, several studies of perceptual processing have demonstrated activation of posterior neocortical regions without a noticeable activation of the anterior left prefrontal cortex (Corbetta 1993). A cognitive analysis of these tasks suggests that with the appropriate cues retrieval of these stimuli would be expected to be above chance. Third, Petrides et al. (Petrides 1995) studied normal subjects as they viewed novel abstract-designs with no specific instructions to memorize them. The PET images revealed activation of the orbitofrontal regions along with the adjoining limbic-cingulate regions but no activation of the dorsolateral prefrontal cortex. A post-scanning recognition test documented successful encoding though comparative figures on the efficiency of this encoding were not provided. Since subjects were able to encode without activation of the dorsolateral prefrontal cortex, it suggests that some encoding can occur in the absence of the left prefrontal cortex.

If the left prefrontal cortex was indispensable for the formation of the engram, one would expect that patients with lesions to this region would have dense anterograde amnesia. This is not the case (Shimamura 1995; Wheeler et al. 1995). In fact, patients with frontal lobe lesions show some impairment in memory, but it is not similar to a classical amnestic syndrome, and the magnitude of the deficit is not as severe as that of patients with temporal lobe lesions (Shimamura 1995; Wheeler et al. 1995). Vogel et al. (1987) studied patients with frontal and medial temporal-diencephalic lesions. Patients performed more poorly than controls. However, patients with prefrontal lesions differed from those with diencephalic and medial temporal lesions in that they were able to benefit when structure and opportunities for deeper processing were provided. This suggests that the prefrontal and medial temporal regions make different contributions to the
process of episodic remembering. The medial temporal contribution is critical to memory performance, while the prefrontal contribution is partially, if not completely, replaceable by externally provided contextual support at encoding and retrieval. It is proposed, therefore, that the left prefrontal cortex facilitates the encoding process, via its role in semantic processing.

Neuroanatomical evidence supports extensive interactions between the prefrontal cortex, the medial temporal cortex, and the posterior neocortical association areas. The prefrontal cortex is connected to the medial temporal structures directly via the uncinate fasciculus (evidence reviewed by Markowitsch (1995b)) and also via its connections to the thalamus-mamillary body-fornix (Warrington and Weiskrantz 1982). At the same time the prefrontal cortex has extensive connections to the posterior neocortical association areas, as does the medial temporal cortex (Goldman-Rakic 1988). These connections may make it possible for the prefrontal cortex to modulate the laying down of the ‘engram’, which may itself reflect changes in the posterior neocortical and medial temporal regions (Damasio 1989; Moscovitch 1992a).

The relationship between learning strategies, intention to learn, the left prefrontal cortex and encoding can be summarized as following. First, subjects encode either when trying to learn intentionally or as an unintentional by-product of processing stimuli. Second, the two most common cognitive strategies used by subjects include semantic elaboration and rote rehearsal. These strategies may be related to the left anterior-inferior and the posterior-mid-frontal prefrontal cortex, respectively. Third, the mental act of semantic processing is subserved at the level of the brain by the anterior left prefrontal cortex and this results in superior encoding. Fourth, the anterior left prefrontal cortex is not mandatory for encoding but its participation results in more retrievable engrams.

Why and how activation of the left prefrontal cortex leads to superior encoding is a project for future study.
The Right Prefrontal Cortex in Retrieval

In addition to contributing further evidence towards the HERA model, this thesis helps specify the role of the right prefrontal cortex in retrieval by demonstrating that i) the activation of the prefrontal cortex is similar in recall and recognition when the two are matched for difficulty (Article #5); and ii) the role of the right prefrontal cortex is compatible with the notion of “retrieval attempt” (Article #4). The following sections discuss these findings.

The right prefrontal, recall and recognition.

The role of the prefrontal cortex in retrieval has a contentious history in neuropsychology. Positions on this issue have ranged from those who contend that frontal damage is associated with “normal recall and recognition memory” (Shimamura et al. 1990), to those who think that prefrontal cortex is not involved in mere recognition or recall but is required to make decisions regarding temporal context (Milner et al. 1985), to more recent findings by Stuss and colleagues (1994) who find both recall and recognition impaired in patients with frontal lesions. A recent empirical review of all the studies which report memory impairment following frontal lesions show that only 8% (1/12) of the studies showed statistically significant impairment in recognition, as compared to 50% (5/10) in cued recall, and 80% (8/10) in free recall. These data have been conventionally interpreted to mean that frontal patients are unimpaired in recognition but are impaired in recall (Wheeler et al. 1995).

Wheeler et al. also show that when the raw data from the experiments, rather than statistical conclusions, are considered more than 80% of the studies of recognition (18/21) show deficits with frontal lesions, as do studies of cued recall (25/27) and free-recall (31/31). This discrepancy between the number of studies which report ‘statistically significant’ deficits and numerical deficits results because the effect size of the deficits in recognition tests is 0.08 as compared to 0.17 in cued recall and 0.16 in free recall. Therefore, Wheeler et al. conclude that all three forms of retrieval (recognition, cued-recall and recall) are impaired in patients with frontal lesions, albeit to different degrees. They also suggest that the prevalent view that recognition is
spared, while recall is impaired, may be an artifact of the limited power of the experiments to detect the differences.

If Wheeler’s conclusion is correct, would it be fair to claim that the prefrontal cortex is more involved in recall than recognition? For a claim of ‘more’ to have validity, one would have to ensure that the tests used to analyze recognition and recall are of equal difficulty. Performance in recognition tests, after equivalent encoding, is usually higher than performance elicited using cued-recall or free recall tests. Since recognition is easier, recognition performance is more likely to be near ceiling in both frontal patients and controls, this may obscure a small effect-size difference between patients and controls (Chapman and Chapman 1973). Thus it was apparent that this issue can be completely resolved only after the comparative study of recall and recognition at their native levels of performance and also when performance is equivalent.

It was the intent of Article #5 to study recognition and recall in tests of equivalent difficulty. To achieve this we manipulated the encoding condition such that targets for the recognition condition were only studied once, while targets for the recall condition were studied twice. The desired effect was achieved since the performance on recognition and recall was statistically indistinguishable (recognition performance = 0.86 ± 0.09; recall performance 0.78 ± 0.19; Paired t-test t_{df=11} = 2.0, p > 0.05. See Article #5 for details). We found an equal activation of the right prefrontal cortex in recognition and recall under conditions of equated performance. This is the only functional neuroimaging study that compares recognition and recall within the same subjects, using matched stimuli, and controlling for the relative difficulty of the two tests. Prior to Article #5 there was no direct comparison of recognition and recall.

Would one find a greater activation of the RPFC when recall and recognition tests are done with their native levels of difficulty (i.e. recall performance poorer than recognition performance). While within-subject data on this subject are not available, a series of studies by Andreasen et al. shed light on this issue.

Andreasen et al. have compared novel retrieval (recall and recognition) to practiced retrieval (recall and recognition) in different modalities (visual and auditory) using different
materials (words, complex narratives and faces) (Andreasen et al. 1995a; Andreasen et al. 1995b; Andreasen et al. 1995c; Andreasen et al. 1995d). Since, the recall and recognition studies were in different groups of subjects and used different modalities and materials a direct subtraction is not feasible. However, a comparison of the results from these studies show that: the right prefrontal cortex is invoked by both recognition and recall, regardless of the level of practice, modality and material. However, recall invoked the thalamus in a way that recognition did not (Andreasen et al. 1995c; Andreasen et al. 1995b) - a finding also observed in Article #5.

While the Andreasen et al. studies do not permit an evaluation of recall vs. recognition within subject, they do address the issue of ‘difficulty’ in a within-subject fashion. In both the recognition and recall studies, novel retrieval following one encoding exposure showed a poorer performance (practiced recognition = 0.96, novel recognition = 0.84; practiced correct recall = 14.2 hits, novel correct recall = 6.6 hits out of a total of 15) than practiced retrieval. At the same time a direct comparison of the novel minus practiced retrieval showed an activation of the right prefrontal area 45 in novel recognition, and right anterior inferior frontal in novel recall. Novel retrieval tasks are more ‘difficult’ as they are associated with poorer performance and are also associated with greater involvement of the right prefrontal cortex. Indirectly, the Andreasen findings also support the role of the right prefrontal cortex in retrieval attempt regardless of the success of retrieval, since retrieval conditions with greatly different correct performance (novel recall: 6.6 hits vs. practiced recall 14.2 hits of a total of 15) showed similar activation of the prefrontal cortex.

In summary then, our study of recall vs. recognition shows equal involvement of the right prefrontal cortex when task difficulty is equated. Andreasen’s studies suggest that while recall and recognition show the same pattern, increasing task difficulty increases the involvement of the right prefrontal cortex. It is reasonable to expect that a within-subject PET study comparing recognition to recall, without equating performance, would demonstrate a greater involvement of the right prefrontal cortex in recall. To the author’s knowledge no such study exists.
The right prefrontal cortex, attention, working memory and "retrieval attempt"

The RPFC has a similar role in recall and recognition - what is this role? Article #4 suggests that the role of the prefrontal cortex is best understood as retrieval attempt. This raises important questions: How reproducible is the finding relating the right prefrontal cortex to retrieval attempt? How does one best understand the concept of "retrieval attempt" in the context of other functional neuroimaging studies? How does "retrieval attempt" correlate with neuropsychological hypotheses regarding the role of the prefrontal cortex (attention, working memory, strategic processing, temporal sequencing)?

Right prefrontal cortex and retrieval attempt - a reliable finding

Since the publication of Article #4, two separate studies have confirmed the notion that the involvement of the right prefrontal cortex in memory is compatible with the notion of retrieval attempt and separable from ecphory. Nyberg and colleagues (1995) compared the retrieval of information that had been encoded with different instructions - either with reference to meaning of the word, or with reference to the speaker’s voice. Regardless of the method of encoding, retrieval was associated with activation of the right prefrontal cortex. Nyberg et al. (1995) interpret this to mean that the role of the right prefrontal cortex reflects "retrieval mode", a concept similar to "retrieval attempt".

Schacter and colleagues (1996) have reported a PET study wherein subjects were asked to recall paired associates learnt prior to PET scanning. Subjects had learnt the words under two different conditions. The word-list intended for "high-recall" was encoded in four attempts by making semantic decisions on the words. The word-list intended for "low-recall" was encoded in a single attempt by making perceptual judgments. As expected (Craik and Lockhart 1972), when subjects were presented three-letter stems they were successful in recalling 79% of the words from the high-recall list, as opposed to 35% of the words from the low recall list. The corresponding PET scans showed that an activation of the prefrontal cortex was associated with the attempt to retrieve the words, regardless of success, whereas hippocampal activation was
observed only in the high recall condition suggesting that this region is especially involved when conscious recollection is successful.

In sum, both Nyberg (1995) and Schacter (1996) replicate the essential claim of Article #4 - that retrieval attempt is distinguishable from ecphory; and that the RPFC activations are related to retrieval attempt and not ecphory.

Several other groups have obtained an exclusive or predominant right prefrontal activation in retrieval. While these studies have not manipulated the experimental tasks to role the right prefrontal contribution, their suggestions regarding the possible role of the right prefrontal cortex are compared here. Petrides and colleagues have carried out a series of studies to delineate the role of the ‘ventrolateral frontal cortex’ (Brodmann Area 45, 47 and 10) in mnemonic processes (Petrides 1995; Petrides et al. 1995). In a particularly interesting experimental design subjects undertook three different tasks on pairs of abstract designs. In one case all designs were familiar, in the other all were novel, and in the third one member of the pair was novel and the other familiar. In the first two conditions, subjects were asked to observe the designs but without any explicit memory instructions. Whereas in the third condition subjects were asked to make an explicit recognition judgment on the novel-familiar pair. Significant activation of the ventrolateral prefrontal cortex was present when the recognition task was compared to the familiar condition. This, along with their previous experiments led the authors to suggest that the role of this region is in the ‘strategic retrieval of information from long-term memory’ and in ‘making decisions on information held in memory’ (Petrides 1995; Petrides et al. 1995). Both these ideas are compatible with our experimental demonstration of the role of this region in ‘retrieval attempt’.

Petrides et al. (1995) do not present results on the regions which were activated in the familiarity minus novelty comparison, though as per our findings one would predict that the spontaneous ecphory that would have been elicited by the familiar stimuli would give rise to an activation in the posterior association cortices.

Shallice and colleagues have also observed an activation of the right prefrontal cortex in their studies of verbal recall. They attribute the activation due to processes of ‘internal
monitoring/verification’ (Shallice et al. 1994; Fletcher et al. 1995). Buckner and colleagues have observed the right prefrontal cortex activation in a series of verbal recall and recognition studies (Buckner et al. 1995a). The suggest that the right prefrontal cortex may contribute to memory processes by ‘searching for the target information and the internal monitoring of whether the retrieved information is connected to the specific context of the previous episode.’ This suggestion is well in keeping with the concept of retrieval attempt. Finally, Andreasen et al. who have observed a right prefrontal activation in novel and practiced recall of word-lists and complex narratives also concur with the foregoing theme and suggest a role of the prefrontal cortex in “initiation of the retrieval process” (Andreasen et al. 1995a; Andreasen et al. 1995b; Andreasen et al. 1995c).

Thus there seems a general agreement about the role of the right prefrontal cortex, at least insofar as it is invoked in retrieval in PET experiments. Our study is the first experimental confirmation of these suggestions - and in turn has been confirmed by Nyberg et al. (1995) and Schacter et al. (1996).

Retrieval attempt and its relationship to attention and working memory

How does the concept of retrieval attempt relate to current PET data on the role of the right prefrontal cortex in attention and working memory? Previous studies have shown that attention to extra-personal space results in the activation of the right prefrontal cortex (Cohen et al. 1988; Meyer et al. 1991; Pardo et al. 1991; Cohen et al. 1992). In light of this finding, as well as neuropsychological studies implicating the right prefrontal cortex in attention (Stuss and Benson 1986), it could be argued that the activation of the right prefrontal cortex in episodic memory studies merely represents attention directed to the presented cue.

A simple claim that the right prefrontal cortex represents “attention” would not suffice because the encoding tasks also require attention but do not activate the right prefrontal cortex. To sustain the attention explanation one would have to qualify it further and claim that there is something special about ‘attention to episodic retrieval’ which distinguishes it from ‘attention to
semantic retrieval.' With such a qualification, the attention explanation would fit our data well. But, if attention is to be understood as task specific - i.e. attention for episodic retrieval differs from attention for semantic retrieval, which in turn differs from attention for face identification etc. - then the parsimonious appeal of the concept of attention greatly diminishes. If attention is conceptualised in such a task-dependent manner, then little can be said about attention which would generalize from one task to another.

Several authors have suggested that working memory mediates the retrieval of long-term memory, and that processes such as "mnemonic search" and "monitoring" are actually carried out in the mental workspace provided by working memory (Stuss and Benson 1986; Moscovitch 1992a; Baddeley 1995). Therefore, it could be argued that the RPFC activations represent the engagement of working memory in the service of episodic retrieval. The proposal is logically appealing, but PET data do not support it. Proposals relating working memory to episodic retrieval claim that the verbal working memory mediates the retrieval of verbal materials from long-term memory (Baddeley 1992). Several neuroimaging studies have localized verbal working memory in the left prefrontal cortex (Koepepe et al. 1993; Smith and Jonides 1995). Since retrieval attempt activations are predominantly, if not exclusively, in the right prefrontal cortex (Kapur et al. 1995b; Nyberg et al. 1995; Schacter et al. 1996) a simple claim that retrieval attempt activations reflect working memory is rather untenable. A few studies on non-verbal working memory have suggested an activation of the right prefrontal cortex (Jonides et al. 1993; Smith and Jonides 1995). Therefore, to conceptualise our retrieval attempt in terms of working memory, it would have to be claimed that only non-verbal working memory mediates verbal retrieval, a claim that is not currently supported by evidence.

Given that no pre-existing framework adequately accommodates this finding, retrieval attempt is perhaps the best term to understand the RPFC activations for the present. First, the term is devoid of prior theoretical baggage and is easily operationalised in experimental designs which can be used with functional neuroimaging. Second, by not pigeon-holing this activation as attention or working-memory, it leaves open the possibility for further theoretical development.
The purpose is not to deny a contribution of attention and working memory to episodic memory retrieval or to RPFC activations. In all likelihood they do play a part. But, the advantage of retaining retrieval attempt is that it will not allow this phenomenon to be absorbed in attention and working memory without a thorough appraisal.

Retrieval attempt and neuropsychological theories.

How does retrieval attempt compare with previous neuropsychological hypotheses regarding the role of the prefrontal cortex? As detailed in chapter 1, several accounts have suggested a role for the prefrontal cortex in "strategic" aspects of retrieval. While the exact terms and specifics of what is "strategic" varies between authors, the broad implications are well captured in the modular framework proposed by Moscovitch (Moscovitch 1992a). In his account the prefrontal cortex subserves two classes of function which are subsumed under the term 'working with memory'. The first is 'mnemonic search' and refers to the ability of the prefrontal cortex to parse incoming perceptual information and organize a retrieval strategy. This function of the prefrontal cortex precedes ephory. Medial temporal and posterior structures, which are seen as modular, are the agents of ephory. Based on the query initiated by the prefrontal cortex, the information stored within the medial temporal and posterior structures may result in ephory. The results of ephory are returned as a 'shallow' output to prefrontal structures. The second function of the prefrontal cortex is to interpret the temporal and spatial appropriateness of this returned information and to use this information to guide future action or further mnemonic search. This post-ephoric role is termed "monitoring". Mnemonic search precedes and initiates ephory. Monitoring succeeds and analyses it.

Our PET data fit the Moscovitch model. Article #4 shows that the prefrontal cortex undertakes non-ephoric related functions - exactly as the Moscovitch model would predict. The Moscovitch model further claims that the prefrontal contribution entails two distinct roles: mnemonic search which precedes ephory, and monitoring of ephoric output. While the present PET data are consistent with either or both of these functions, PET does not have the temporal
resolution to determine whether the right prefrontal activation precedes or succeeds the ephoric activation. It is unlikely that PET, or for that matter any cerebral blood flow based technique will ever have the millisecond temporal resolution required to resolve the pre-ephoric versus post-ephoric question - such questions may need other techniques such as evoked response potentials which have finer temporal resolution.

In summary, as HERA would predict, our studies (Article # 4 and Article # 5) find that episodic retrieval differentially activates the right prefrontal cortex. This role is best understood as ‘retrieval attempt’ and is invoked by both recall and recognition, if the level of difficulty of these tests is equated. Retrieval attempt is operationally and neuroanatomically distinguishable from ephory. Future research will have to specify precisely which cognitive processes mediate retrieval attempt and how retrieval attempt leads to ephory.

What leads to the hemispheric asymmetry of the HERA model?

The HERA model as explicated by Tulving et al. (1994a) is a statement regarding an empirical regularity - not an explanation of it. As a result the HERA model can only predict itself, i.e. the left prefrontal cortex will be invoked in encoding and the right in retrieval, but cannot make predictions beyond this domain. If it could be shown that the left and right hemispheres have certain distinct information processing attributes, and if encoding and retrieval could be related or accommodated within those abilities, then one could understand HERA as a special instance of a more general mind-brain asymmetry theory.

There is general agreement that the left and right hemispheres make different contributions to cognition - however, there is no general agreement about how to best conceptualise these differences (Allen 1983). Data regarding functional asymmetry comes from different experimental techniques (Hellige 1990). In neurologically normal individuals presentation of stimuli to only one hemisphere (tachistoscopic, dichotic or dichaptic) followed by an analysis of their responses has provided the other main source of information. Patients with asymmetric lesions, patients with commissurotomies as well as asymmetric sodium-amytal infusions (Wada Test) provide additional
information. To this corpus of information is added the recent data from functional neuroimaging (ERP, PET and fMRI) techniques.

The most well established asymmetry is the left hemispheric dominance in the production of speech, followed by the left-hemispheric dominance in language perception, comprehension and semantic processing. While the left hemispheric dominance in speech production seems to be exclusive (the right hemisphere produces little, if any, speech), the left dominance in other aspects of language is more a matter of degree (Allen 1983; Hellige 1990; Kolb and Wishaw 1990). On the other hand, no one has yet documented the exclusive dominance of the right hemisphere for any task or cognitive process, though several lines of evidence suggest that the right hemisphere is superior in aspects of visuo-spatial and manipulo-spatial processing. Despite these documented behavioral asymmetries, there is still no fundamental dichotomy that can convincingly differentiate the left from the right, and several authors doubt if there ever will be one (Allen 1983; Hellige 1990).

How then does one understand the asymmetry of HERA? Given the present information it would be a reasonable speculation that the left prefrontal cortex is invoked in encoding because language is a left lateralized function in humans. Therefore, whether subjects encode verbal materials (Table IV-1); or non-verbal objects such as faces or object-location (Table IV-1), they invoke semantic processing and semantic elaboration - cognitive processes which in turn involve the left prefrontal cortex.

While the association between verbal encoding, semantic processing and left prefrontal activation is well established by our studies, the case with respect to non-verbal materials is not as well established. Grady and colleagues (1995) have recently demonstrated that young subjects engage the left prefrontal cortex in encoding faces; while Owen et al. (1996) have shown the same asymmetry when subjects encode the object-features or object-location. While this evidence confirms the role of the left prefrontal in non-verbal encoding, it is still unclear why this region is activated in non-verbal encoding. Future research should investigate if subjects activated the left prefrontal cortex in non-verbal encoding due to semantic processing. If it can be demonstrated
that the asymmetry in encoding results from the fact that semantic processing mediates encoding of verbal as well as non-verbal materials, we would have moved a step closer to a general understanding of the encoding process and relating them to the known left-superiority for language processes.

Why does retrieval localize to the right prefrontal cortex? We have suggested that the right prefrontal contributes to the processes of retrieval attempt - why is this seemingly verbal process not mediated by the left prefrontal cortex? Unfortunately, there are at present no widely accepted general theories regarding right hemispheric processing. Several have been forwarded: a special role for the right hemisphere in non-verbal processing of any stimuli; right hemisphere as a seat of ‘holistic’ processing as opposed to the ‘analytic’ mode of the left; right hemisphere as seat of ‘parallel’ processing as opposed to the serial sequential mode of the left (Allen 1983; Hellige 1990; Kolb and Wishaw 1990); right hemisphere as a monitor of perceptual information as opposed to the left which is the source of inference and ideation (Gazzaniga 1995); right hemisphere superiority in ‘structural matching’ vs. a left superiority in ‘conceptual matching’ (Nebes 1985); right as important for ‘co-ordinate based’ image generation while the left is superior in ‘categorical relation’ based image generation (Kosslyn 1988). The problem with these theories are twofold. Those that are broad enough are not specific or operationalised enough to be refutable (Allen 1983; Hellige 1990; Kolb and Wishaw 1990). Those theories that are well substantiated and easy to operationalize, have applications in very narrow domains (e.g. Kosslyn’s ideas are best applied to visual imagery).

One could suggest that episodic retrieval, since it involves a recapitulation of the learning episode, is in some sense a veridical ‘structural match’ and thus localizes to the right (as opposed to the left which is better at conceptual matches) (Nebes 1985). Owen et al. (1996) have made a similar suggestion to explain why encoding of object location prefers the left prefrontal, while retrieval of object location prefers the right. Extending the same line of reasoning one could argue that verbal recognition and verbal cued-recall require a partial or complete reinstatiation of the memorised episode and localize to the right because of right-superiority at veridical structural
matches. However verbal free recall also shows a clear right preference, and it is not immediately obvious how verbal free recall is a ‘structural match’ of the initial exposure. In either case, all the above suggestions are post hoc. Experimental proof for the above is lacking. Future studies could explicitly manipulate the strategies used in retrieval, and demonstrate how a ‘structural match’ strategy (being the default strategy) localizes retrieval to the right; while other strategies (conceptually mediated) use other brain regions.

It would be fair to suggest that at present we have no satisfactory theories of hemispheric function, only models which document and explain ‘local’ empirical regularities (Allen 1983; Hellige 1990; Kolb and Wishaw 1990). And, perhaps, a search for an overarching left-right dichotomy may in itself be misleading. There is no a priori reason to believe that the information processing in the brain is organised along hemispheric dichotomies. Allen (1983) has suggested that rather than the hemisphere being a basic unit of analysis, we should reformulate the problem in terms of smaller, regionally segregated, neural subprocessors. Under this formulation a search for hemispheric theories reduces to a study of subprocessors, their distinctions and their interactions. Our conclusions that the left prefrontal ‘works with meaning’, while the right prefrontal subserves ‘retrieval attempt’ moves HERA in that direction.

Where's the Hippocampus?

Medial temporal structures, in particular the hippocampus, perirhinal and the parahippocampal regions, play a crucial role in episodic memory as revealed by most neuropsychological studies of memory (Squire and Knowlton 1995). Yet, most PET studies of encoding and retrieval have not shown reliable activations of the hippocampus. There are a few exceptions (Squire et al. 1992), but by and large, this region has been silent. Why is this so?

Before attempting to address this discrepancy one has to clarify when during an act of memory one would expect hippocampal involvement: at encoding, during consolidation, or at retrieval. Studies in patients who have sustained hippocampal lesions show they suffer from profound anterograde amnesia, along with a temporally graded retrograde amnesia. These
findings are interpreted to suggest that the hippocampus and related medial temporal regions have distinct role in encoding of memories - for little is learnt after a hippocampal lesion (Squire and Knowlton 1995). Furthermore, it may also have a role in the retrieval of recently learnt memories, though, with the passage of time certain memories may be retrieved independently of the hippocampus. Therefore, one would expect the hippocampus to be activated in studies of encoding, and perhaps in studies of retrieval. Furthermore, neuropsychological studies reveal a differential role for left vs. right hippocampus, with the left hippocampus being crucial for verbal materials, and injury to the right hippocampus interfering little, if at all, with verbal retrieval (Kolb and Whishaw 1990). Therefore, one would expect activation of the left hippocampus and adjacent regions in our studies of encoding as well as retrieval.

PET data fail to support this expectation. We found no hippocampal activation in Article #1 (Encoding). Similarly, more than a dozen studies (Table IV-1) have used the levels of processing paradigm and functional neuroimaging, and while they have all shown a reliable activation of the prefrontal cortex, they do not show a reliable activation of the medial temporal region. We do observe an activation of the parahippocampal region in Article #3, where encoding was intentional. However, intention is not crucial in invoking the hippocampus because: i) PET data from other groups who have studied intentional encoding of verbal materials do not show an activation of the hippocampus (Grasby et al. 1993b; Shallice et al. 1994; Fletcher et al. 1995); and ii) neuropsychological evidence has never shown that “intention” to encode is the only facet of encoding disrupted by the hippocampus. It is fair to conclude that functional neuroimaging studies of encoding verbal material have not revealed the hippocampus as robustly and as prominently as would be expected based on neuropsychological data.

Studies of retrieval of verbal material have been similarly negative. Considerable impetus was generated by the first report of Squire and colleagues ‘sighting’ the hippocampus in verbal retrieval (Squire et al. 1992). Subsequent efforts by their group to replicate that finding have failed (Buckner et al. 1995a) and five studies by our group (Tulving et al. 1994b; Kapur et al. 1995b; Moscovitch et al. 1995; Nyberg et al. 1995; Cabeza et al. 1996), and several studies by
others (Shallice et al. 1994; Andreasen et al. 1995a; Fletcher et al. 1995; Petrides et al. 1995; Cabeza et al. 1996), have not found the hippocampal activations. Is one to conclude that the hippocampus is not involved in verbal memory.

It is suggested here that neuropsychological and PET imaging differ conceptually. These conceptual differences and current methodological limitations may be obscuring the hippocampus in PET studies.

**Testing a behavioral dimension vs. all invoked processes**

Neuropsychological studies usually test a single, or a limited number of behavioral dimensions. On the other hand, PET scanning is likely to point regions invoked by all cognitive processes unleashed by the stimulus - the intended ones as well as the unintended ones. This point is better understood with reference to a hypothetical situation. Let's assume that reading a word requires the participation of a set of regions A. Now let us design a PET study to identify these regions. Such a PET study is likely to involve two tasks - one involving reading words and another involving viewing non-words which are equal in their visual characteristics. However, when subjects will carry out these tasks and read words, they not only read words but also spontaneously encode them (involving region B), make spontaneous semantic elaborations in their mind (region C), and the words may evoke an affective response (region D). Therefore, a PET subtraction intended to identify the neural correlates of word reading will point to not only to region A, but also to B, C and D. Now, B, C and D are not essential for word-reading, but are customarily invoked whenever human beings read a word. A neuropsychological analysis, using a conventional test of reading may show that patients reading ability is impaired only if region A is lesioned, and not if regions B or C or D are lesioned.

This example illustrates the possibility that PET may give a more comprehensive, but confounded, analysis of the brain regions involved in reading. On the other hand, neuropsychological analysis may point one to the bare-essential region involved in reading, but may not capture the different regions which are usually invoked when humans undertake reading
in naturalistic settings. This may explain why the PET memory experiments tend to invoke a broad network of regions many of which are not known to be implicated in amnesic syndromes.

**Neuropsychological localisation vs. Cognitive-PET localisation**

Another possible reason for the discrepancy between functional neuroimaging in normal subjects and neuropsychological studies in lesioned patients results from their differential sensitivities to lesion/activation size. I illustrate this with the help of a schematic diagram. It is a generally accepted fact that most cognitive tasks are subserved by a network of regions which are anatomically heterogeneous and widely distributed. In Figure IV-1 this is shown as region A, B and C. Region A and C are large, have multiple neuronal connections within them and have in-built functional redundancy; region B forms a bottleneck which transmits data to region C. A mental function, say memory, is obtained as a function of neural impulses through this system from A to B to C.

Neuropsychological research accords function to a region if selective lesions in that area disrupt performance on a particular task. Since one has no control over size and location and lesion, neuropsychological studies try and select patients with focal and homogeneous lesions. Therefore, neuropsychological research will point to that region, where a small lesion will consistently disrupt function. This is most likely to happen at site B, because at A and C there is considerable overlap and redundancy built into the system. Furthermore, since regions A and C are spatially extended it is less likely that one will find homogenous populations with focal lesions which encompass the entire region, but do not involve adjoining regions. On the other hand, PET imaging points to those regions which show maximal neuronal mass-firing. Therefore, PET imaging is likely to point to site A and C since this is site of the bulk of the neuronal activity which support the function.
Lesion Based Localization and subiemes a certain function. Region A and C are spatially extended, have multiple connections and have in-built functional redundancy. Region B is a neuronal bottleneck. Lesion based localization of function is likely to assign the function to site B since a small lesion at B (stippled) is likely to completely disrupt the functioning of this pathway. PET studies on the other hand are likely to localize the function to region A and C, since these regions are spatially extended and include large numbers of neurons.

Figure IV-1. The figure is a schematic depiction of a neuronal circuit that includes regions A, B and C and subserves a certain function. Region A and C are spatially extended, have multiple connections and have in-built functional redundancy. Region B is a neuronal bottleneck. Lesion based localization of function is likely to assign the function to site B since a small lesion at B (stippled) is likely to completely disrupt the functioning of this pathway. PET studies on the other hand are likely to localize the function to region A and C, since these regions are spatially extended and include large numbers of neurons.

Whether this scheme captures the neuronal circuits is not as yet clear - but it provides an understandable mechanism why one may find discrepancies between these two different ‘windows’ into the mind-brain.

The hippocampus is continuously active: One of the loopholes of a subtraction approach is that it highlights the regions that differ between two tasks - not the regions which are involved in the two tasks (Sergent 1994). Therefore, if a region is involved in both the tasks equally, it would not show up on the subtraction technique. If the role of the hippocampus is in assisting the transfer of information from short-term memory stores to long-term memory stores then it could be active in all tasks. Even though no explicit instructions to remember are given to the subject in
the baseline task the hippocampus may be active nonetheless, assisting in the encoding of attributes of the baseline task environment which are of no interest to the experimenter e.g. “memory of taking the baseline task” or “memories of perceptual characteristics of the PET setup”.

This position provides a convenient way to reconcile hippocampal absence in functional neuroimaging and yet maintain the central role of hippocampus in neuropsychological theorizing. But, in its simplest form (i.e. the hippocampus is always equally active) this hypothesis is virtually untestable using the standard subtraction approach. However, one does not encode all events in life with equal facility. Therefore, if the hippocampus is to have a crucial role in encoding, it must play some differential role in different perceptual experiences. The differential role may not necessarily entail a change in rCBF, but may involve a change in the functional relationship between the hippocampus and the other brain regions (McIntosh et al. 1995b).

Differential interactions instead of more activity: The subtraction method underscores the ‘involvement’ of a region only if it results in a measurable changes in rCBF. It is conceivable that the hippocampus involves itself in memory formation and retrieval not by increasing or decreasing the number of neurons that are firing, but instead a) by changing the relation of the inhibited and excited neurons within the hippocampus, such that there is a change in the pattern of hippocampal firing but no change in the bulk number of neurons firing; b) by altering the relation of its neuronal firing with respect to the brain regions with which it is associated, rather than increasing or decreasing the number of neurons firing.

The proposition that the hippocampus is involved via differential interactions is testable using correlational and network analysis (McIntosh and Gonzalez-Lima 1994). A preliminary analysis by McIntosh and colleagues of data from PET studies of recognition suggests that the hippocampus is involved in the retrieval of verbal materials, but does so by its interaction with anterior cingulate regions (McIntosh et al. 1995b). Thus network analysis, rather than subtraction, may provide an avenue to investigate and evaluate hippocampal contribution.
Anatomic and functional variability: The current mode of analysis of PET data requires the averaging of images across subjects. We have shown that the average activation reported is around 2 to 4% while the average coefficient of variance is 2.4% (Kapur et al. 1995c). This high noise to signal ratio necessitates some method of image-averaging which would permit the averaging of data from a group of individuals. If there is anatomical heterogeneity (that is the hippocampus is not the same shape and size across subjects), or if there is physiological heterogeneity (that is the hippocampus does not activate in the same way across subjects) averaging will lead to a diminution of the effect size of the signal.

The above confound reduces the statistical power of PET studies to detect ‘significant’ changes in rCBF. In fact, in an average PET study, the power to detect a 2% change may be as low as 10% if only 12 subjects are used and task is not repeated within-subject (Kapur et al. 1995c). Therefore, if technical solutions are found to deal with the problem of image averaging, or if large enough samples are used, we may find activations of the hippocampus even using a subtraction approach.

rCBF and neuronal activity: The enterprise of using rCBF to identify the neural correlates of cognitive processes is based on the premise that rCBF changes localize changes in neuronal activity (Raichle 1987). For the rCBF changes to be useful as indicators of neuronal function the relationship between the two measures should be linear and invariant across the brain regions. There is at present no convincing evidence that in all regions of the brain, when synaptic transmission changes by x% that blood flow changes by the same y%. If the rCBF response characteristics of the hippocampus are different from that of the prefrontal cortex it is conceivable that there may be a change in synaptic activity in both regions, but, may be large enough to be detectable only in the prefrontal cortex.
Temporal averaging: Another limitation of the present technology is that a PET image represents the composite data of 45-60 seconds of brain activity. The effect is analogous to image-averaging across subjects (as above), except that now one is averaging in the temporal domain. If the hippocampal structures are neuronally invoked only for a short duration, which lead to brief spikes of rCBF change, these changes may be smoothed out by long periods of non-activity. Initial efforts have been made to narrow this temporal window (Hurtig et al. 1994; Silbersweig et al. 1994). But PET, as well as functional MRI, tracks changes in blood flow. And these changes show a lag of the order of 2-10 seconds (Houle et al. 1994; Hurtig et al. 1994). Therefore, it may well be physically impossible to monitor events that happen within milliseconds using rCBF as an index.

In summary, the absence of hippocampal involvement in rCBF functional neuroimaging is a surprise. This discrepancy between PET and neuropsychological findings raises a number of interesting questions regarding the role of the hippocampus, about PET technology as it is applied to the study of cognition and about our current analytic strategies. This discrepancy should not be viewed as “PET is right” versus “neuropsychology is right.” Both methods provide reliable information about memory and the brain, but, at different levels of analysis. Both are right in what they tell us. It is the job of neuroscientists to understand this discrepancy - and from the study of this discrepancy will emerge a better understanding of the role of hippocampus in memory and PET and neuropsychology as methods of investigation.

A rudimentary neurocognitive model of episodic memory

This section collates the PET findings into a model of episodic memory. Models such as this have been presented previously (Tulving 1983; Damasio 1989; Mesulam 1990; Moscovitch 1992a; Squire and Knowlton 1995). What is new here is the collation of PET data into this model. Specifically, an effort is made to link the concepts of learning, encoding, retrieval attempt and ecphory as operationalized and investigated by PET studies into a more general model of episodic memory.
A rudimentary neurocognitive model of Episodic Memory

Neural correlates of Encoding

IV-2a. Perception without semantic processing
IV-2b. Semantically processed material

Figure IV: Figure IV-2a shows the stimulus being perceived and leaving an engram in the posterior neocortical areas without the involvement of the medial temporal and prefrontal regions. Figure IV-2b shows the brain activity that accompanies the subject attending to the stimulus and semantically processing it. This activity involves the prefrontal and medial temporal cortex, and leaves a more enduring engram as a result.

Neural correlates of Retrieval

IV-3a Memory without conscious awareness
IV-3b Memory with attempt

Figure IV: Figure IV-3a shows the target giving rise to priming. It is achieved through facilitated neural processing throught the posteriorly located trace, but does not require medial temporal or frontal involvement. On the other hand conscious attempts at retrieval are mediated via the prefrontal cortex and involve the medial temporal cortex as well as rekindle posteriorly located engrams.
The model is explicated in Figure IV-2 and Figure IV-3. The figures deal with visually presented stimuli only, though the ideas could extend to encoding via all modalities.

Encoding: Encoding occurs as a function of stimulus processing, which can broadly be separated into two classes: shallow processing (Figure IV-2a) and deep processing (IV-2b). These terms are borrowed from the levels of processing framework (Craik and Lockhart 1972). Shallow processing refers to a subject’s encounter with a stimulus which leads to a predominantly perceptual analysis. As shown in the figure this results in neuronal activation of the relevant perceptual primary, secondary and association areas. In the above model nothing apart from perception, and its attendant activation of perceptual regions, needs to occur to support subsequent implicit memory. It is claimed, therefore, that all PET stimuli which show perception specific activation of the primary and association posterior neocortical regions would lead to implicit learning. This claim is plausible since is has been shown repeatedly that mere exposure leads to lasting implicit memory (Schacter 1995).

If the subject makes a conscious decision to ‘learn’ this usually entails some aspect of semantic elaboration and rote-rehearsal. Semantic processing leads to the activation of the anterior left prefrontal, or anterior plus the posterior mid-frontal prefrontal cortex if rote-rehearsal accompanies the attempt to learn. These claims have been substantiated by the PET data presented in this thesis (Article #1, Article #2, Article #3).

It is a further claim of this model that the involvement of the anterior prefrontal cortex in the processing of information leads to a more enduring memory trace. This is implemented by a recruitment of the medial temporal region. While the PET data do not currently divulge activation of the medial temporal region, this aspect is included in the model to accommodate the considerable neuropsychological evidence regarding the role of the hippocampus in learning. It is argued that stimuli which are processed deeply engage the prefrontal cortex and this engagement of the prefrontal cortex leads to a more retrievable trace via the involvement of the medial temporal region. The prefrontal cortex facilitates the formation of the engram - while the medial
temporal region seems crucial for it. The medial temporal region may function as a catalogue or
the node that binds together all the disparate neuronal events which constitute the engram
(Moscovitch 1992a).

The model does not claim any particular site as the identity of the engram. It is speculated,
that the activation of the perceptual, prefrontal and medial temporal by a stimulus constitutes a
neuronal synchrony (called time-locked synchrony by Damasio (1989)) which constitutes an
engram. In other words, the engram is not a special end-product stored for subsequent retrieval, it
is the change that the brain has undergone in the process of a shallow or deep encounter.

Retrieval: At retrieval, the situation depends on the manner in which it is achieved. These
different modes of retrieval are pictured in Figure IV-3. The model attempts to explain retrieval
without any conscious recollection (Fig IV-3a) and conscious recollection following an intentional
attempt (Fig IV-3b).

Implicit retrieval, or retrieval which results in the absence of conscious recollection
involves only the posterior perceptual regions. As shown in Figure IV-3a the process of having
perceived a stimulus before, changes the neural substrate. When the subject re-encounters the
stimulus there is a facilitated neuronal processing of the stimulus. This is supported by reports by
Squire and Buckner which show that when subjects undertake an implicit-instruction stem-
completion task, it is associated with decreased activity in a subset of the perceptual region and
that this mode of retrieval requires no involvement of the prefrontal cortex (Squire et al. 1992;
Buckner et al. 1995a). It is conceivable that because this retrieval is achieved without
participation of the prefrontal cortex and hippocampus it engenders no conscious recollection.
This would be consistent with data that patients with medial temporal and prefrontal lesions show
preserved implicit memory (Schacter 1995).

Appropriate conscious recollection in this model requires appropriate functioning in the
perceptual regions, the medial temporal region as well as the prefrontal cortex. The perceptual
regions process the target/cue; the medial temporal regions are crucial in relating the cue to the
engram and the prefrontal cortices drive and monitor the process. It is this synchronous activity of the prefrontal cortices that may account for the autonoetic phenomenological experience of a conscious recollection.

This model deals with intentional retrieval in the following fashion: the intention to retrieve is implemented as an activation of the prefrontal cortex (Fig. IV-3b). Therefore, the information is transferred from the perceptual to the prefrontal regions which initiate retrieval. The frontal activation presents the perceptual cue to the medial temporal cortex possibly using the fronto-temporal connection via the uncinate fasciculus (Markowitsch 1995a). This process leads to ecphory, if the attempt is successful. And accordingly the prefrontal cortex monitors the output of the ecphoric process for its contextual correctness.

Any model attempting to explain a phenomenon as complex as episodic memory cannot, at this stage of incomplete knowledge, be too precise. It is becoming increasingly clear that the anterior cingulate, cerebellum and the subcortical nuclei are important nodes in a cognitive network (Andreasen et al. 1995c) - the rudimentary model above does not deal with them. The purpose here was not to encompass all that is known about the neurobiology of memory but to draw the outlines of a neurocognitive network within which one can begin to collate the current PET and neuropsychological data.

Contributions of this thesis, its major limitations and future directions
Role of the left prefrontal cortex in encoding, regardless of intention.

A major contributions of this thesis is to draw attention to the role of the left prefrontal cortex in encoding. Article #1 was the first published study which emphasized this issue (Kapur et al. 1994a) followed immediately by Shallice and colleagues making a similar point (Shallice et al. 1994). This fact has now been confirmed by several other studies by our group (Kapur et al. 1996) as well as studies by several other groups (Fletcher et al. 1995; Grady et al. 1995).

Article #2 has helped answer whether the role of the prefrontal cortex in these studies of encoding should be regarded as "willed action" or whether it should be understood as semantic
processing. And Article #3 has replicated the role of the prefrontal cortex in intentional encoding, providing further support for HERA, and showing that different regions of the prefrontal cortex make different functional contributions to encoding.

Role of the right prefrontal cortex in retrieval and the notion of "retrieval attempt"

The other major contribution is demonstrating and specifying the role of the right prefrontal cortex in retrieval (Article #4 and Article #5). Article # 4 is the first demonstration, using PET data, that the process of retrieval can be fractionated into retrieval attempt and ecphory - and that these processes can be separated anatomically. Article # 4 identifies the role of the prefrontal cortex as retrieval attempt, a finding that has been replicated by others - Nyberg (1995) and Schacter (1996); and is consistent with expectations based on neuropsychological data (Moscovitch 1992a).

Article #5 constitutes the first direct comparison of recall versus recognition using a within-subject design. By demonstrating that the prefrontal cortex is equally invoked in recall and recognition it calls into question some of the conventionally held notions regarding a differential involvement of the prefrontal cortex in recall and recognition. The findings, and the assertions above raise important questions. Some of the questions which should be the subject of future research are outlined below.

Limitations of this work

This effort, as any such, has several limitations. Those limitations that relate to each experimental design have been dealt with in the individual articles. Only the overarching limitations which restrict the generalization of these findings are listed here. First, all our studies (with the exception of Article # 5) involved males, and all of them young and right handed. Since the major finding has to do with asymmetry - and there is already evidence of differential asymmetry between men and women in language processing (Buckner et al. 1995b) and between
young and old in memory function (Grady et al. 1995) - one has to be careful in extrapolating these findings to women, and to the elderly.

Furthermore, this work is limited to the use of verbal material, and that too in orchestrated multiple-stimuli lists. Memory in real life usually involves non-verbal materials, usually in without a clearly imposed order. Those conditions are likely to invoke different brain regions. It is reassuring then that at least one comparison of recall of word lists to a recall of complex naturalistic narratives shows that similar patterns were invoked by both (Andreasen et al. 1995c; Andreasen et al. 1995b).

At a methodological level all our studies involved a group analysis. The average pattern identified for the group as a whole may not correctly represent the true pattern for any individual in the group. This is a limitation of PET technology, in that it permits reliable statistical conclusions only at a group level. Therefore, the entire issue of inter-individual differences in strategy, and neural implementation remain unaddressed for the present.

Future work related to the left prefrontal cortex and encoding:

A central assertion of this thesis is that the left prefrontal cortex “facilitates” encoding but is not mandatory for it. The left prefrontal cortex is activated in our studies because it subserves semantic processing or “working with meaning,” and that good encoding is a valuable by-product. This view is in fact a neurally informed reassertion of the levels of processing concept (Craik and Lockhart 1972; Lockhart and Craik 1990) and would predict that:

i) It should be possible to invoke the left prefrontal cortex in the processing of non-verbal stimuli (a situation where left-sided activations would not be expected) by requiring that subjects use a semantic processing strategy for encoding.

ii) It should be possible to show that activation of the left prefrontal cortex can be dissociated from the end result of successful encoding.

Prediction (i) above would be confirmed if one could invoke the left prefrontal cortex in a counter-intuitive situation by manipulating the instructions to the subject. Face-stimuli are usually
processed in the right hemisphere. Therefore, one could use face-stimuli and ask subjects to encode them using two different strategies. One strategy could emphasize the perceptual relationships and the other strategy could emphasize the formation of meaningful associations or judgments on the faces. It would be predicted that the perceptual strategy would require little if any left prefrontal activation, whereas the ‘meaningful’ strategy would invoke the left prefrontal cortex even though subjects are processing non-verbal material. Evidence for this can be inferred from Grady et al. (1995) which reported left prefrontal activation in face-encoding; and Owen et al. (1996) which shows left prefrontal predominance for object-feature and object-location encoding. However, neither of these studies controlled for the learning strategies that the subjects invoked. Manipulating the strategies used for encoding, and showing a shift in activation to and from the left prefrontal cortex would define the role of the LPFC more convincingly.

Prediction (ii) would be confirmed if it were possible to dissociate the attempt at encoding from the success at it. One good opportunity for this is provided by pharmacological interventions. When subjects are administered benzodiazepines or anticholinergics they are reasonably alert and cooperative at the time of learning, however there is a deficit in encoding, as observed on deficits on subsequent retrieval. If our assertions regarding the role of the left prefrontal cortex are correct, one would predict that pharmacological challenges (such as above) would not influence the activation of the left prefrontal cortex, yet would show a deficit of encoding. Such a study would demonstrate that the left prefrontal subserves the process of ‘working with meaning’ in the present, but that its activation is not by itself sufficient to form a retrievable engram. It has been known for some time that cognitive tasks can be combined with pharmacological challenges to address such questions meaningfully (Friston et al. 1992) and more recent studies show that this can be done in the domain of memory studies (Grasby et al. 1995).

Taken together these two experiments would further confirm the our current speculations: that the left prefrontal cortex facilitates encoding and does so by its involvement in ‘working with meaning’
Future research regarding the right prefrontal cortex in retrieval:

One of the central features of our assertions about the right prefrontal cortex is that it is involved in the attempt to remember. The next step would be to characterize this contribution further in terms of the sub-processes, and anatomically in terms of sub-regions subserving special functions.

At present our paradigms are unable to differentiate whether retrieval attempt entails "mnemonic search" alone, "monitoring" alone or a combination of the two. If the role of the right prefrontal cortex is in mnemonic search alone, one would not expect it to be activated in unintentional ecphory. If it subserves both mnemonic search and monitoring it would be expected to be activated in intentional and unintentional retrieval.

A possible design to test this distinction would entail subjects familiarizing themselves with a set of stimuli - such that they have clear episodic memory for the materials. During PET they can then be shown these stimuli, but rather than being asked to retrieve whether they have seen them before (episodic task), they should be asked to make living/non-living decisions on the stimuli (semantic task). If the stimuli are well learnt one would expect them to have spontaneous ecphory, a phenomenon which could be confirmed by self-report. However, since the subjects were not attempting to retrieve, this task should involve no “mnemonic search” though it may entail “monitoring”. If the right prefrontal subserves only the former one would expect no activation of the right prefrontal cortex since the subjects would not make any attempt to retrieve the material. On the other hand if it entails both, or just monitoring, one would expect an activation of the right prefrontal cortex.

A second question is whether the same region of the right prefrontal cortex is involved regardless of the material and the modality in which the targets and the cues are presented. There are several reasons to believe that the right prefrontal cortex should entail functional specialization. First, it is an anatomically heterogeneous structure, with distinct and specific connections to other posterior brain regions (Stuss and Benson 1986). Second, there is clear anatomical distinction in the prefrontal brain regions subserving verbal vs. non-verbal working
memory (Goldman-Rakic 1988; Goldman-Rakic 1994). However, PET data on this issue are not unequivocal.

This idea has been put to direct test by our group (Nyberg et al.; Appendix I) and we have found indeed statistically indistinguishable regions of the right prefrontal cortex are invoked by attempts to retrieve stimuli encoded while making voice-judgments versus stimuli encoded while making judgments regarding meaningfulness. On the other hand, in a study by Moscovitch et al. (1995) the precise regions of the right prefrontal cortex involved in object retrieval were differentiable from the regions involved in retrieval of spatial relationships. The systematic investigation of the fractionation of right prefrontal contributions has just begun. Buttressed by primate data showing material specific specialization of the prefrontal cortex in working memory experiments, it is very likely that future studies will point to specificity in the precise regions of the prefrontal cortex which are involved in mediating retrieval from different modalities and of different materials.

From subtraction analysis towards network analysis

One of the 'missing-links' in our PET data has been the medial temporal cortex. The chapter raises several issues why we may have missed the involvement of the medial temporal cortex, even though it is robustly supported by neuropsychological data. One plausible reason is that most of the present analytic techniques undertake the subtraction analysis to identify candidate regions. This technique can only identify regions which are "more" active in one task as opposed to the other. If the medial temporal cortex regions are continuously active, or if they become involved in information processing by altering neuronal connectivity then they would not reveal themselves in subtraction studies. The problem can be potentially solved with the use of covariance based analyses (McIntosh and Gonzalez-Lima 1994).

In one such demonstration McIntosh and colleagues have shown that even though there was no evidence of activation of the hippocampus on a subtraction analysis in a study of retrieval, there was a robust change in the interaction between the prefrontal cortex and the hippocampal
region in the retrieval scan as compared to the scan where all the stimuli were new (McIntosh et al. 1995b). While the report is still preliminary it shows the value of multivariate covariance based analysis, in particular network-analysis, in revealing the underlying connectivity between the different brain regions.

Several of the claims made in this discussion, as well as in the proposed rudimentary model of episodic memory, speak of differential involvement of the medial temporal cortex in studies of encoding and retrieval. One of the major thrusts of future research should be to design experiments that are best suited for network analysis (McIntosh et al. 1995a), as opposed to subtraction-analysis, in an effort to identify the role of the medial temporal cortex, especially in relationship to the perceptual and prefrontal regions.
Appendix

Abstracts of other published research which relates to memory and PET and was completed during my doctoral work.
Hemispheric Encoding/Retrieval Asymmetry in Episodic Memory: Positron Emission Tomography Findings

Endel Tulving, Shitij Kapur, Fergus I.M. Craik, Morris Moscovitch, Sylvain Houle

ABSTRACT

Data are reviewed from positron emission tomography studies of encoding and retrieval processes in episodic memory. These data suggest a hemispheric encoding/retrieval asymmetry model of prefrontal involvement in episodic-memory encoding and retrieval. According to this model, the left and right prefrontal lobes are part of an extensive neuronal network that subserves episodic remembering, but the two prefrontal hemispheres play different roles. Left prefrontal cortical regions are differentially more involved in retrieval of information from semantic memory and in simultaneously encoding novel aspects of the retrieved information into episodic memory. Right prefrontal cortical regions, on the other hand, are differentially more involved in episodic memory retrieval.
Neuroanatomical Correlates Of Retrieval In Episodic Memory: Auditory Sentence Recognition

Endel Tulving, Shitij Kapur, Hans J. Markowitsch, Fergus I.M. Craik, Reza Habib, Sylvain Houle

ABSTRACT

This study investigated the neuroanatomical correlates of remembering previously experienced events using positron emission tomography (PET). Twelve young healthy adults listened to 'old' meaningful sentences which they had studied 24 hours previously. As a control task the subjects listened to comparable 'new' sentences that they had never heard before. Regional cerebral blood flow associated with each task was measured using $^{15}$O-water PET scans. Comparison ('old'-sentence task minus 'new'-sentence task) of the PET images revealed an extended strip of increased blood flow in the right dorsolateral prefrontal cortex (Brodmann's areas 10, 46, and 9) and the anterior portion of area 6. Other principal regions of increased blood flow were situated around the left anterior cingulate sulcus and bilaterally in the parietal lobes (areas 7 and 40). Major decreases in blood flow were situated bilaterally in the temporal lobes (areas 21, 22, 41, and 42). A high proportion of activity changes seemed to be located in the depths of cortical sulci. Increases in blood flow are seen as reflecting the operations of a widely distributed neuronal network involving prefrontal and parietal cortical regions that subserves the conscious recollection of previously experienced events. Decreases in blood flow in the temporal auditory areas are interpreted as reflecting auditory priming. The prevalence of sulcal blood-flow changes may reflect extensive cortical gyrification; it may also indicate that memory-related processes rely on the densely packed neuropil of sulcal regions.
Distinct neural correlates of visual long-term memory for spatial location and object identity: A positron emission tomography study in humans.

Moscovitch, M., Kapur, S., Kohler, S., & Houle, S.

The purpose of the present study was to investigate by using positron emission tomography (PET) whether the cortical pathways that are involved in visual perception of spatial location and object identity are also differentially implicated in retrieval of these types of information from episodic long-term memory (LTM). Subjects studied a set of displays consisting of three unique representational line drawings arranged in different spatial configurations. Later, while undergoing PET scanning, subjects' memory for spatial location and identity of the objects in the displays was tested and compared to a perceptual baseline task involving the same displays. In comparison to the baseline task, each of the memory tasks activated both, the dorsal and the ventral pathways in the right hemisphere but not to an equal extent. There was also activation of the right prefrontal cortex. When PET scans of the memory tasks were compared to each other, areas of activation were very circumscribed and restricted to the right hemisphere: For retrieval of object identity the area was in the inferior temporal cortex in the region of the fusiform gyrus (area 37) whereas for retrieval of spatial location it was in the inferior parietal lobule in the region of the supramarginal gyrus (area 40). Thus, our study shows that distinct neural pathways are activated during retrieval of information about spatial location and object identity from LTM.
Dissociation of pathways for object and spatial vision: A PET study in humans

Kohler, S., Kapur, S., Moscovitch, M., Winocur, G., Houle, S.

ABSTRACT

A positron emission tomography (PET) study was conducted to determine which brain regions are differentially involved in visual object identification and object localization. Subjects engaged in a spatial task in which they matched the location of common objects, and an object task in which they matched the identity of common objects. In both tasks, the stimulus arrangements used were of the same kind. Regional cerebral blood flow data showed that a right-sided region in the inferior parietal lobule was more activated during spatial than object matching. In contrast, bilateral occipitotemporal regions, with the left more predominant, were more activated during object than spatial matching. These results provide support for Ungerleider and Mishkin's dual pathway model of vision and indicate important patterns of lateralization in the human visual system.
Functional brain maps of retrieval mode and recovery of episodic information

Nyberg, L; Tulving, E; Habib, R; Nilsson, L-G; Kapur, S; Houle, S; Cabeza, R; McIntosh, AR

ABSTRACT

Positron emission tomography (PET) was used to identify brain regions associated with two component processes of episodic retrieval; those related to thinking back in subjective time (retrieval mode) and those related to actual recovery of stored information (ecphory). Healthy young subjects recognized words that had been encoded with respect to meaning or the speaker's voice. Regardless of how the information had been encoded, recognition was associated with increased activation in regions in right prefrontal cortex, left anterior cingulate, and cerebellum. These activations reflect retrieval mode. Recognition following meaning encoding was specifically associated with increased activation in left temporal cortex, and recognition following voice encoding involved regions in right orbital frontal and parahippocampal cortex. These activations reflect ecphory of differentially encoded information.
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