# The functional roles of subregions of the medial temporal lobe in human memory

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# Declaration

This dissertation is the result of my own work, with the exception of the structural ratings of MRI scans described in Chapters 2 and 3, which were conducted by Drs Rhys Davies, Sian Thompson and Peter Nestor of the Department of Neurology, and Dr. Andy Lee of the MRC Cognition and Brain Sciences Unit. The remainder of the thesis includes nothing which is the outcome of work done in collaboration. This dissertation has not been submitted, in whole or in part, for any other degree, or qualification. Finally, this dissertation does not exceed the limit of length prescribed by the Biology Degree Committee.

Chapter 2 is based on the following published article: Taylor, K. J., Henson, R. N. A., & Graham, K. S. (2007). Recognition memory for faces and scenes in amnesia: Dissociable roles of medial temporal lobe structures. *Neuropsychologia*, 45(11), 2428-2438.

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# Abstract

The medial temporal lobe (MTL) comprises the hippocampus and adjacent entorhinal, perirhinal and parahippocampal cortices. The contribution made by these subregions to memory in humans has been the topic of intense debate for several decades. One influential view suggests that all components of the MTL work in concert to support a unitary, long-term declarative memory system, and states that there is currently no persuasive empirical evidence for simple functional dissociations within this system.

Several theories have challenged this view, however, and proposed distinct roles for MTL subregions. For example, evidence from the animal literature has suggested crucial roles for the hippocampus and perirhinal cortex in spatial and object processing respectively, and recent neuropsychological and neuroimaging studies of non-mnemonic tasks have provided support for this view in humans. Chapters 2 and 3 of the current thesis extend these findings by demonstrating impairments in scene recognition memory in patients with damage to the hippocampus, and in face recognition memory in those with damage to the perirhinal cortex.

In contrast, dual-process theories propose that whereas the hippocampus supports recollective aspects of memory (for example, the association between an item and its temporal-spatial context), the perirhinal cortex supports item familiarity. Chapter 4 reveals some evidence that recognition memory for scenes may disproportionately rely on recollection, relative to recognition memory for faces. This raises the possibility that the stimulus-specific dissociations revealed in Chapters 2 and 3 can be explained by dual-process models of MTL function.

This hypothesis is explored further in Chapter 5, using functional magnetic resonance imaging (fMRI). The results reveal specialisation in the MTL according to stimulus category, but not according to recollection versus familiarity. The stimulus-specific effects do not appear to be mnemonic in nature, however, and are more consistent with a role for the hippocampus and parahippocampal cortex in building representations of scenes, and for the perirhinal cortex in building representations of faces. In addition, each region appears to make some contribution to both recollection and familiarity for faces and scenes.

Together, these findings suggest a radical revision to models of MTL function, taking into account the roles played by the hippocampus and parahippocampal cortex in spatial processing and the perirhinal cortex in object processing.

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# Chapter 1
# Introduction

The description by Scoville and Milner (1957) of severe amnesia, as the result of bilateral medial temporal lobe (MTL) resection in patient HM, put the MTL, defined here as the hippocampal formation and adjacent perirhinal, entorhinal and parahippocampal cortices, firmly on the map as a crucial structure in human memory. Fifty years have passed since this pivotal discovery, and yet a great deal of controversy remains regarding the role of the MTL, and its various sub-regions, in human cognition.

One dominant theory, developed by Squire and colleagues (Squire & Zola-Morgan, 1991), posits that the sub-regions of the MTL work in concert to support long-term declarative memory. Although this model is still influential, it has never been universally accepted and there is mounting evidence that this account cannot adequately explain all the available data on this topic. Challenges to the theory can be roughly divided into three categories: (i) categories of memory other than long-term declarative memory may be supported by the MTL; (ii) sub-regions of the MTL can be functionally dissociated; (iii) the role of the MTL may extend beyond memory to include some perceptual functions.

The present thesis will focus on the second of these challenges and will contrast alternative accounts of how the division of labour in the MTL, if such a division does exist, can be best described. More specifically, the experiments reported in the thesis were designed to investigate two prominent groups of theories which have been developed to explain the division of labour within the MTL. Domain-specific theories suggest that subregions of the MTL can be distinguished according to the categories of stimuli they process (e.g. Buckley & Gaffan, 2006; Lee, Barense, & Graham, 2005; Murray, Bussey, & Saksida, 2007). In contrast, many dual-process views claim that different components of the MTL support different kinds of mnemonic processes (e.g. Aggleton & Brown, 1999; Eichenbaum, Yonelinas, & Ranganath, 2007; Mayes, Montaldi, & Migo, 2007). Although these two groups of theories are not mutually exclusive, the aim of the present thesis is to investigate some situations in which the two theories make contradictory predictions, and to see, in such cases, which factor, stimulus category or memory process, has the greatest influence on the roles played by each MTL region.

Each of these models of MTL function has its origins in early work investigating cases of MTL amnesia, in particular HM, as well as early attempts at producing an animal model of his deficits. As technological and theoretical advances were made during the 1970's, different research groups began to diverge and several theories developed which each claimed to explain the roles of the MTL in cognition. Following the description of the common foundation to these various theories, they will each be explored in turn. Finally, the main bones of contention between these differing theories will be explored and the motivation behind, and the methodological approach of the current thesis, will be outlined in detail.

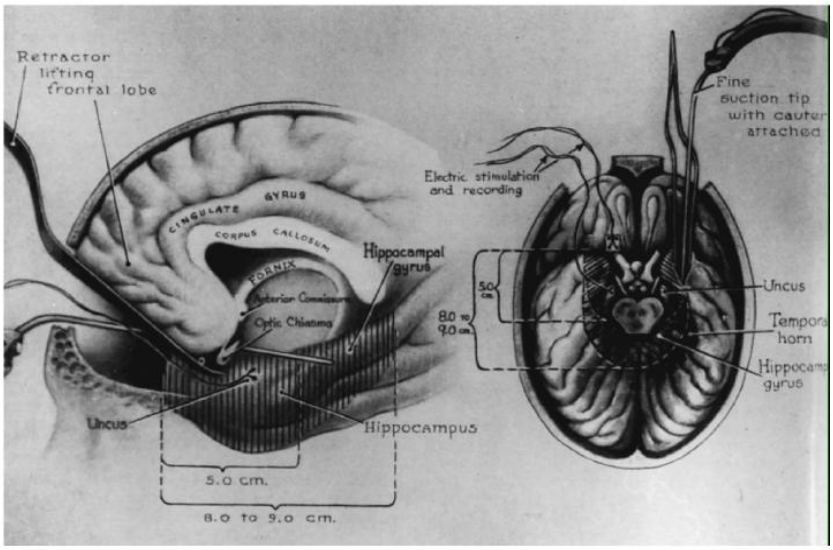
# Medial temporal lobe amnesia

## *Early case studies of human MTL amnesia*

In 1953, radical surgery was undertaken to treat a patient, known as HM, who had been incapacitated by his intractable epilepsy (Scoville & Milner, 1957). The surgery involved the removal of the majority of the medial temporal lobes, beginning at the temporal poles and extending posteriorly by 8cm to include the majority of the hippocampus, hippocampal gyrus, uncus, and the amygdala bilaterally (Figure 1.1). It was ostensibly a success, reducing the frequency and severity of his seizures. Unfortunately, the somewhat experimental procedure instantly reduced HM's experience of life to a series of isolated moments, since he became unable to retain new information for any longer than a few minutes. A good illustration of HM's deficit was his repeated inability to recognise Milner when she returned to the room following a brief absence. Indeed, despite meeting her on an almost monthly basis for several years, HM would always greet Milner as though meeting her for the first time.

Formal assessment of HM's abilities using standard neuropsychological tests confirmed that his deficits appeared to be restricted to the memory domain. Administration of the Wechsler Memory Scale (Wechsler, 1945), highlighted severe impairments in immediate recall of stories and drawings as well as impairments in associative learning. In fact, once he had moved onto another test, HM was unable to recollect the previous one and could not even recognise it if he was shown it again. Further testing, however, failed to reveal any deficits in perception, abstract thinking or reasoning; his motivation was excellent and his postoperative IQ was, if anything, slightly higher than before (Scoville & Milner, 1957).

a

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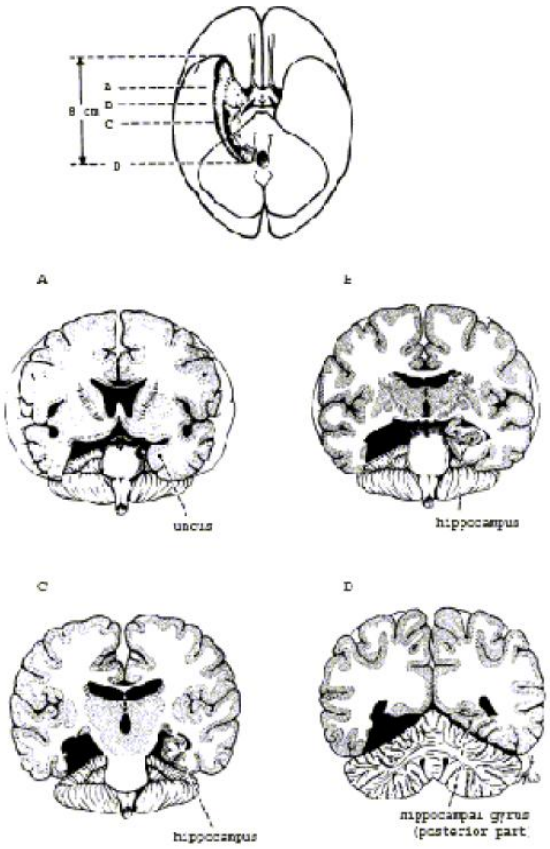


***Figure 1.1 (a) Area removed bilaterally from the medial temporal lobes. Both the 5cm and 8cm removals are depicted, with the 8cm removal corresponding to the procedure performed on HM . (b) Diagrammatic cross-sections of the human brain illustrating the extent of the attempted bilateral medial temporal lobe resection in HM. For diagrammatic purposes the resection has been shown on one side only. (Both figures from (Scoville & Milner, 1957).***

Subsequent investigations in HM as well as other patients with gross MTL amnesia, revealed that these deficits in long-term memory were pervasive and were common to all sensory modalities, stimulus materials and test procedures (Corkin, 1968, 2002; Milner, Corkin, & Teuber, 1968). Some striking preservations in other aspects of memory have, however, been identified. For example, investigations have revealed normal short-term memory in such patients, as evidenced by normal digit span (Drachman & Arbit, 1966). This highlights an ability to acquire new information over very short periods, but an inability to consolidate such memories.

In addition, amnesic patients can acquire new *skills* which can last for months, if not years. The first demonstration of such a preservation of learning was Milner's report of HM's performance following three days of training on a mirror-tracing task (Milner, 1962). This task requires the participant to draw a line in between two concentric outlines of a star, whilst their visual cues are limited to the reflection of their hand and the picture in a mirror. Despite having no recollection of ever having performed the task before, HM's performance improved steadily over the course of training. Further investigations have revealed that this type of skill learning can be retained in amnesia for as long as a year (Gabrieli, Corkin, Mickel, & Growdon, 1993). This preservation of skill learning is reminiscent of intact emotional conditioning in amnesia reported decades earlier by Claparède (1911). The Swiss psychiatrist pricked the hand of his amnesic patient with a hidden pin while shaking hands, and the following day, the patient refused to shake hands despite having no recollection of why!

These investigations of patient HM led to some key ideas which were central to the models of long-term memory which subsequently developed. First, they revealed evidence of multiple memory systems in the brain (Drachman & Arbit, 1966). Whereas the MTL appeared to be crucial to long-term memory, it was concluded that distinct systems with different anatomical substrates must support short-term memory and motor-learning (Corkin, 1968). Second, it was noted that other patients who had undergone similar surgery to HM also showed similar mnemonic impairments, provided that the removal included the hippocampus and parahippocampal gyrus: lesions limited to the uncus and amygdala did not appear to produce a memory deficit (Scoville & Milner, 1957), highlighting the importance of the former but not the latter structures in long-term memory. Third, larger MTL lesions were associated

with greater mnemonic impairments (Scoville & Milner, 1957). Despite the focus given to the hippocampus in thier original article, and in many which followed (for example, Cummings, Tomiyasu, Read, & Benson, 1984; DeJong, Itabashi, & Olson, 1969; Drachman & Arbit, 1966; Victor, Angevine, Mancall, & Fisher, 1961; Zola-Morgan, Squire, & Amaral, 1986), Scoville and Milner realised that the range of memory deficits observed were not necessarily the exclusive result of damage to the hippocampus, and went on to suggest that testing of animals with circumscribed lesions would be required to clarify the situation.

## *Early animal models of MTL amnesia*

Early attempts to duplicate the global amnesic syndrome of HM in monkeys met with little success: tests of matching-to-sample (see below) and visual discrimination learning, both of which were known to be impaired in humans with MTL amnesia (Milner, 1972; Oscar-Berman & Zola-Morgan, 1980), revealed, at most, very modest impairments in performance following extensive lesions to the MTL in monkeys (Correll & Scoville, 1965a, 1965b, 1967; Orbach, Milner, & Rasmussen, 1960). These negative results seemed to suggest that either a rethink of the interpretation of HM's amnesia as being the result of his MTL damage was necessary; or that there were some fundamental differences between the roles of the MTL in humans versus monkeys.

Vital progress was made during the 1970's, as researchers began to realise the importance of designing tests which would provide appropriate models of human long-term memory. Delayed nonmatching-to-sample (DNMS, or its variant, the delayed matching-to sample task, DMS) was a popular paradigm amongst researchers. This task is equivalent to the recognition memory tests commonly used to assess memory in humans. During the study phase, a sample stimulus, commonly a three-dimensional object, is presented to the subject. Then, following a delay, the sample stimulus is presented alongside a novel foil stimulus. The subject must then either select the sample stimulus, or the foil, depending on whether the rule is to match or not. In tests using animals, a reward is generally given if the animal chooses the correct stimulus. Gaffan (1974) and Mishkin and Delacour (1975), however, highlighted the importance of using large stimulus sets, so that all stimuli were trial unique (each stimulus appeared in only one trial). Gaffan also suggested that subjects be required to remember a series of objects during each sample phase to increase the memory load, and also that the delay length be increased.

In 1978, two influential articles were published, presenting opposing views regarding the anatomical basis of MTL amnesia. Mishkin, having adopted the newly modified DNMS task described above, proposed that combined damage to both the hippocampus and amygdala was required to produce the global amnesic syndrome of HM. He found that monkeys with bilateral lesions restricted to either the hippocampus or the amygdala performed almost as well as controls on the DNMS. Those with combined bilateral lesions to the hippocampus and amygdala, however, were significantly impaired, provided the delay was at least 30 seconds long, with performance deteriorating as the length of the delay was increased. Since HM's damage included both the hippocampus and amygdala bilaterally, it seemed plausible that damage to these structures was the cause of his global amnesia. This conclusion was strengthened by the demonstration of deficits following combined amygdalo-hippocampal ablation in monkeys in other modalities, for example tactual recognition memory (Murray & Mishkin, 1983, 1984), a pattern mirroring that seen in HM.

In stark contrast to this view, Horel (1978) suggested that the root of the problem was not damage to the MTL itself, but rather concomitant damage to the temporal stem white matter which lies adjacent to the amygdala. Given the nature of the surgery, this was likely to have been damaged in HM. Horel and Misantone (1976) had previously demonstrated that damage to this tract in monkeys, sustained in a surgical procedure similar to that used by Scoville in HM, caused deficits on a test of visual discrimination learning. In this task, pairs of visual stimuli are presented and the subject must learn, through trial and error, which item in each pair is rewarded. Performance is generally measured as the number of trials required to reach a criterion level of accuracy. Since this task differed to that used by Mishkin (who had used the DNMS task), however, a fair comparison could not be made between the two hypotheses.

In order to resolve this debate, Zola-Morgan, Squire and Mishkin (1982) tested macaques with either temporal stem sections or amygdalo-hippocampal lesions on both the DNMS task and visual discrimination learning. They observed a double dissociation: whereas monkeys with temporal stem sections performed well on the DNMS task, but not on the visual discrimination learning task, those with amygdalo-hippocampal lesions demonstrated the reverse pattern of performance, with one caveat: whereas performance on the discrimination learning task, as measured by trials-to-criterion, was not impaired, there was evidence of a

significant impairment in errors-to-criterion. Hence, this study provided evidence that these two tasks, at least in monkeys, tapped into different processes. Since both recognition memory and visual discrimination learning were known to be impaired in human amnesia (Milner, 1972; Oscar-Berman & Zola-Morgan, 1980), however, the question remained as to which test in animals provided the best model of human amnesia.

According to Mishkin, Malamut and Bachevalier (1984), the answer to this question lay in the way in which discrimination learning tasks are performed by humans compared with animals. In humans, visual discrimination learning was seen as a true test of long-term memory, with discriminations being learnt rapidly over a small number of trials. It was considered, therefore, to rely on MTL-mediated associations. Monkeys, on the other hand, learn a given discrimination over hundreds of trials, making the task equivalent to habit learning (Iversen, 1976). It was suggested that this would require a strategy based on simple stimulus-response associations, dependent on an inferior temporal lobe-neostriatal circuit (Malamut, Saunders, & Mishkin, 1984; Mishkin & Appenzeller, 1987). Thus it was concluded that impairments in visual discrimination tasks in animals are an inappropriate model for human amnesia. Accordingly, tests of recognition memory were widely accepted as the favoured method for assessing human MTL amnesia.

To summarise this early work, damage to the MTL which included the hippocampus and the amygdala produced an isolated deficit, in both animals and humans, in their ability to form long-term memories. These deficits did not extend to the retention of habits and skills, but rather only affected what would later be defined as "declarative memory" (see below).

A major flaw of this early work was the neglect of regions outside the hippocampus and amygdala which, due to the surgical techniques employed in both human surgery and animal lesion studies, were also damaged (Buckley, 2005). The lesions were generally performed by entering the temporal lobe through its ventral surface and aspirating the required tissue. As can be seen in Figure 1.2, in the macaque brain, the anterior extent of the rhinal cortex lies beneath the amygdala, and posterior rhinal and some parahippocampal cortex lies beneath the hippocampus. Lesions to the hippocampus and amygdala either separately, or combined therefore also affected other regions of cortex, including the perirhinal, entorhinal and parahippocampal cortex, that could be involved in mnemonic processing. Initially this fact

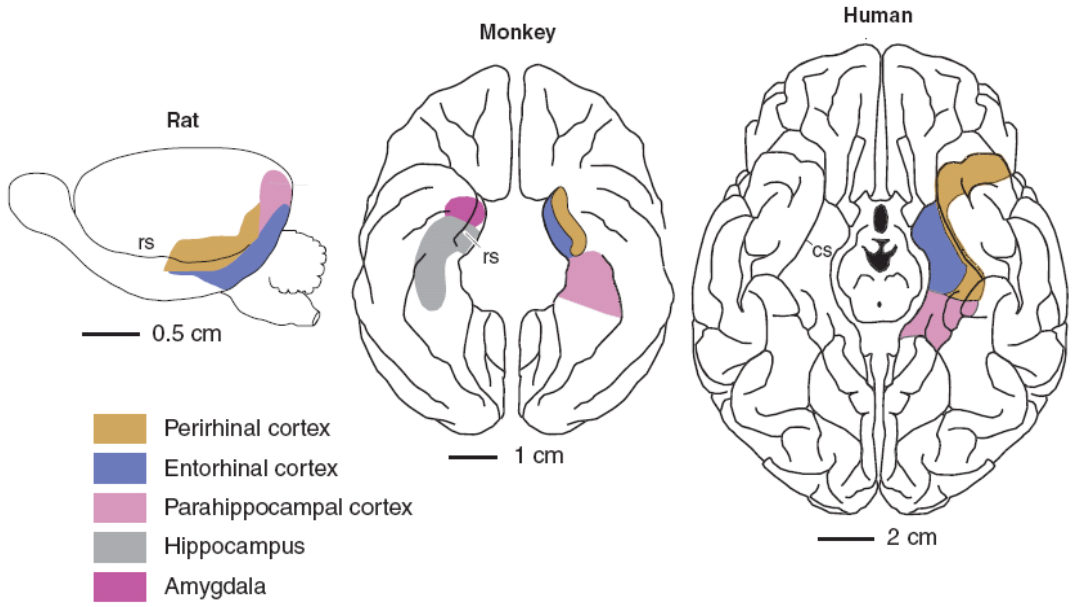


***Figure 1.2 Lateral view of a rat brain and ventral views of the brains of a rhesus monkey and a human highlighting the extent and location of selected structures in the MTL. Note that the region labelled as the parahippocampal cortex in the rat actually corresponds to the postrhinal cortex, which is the rat homologue of this structure. The approximate locations of the hippocampus and amygdala, which lie deep in the temporal lobe, are depicted on the left side of the monkey brain. The boundary between the entorhinal and perirhinal cortices is located near the fundus of the rhinal sulcus (rs) in rats (Burwell, 2001) and macaque monkeys. In humans, the lateral boundary of the perirhinal cortex is generally considered to be the lateral bank of the collateral sulcus (cs), although it has been argued, on the basis of its anatomical connectivity, to extend further to the anterior middle temporal sulcus (Insausti, Amaral, & Cowan, 1987; Suzuki, Zola-Morgan, Squire, & Amaral, 1993). Rostrally it borders the temporopolar cortex, and caudally it surrounds all but the most medial aspect of the entorhinal cortex (Insausti et al., 1998). Figure from Murray et al. (2007).***

was ignored, perhaps because the precise location and extent of this concomitant damage varied between subjects, and therefore did not seem significant. Eventually, researchers began to consider whether damage to such neighbouring cortical structures may have been contributing to the mnemonic deficits produced by lesions to the hippocampus and amygdala (Horel, Voytko, & Salsbury, 1984; Murray & Mishkin, 1986; Zola-Morgan, Squire, & Amaral, 1989; Zola-Morgan, Squire, Amaral, & Suzuki, 1989).

Meunier et al. (1993) provided the first piece of direct evidence for a role for the perirhinal cortex in object recognition memory in monkeys using a DNMS task. Impairments following combined lesions to the entorhinal and perirhinal cortices, which spared the amygdala and

hippocampus, were almost as severe as those observed by Mishkin (1978) following combined aspiration lesions to the amygdala and hippocampus, which caused inadvertent damage to the rhinal cortex. Crucially, whereas damage to the perirhinal cortex in isolation almost matched this level of impairment, damage to the entorhinal cortex produced only a modest deficit (see also Leonard, Amaral, Squire, & Zola-Morgan, 1995). Meunier and colleagues concluded that DNMS impairments caused by damage to no other single structure in the MTL could match those found following damage to the perirhinal cortex. This conclusion was bolstered by a study in which combined amygdala and hippocampal lesions, performed using an excitotoxic lesion technique which spared fibres of passage and neighbouring cortex, produced no effect on DNMS (Murray & Mishkin, 1998). Several studies have since replicated the impairment following perirhinal cortex lesions on tests of both visual and tactual recognition memory, such as the DNMS (Buckley & Gaffan, 1997; E. A. Buffalo et al., 1999; Nemanic, Alvarado, & Bachevalier, 2004; Suzuki et al., 1993; Zola-Morgan, Squire, Amaral et al., 1989).

These studies revealed a crucial role for the perirhinal cortex on a task which was widely considered to be the canonical test of the kind of memory disrupted in human MTL amnesia. Importantly, they also suggested that the hippocampus may not actually be necessary for successful DNMS performance. It was impossible to establish whether the deficits previously attributed to hippocampal damage were actually the result of damage to the rhinal cortex, since concurrent damage to both structures was so ubiquitous. As a result, researchers began to perform much more circumscribed lesions in animals, and to thoroughly assess the location of damage in humans with memory problems, in order to fully understand the precise role of each MTL component. The discoveries made by different groups were frequently contradictory and thus several diverging theories designed to explain the division of labour in the MTL gradually emerged.

# Theories of MTL function

## *Squire's MTL declarative memory system*

One of the most influential theories describing the role of the MTL in memory is Squire and colleagues' "Medial Temporal Lobe memory system" (Squire & Zola-Morgan, 1991). According to this view, the structures contained within the MTL, i.e. the hippocampus and

adjacent entorhinal, perirhinal and parahippocampal cortices, work together in the support of a unitary, temporary, long-term "declarative" memory system (Figure 1.3). Declarative, or "explicit" memory refers to an individual's memory for facts and events (which are supported by a further subdivision of *semantic* and *episodic* systems respectively, Tulving, 1972) and is accessible to conscious recollection. This is distinguished from "non-declarative" or "implicit" memory, which includes skills and habits, priming, associative learning (or classical conditioning) and non-associative learning (Figure 1.4). This type of memory is not accessible to conscious recollection but instead is expressed through action. The amnesic syndrome arising from damage to the MTL, such as that of HM, is therefore characterised by intact short-term and non-declarative memory combined with impairments in long-term declarative memory.

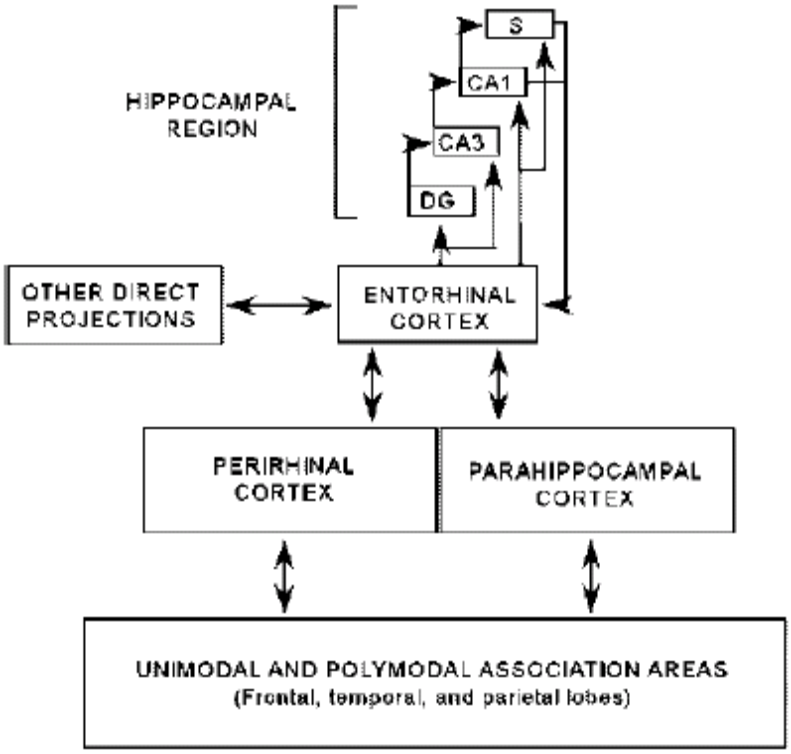


***Figure 1.3 Schematic diagram of the MTL memory system which, according to Squire and colleagues supports declarative memory. The hippocampal region comprises the dentate gyrus (DG), the CA fields, and the subiculum (S). Figure from Squire et al. (2004).***

Squire and Zola-Morgan (1991) proposed that the MTL supports declarative memory by forming links between distributed representations of events and stimulus features in the neocortex. Although the neocortex is able to provide adequate representations of events on which an individual can react, these representations are only temporary and are replaced once

attention has been shifted. Thus, the neocortex can support short, but not long-term memory. The MTL therefore provides a long-term "index" of links between neocortical sites so that representations can be reinstated when a memory is retrieved. This system allows for the "rapid acquisition of new information about facts and events", or, declarative memory. Through a gradual process of reorganisation and consolidation in the neocortex, these long-term memories eventually become independent of the MTL, freeing the latter region up to continue supporting the formation of new memories.

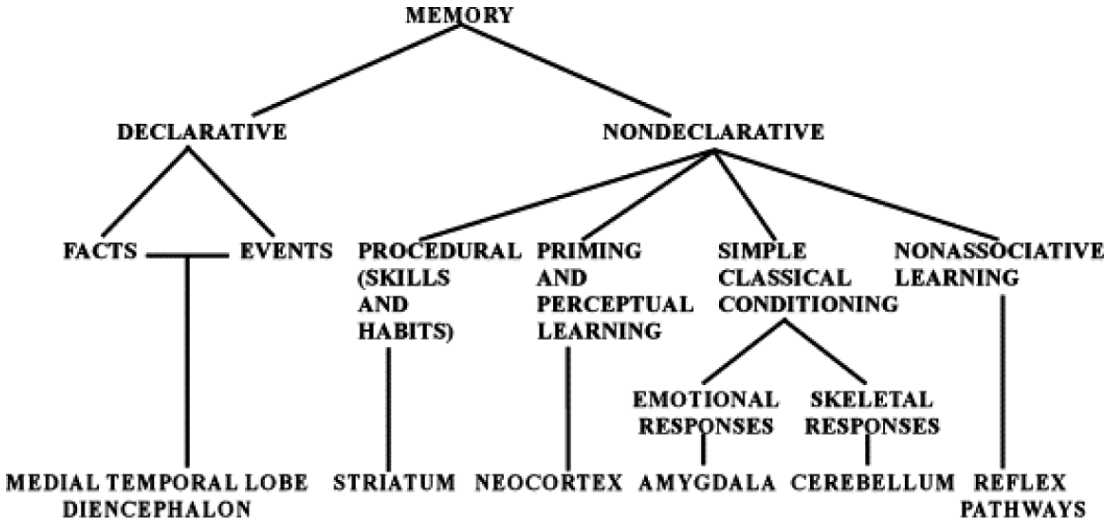


***Figure 1.4 Taxonomy of mammalian long-term memory as proposed by Squire and colleagues, including the brain regions proposed to be required for each form of memory. Figure from Squire and Knowlton (2000).***

Of crucial importance in the development of this model was the investigation of patient RB, who developed amnesia following an ischemic incident during cardiac bypass surgery (Zola-Morgan et al., 1986). The characteristics of his amnesia appeared to be very similar to those of HM, as demonstrated by his impaired word, story, paired associates and complex figure recall as well as impaired word recognition. His general memory impairment was less severe than that of HM, however, as indexed by the difference between his Wechsler Adult Intelligence Scale (WAIS) IQ and his Wechsler Memory Scale (WMS) score. Examination of his brain upon post-mortem revealed that damage was restricted to the pyramidal cell layer of the CA1 subfield of his hippocampi bilaterally. This case therefore appeared to provide crucial evidence that damage to the hippocampus in isolation could produce a memory deficit, albeit a mild one. This contradicted the findings of Mishkin and colleagues above (Mishkin, 1978), who had found that hippocampal damage only produced memory deficits

when it was combined with damage to the amygdala. Further support for this view came from similar findings in several subsequent cases of amnesia following apparently isolated damage to the hippocampus (Press, Amaral, & Squire, 1989; Rempel-Clower, Zola, Squire, & Amaral, 1996; Victor & Agamanolis, 1990). Since the degree of amnesia in these cases was less severe than that in HM, however, it was concluded that MTL structures beyond the hippocampus must also be crucial for normal declarative memory processes.

The observation that lesions to the amygdala in isolation did not impair performance on a range of memory tasks, including the DNMS task, and that impairments following hippocampal lesions which extended into the amygdala were no worse than those which spared this structure (Zola-Morgan, Squire, Amaral et al., 1989) appeared to rule out a role for the amygdala in declarative memory. When hippocampal lesions were extended to include the perirhinal and entorhinal cortex, however, rather than the amygdala, impairments on the DNMS did increase (Zola-Morgan, Squire, Clower, & Rempel, 1993). Lesions limited to the perirhinal and parahippocampal cortex, which spared the hippocampus, also produced an impairment on this task (Zola-Morgan, Squire, Amaral et al., 1989). These findings therefore led to the exclusion of the amygdala and the inclusion of the perirhinal, entorhinal and parahippocampal cortices in addition to the hippocampus in the MTL memory system.

A key tenet of Squire's theory is that each component of the MTL memory system makes a contribution to every category of declarative memory task. The only rule governing the outcome of damage to different subregions is that the greater the total damage to the MTL, the larger the deficits in declarative memory, regardless of the particular location of damage or type of task (Squire et al., 2004; Squire & Zola-Morgan, 1991). Despite the fact that, by Squire and his colleagues' own admission (Squire et al., 2004; Squire & Zola, 1997), the anatomical connectivity of different subregions of the MTL appear to make them ideally suited to different functional specialisms (as will be discussed below), they maintain that there is currently no compelling empirical evidence for functional dissociations within the MTL memory system. As such, the alternative models of MTL function which will be discussed below can be viewed as a direct challenge to this particular aspect of Squire's model. Some accounts also make additional challenges, for instance, suggesting that the MTL should not be viewed as a memory system at all (for example (Gaffan, 2002).

## *Dual-process theories of MTL function*

In their influential article of 1999, Aggleton and Brown suggested that subregions of the MTL could be dissociated in terms of their contribution to *recollection* and *familiarity:* two processes which, according to long-established "dual-process" theories, support recognition memory. The distinction between recollection and familiarity can be illustrated by Mandler's (1980) famous "butcher on the bus" phenomenon, in which a person sees their butcher on the bus and, although sure that the butcher seems *familiar*, they are unable to *recollect* where they know him/her from. This occurs since the surroundings of the bus provide none of the usual contextual cues which would, for example, be present at the butcher's shop and would normally aid recollection of the butcher. According to Aggleton and Brown, recollection is supported by a circuit which includes the hippocampus, whereas familiarity is supported by a distinct circuit which includes the perirhinal cortex. The current section describes the development of dual-process models and the experimental evidence relating Aggleton and Brown's view of the contributions made by MTL regions to recognition memory.

### Dual-process models

Dual-process models of recognition memory date back at least as far as 1969, when Mandler suggested that two distinct processes supported performance on a recall/recognition test involving a variable delay. He proposed that on tests of immediate recognition, subjects initially use "occurrence information about the target event" which he later suggested was equivalent to item familiarity. If this initial process fails, subjects perform a more laborious "retrieval check", in which they search through the items which they can recall for a match with the target item.

Mandler (1980) later modified his model and stated that recollection and familiarity occur in parallel and independently of one another, although familiarity was still thought to be the more rapid of the two processes. Jacoby (1991) also proposed that recollection and familiarity are independent. According to his model, previous experience of an item leads to an increase in perceptual and/or conceptual fluency of the processing of that item. If this increase in fluency is attributed to past experience of the item, this produces a feeling of familiarity. If it is not attributed to the past, and there is, therefore, no increase in familiarity, it may still result in improved performance on tests of implicit memory. So rather than thinking of familiarity as a characteristic of an item, as proposed by Mandler (1980), it was

thought of as the conscious feeling that an item had appeared previously. Recollection was thought to arise from the retrieval of contextual information and, unlike familiarity, which occurs automatically, was viewed as a controlled, effortful process.

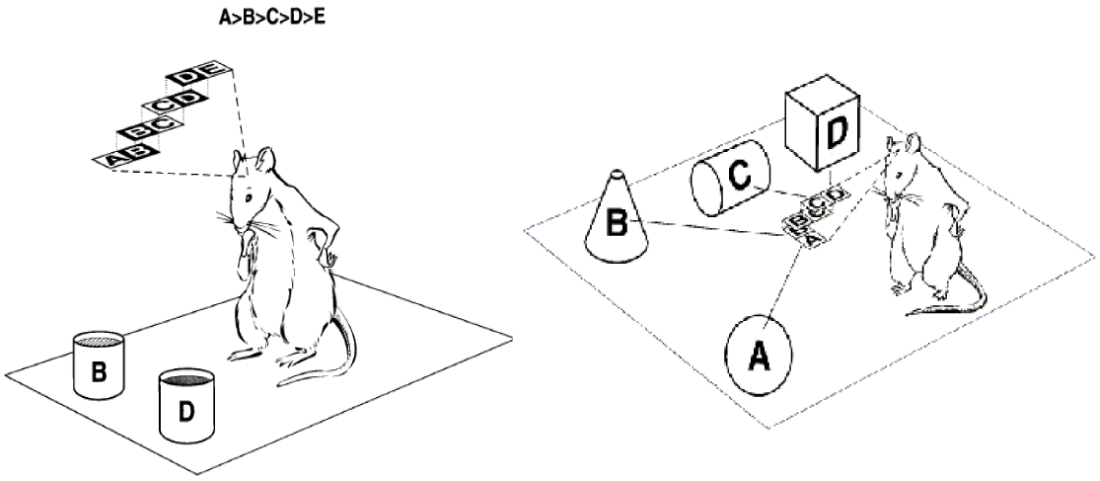


***Figure 1.5 Schematic view of a relational representation of an odour series used to solve a transitive inference task (left) and a relational representation of space (right). In both cases, cells represent the pair-wise relationship between adjacent elements, and nodal representations (dotted lines) link the common elements between the pairs. According to Eichenbaum and colleagues, both types of representation can be supported by a common neural network centred in the hippocampus (Eichenbaum et al. 1999).***

Although not generally classified as a dual-process model, Eichenbaum and colleagues' theory of MTL function, originally proposed in 1994, is closely related to the ideas expressed in many dual-process models. Indeed, a recent review article discussed below (Eichenbaum et al., 2007), highlights the parallels between this model and the dual-process model developed during the same period by Yonelinas (Yonelinas, 1994, 2002). According to this view, the "parahippocampal region" (ie. the entorhinal, perirhinal and parahippocampal cortices) can support recognition of items whereas the hippocampus supports memory for flexible relations between those items (Cohen, Poldrack, & Eichenbaum, 1997; Eichenbaum, 2004; Eichenbaum & Cohen, 2001; Eichenbaum et al., 1994). For example, hippocampal lesions in rats impair performance on a "transitive inference" task (Dusek & Eichenbaum, 1997). In this task, rats learn pair-wise odour discriminations: A+B-, B+C-, C+D-, D+E- where "+" indicates a rewarded item and "-" indicates a non-rewarded item. Control rats are able to infer that given B and D, B will be rewarded. Rats with hippocampal lesions fail to make this inference. Memory for spatial relations represents a special case of this type of relational memory function (Figure 1.5). This theory has been criticised on the grounds that

the term "relational" is somewhat vague (for example, O'Reilly & Norman, 2002), but despite this, it has helped to explain many findings in animal lesion studies and has thus been very influential. The alignment of this view and that of Yonelinas et al. may help to rectify some of the imprecision of Eichenbaum's original theory.

According to the Yonelinas model (Eichenbaum et al., 2007; Yonelinas, 1994, 2002), recollection and familiarity can be distinguished in two key ways: the nature of the information they provide and the level of confidence in a recognition decision which they engender. Familiarity is conceptualised as a "quantitative" measure of memory strength which, as suggested previously by Atkinson and colleagues (Atkinson & Juola, 1973; Juola, Fischler, Wood, & Atkinson, 1971), can be modelled using an adaptation of signal detection theory. Feelings of familiarity generally engender a range of levels of confidence that an item has appeared previously. Recollection, on the other hand, is conceptualised as a qualitative process involving the retrieval of temporal and spatial contextual information, as well as the associations between elements of an event. Recollection of a particular detail is an all-or-none process, with retrieval only occurring once a threshold has been exceeded. Recognition which is accompanied by recollection of this type will generally lead to high confidence endorsement of old items. Similarly to most dual-process models, the model assumes that recollection and familiarity are independent processes.

**Measuring recollection and familiarity**

As discussed by Yonelinas (2002), methods for assessing the contribution of recollection and familiarity to recognition memory roughly fall into two categories: "task-dissociation methods" and "process-estimation methods". Task-dissociation methods rely on the assumption that certain types of test disproportionately depend on one or other of the two processes. This allows a researcher to measure each process relatively independently and also to investigate the effect of experimental manipulations on each process in isolation. A common method of isolating familiarity is to take advantage of the fact that this process is thought to occur more rapidly than recollection. Assessments of recognition memory under speeded-response conditions should therefore provide a measure of familiarity, with very little contribution from recollection (for example, Hintzman, Caulton, & Levitin, 1998). It seems unlikely, however that the contribution of recollection to these fast responses can ever be completely eradicated. In contrast, recollection is commonly isolated by the use of free recall and associative memory tests, since familiarity is often assumed not to contribute to

either of these task categories (Hockley & Consoli, 1999; Mandler, 1980; Yonelinas, Kroll, Dobbins, & Soltani, 1999 but see Mayes et al., 2004; Quamme, Yonelinas, & Norman, 2007).

Associative memory tests can be sub-divided into two broad classes: tests of item-context associations and tests of item-item associations. The former category are often referred to as "source memory" tests, and generally require the subject to recollect the temporal or spatial position of each item, or alternatively, the task that was performed on the item during study (for example, living/non-living versus bigger/smaller than a shoe-box). These kinds of source memory judgements appear to provide a straightforward index of recollection, as conceptualised in the models described above, since they assess memory for the context of a study event. One limitation of this method, however, is that although recollection of a particular detail is an all-or-none process, overall recollection is not, which may lead to a failure to recollect the particular detail requested, in spite of recollection of other, un-probed details; in other words, "non-criterial recollection". This method may therefore underestimate the frequency of recollection. A further disadvantage is that some source memory judgements may be indirectly aided by familiarity, for example, more recent items may seem more familiar and this increase in familiarity may be correctly attributed to temporal recency in a temporal source task (Yonelinas et al., 2002). Source memory judgements may not, therefore, be completely "process pure". This method does, however, have the advantage of being objective and quantifiable.

In tests involving item-item associations, a study list is presented comprising pairs of objects, or words, and at test, subjects view pairs of items and must decide whether they are intact (a pair of items which were viewed together at study) or re-arranged (a pair of items which were both shown during study but in different pairings). Like the source memory tasks described above, this method has the advantage of being objective and quantitative, but also the disadvantage of the potential for non-criterial recollection. A further problem is that it is not clear whether familiarity may sometimes contribute to memory for associations, perhaps particularly when two items have been "unitised", for example, when words are associated to form compounds during encoding, e.g. black-bird (Quamme et al., 2007), or even in the absence of unitisation, particularly when the association is within- (e.g. face-face) rather than between- (e.g. face-word) domain (Mayes et al., 2007). This issue will be discussed in more detail below.

These various task-dissociation procedures can make a useful contribution to the study of recollection and familiarity, but several limitations must be taken into account. As discussed above, the tasks described may not necessarily be truly process-pure, with familiarity potentially "contaminating" associative memory tests. Furthermore, tasks which are thought to depend more on one process than the other may also differ in terms of difficulty and the involvement of additional processes other than recollection and familiarity. There may also be scaling issues; for example, the relationship between measures of recall and recognition may not be linear, particularly at extreme ends of the scale (Loftus, 1978), making direct comparison between the two tests difficult. An alternative is therefore to use process-estimation methods, which attempt to estimate the contribution of recollection and familiarity to recognition memory by using models which describe the relationship between the two processes (Yonelinas, 2002).

One popular process-estimation method is Tulving's (1985) remember/know procedure, a modified version of which will be employed in Chapters 4 and 5 of the current thesis. In the procedure, subjects study a series of items and then at test, if subjects believe an item to be old, they are asked to indicate whether they are basing their decision on the fact that they *remember* the item or on the fact that they *know* the item. A *remember* response indicates that they can recollect at least one contextual aspect of the study event, such as its temporal or spatial position, or an internally generated association. A *know* response indicates that the item seems familiar in the absence of contextual recollection.

How *remember* and *know* responses relate to measures of recollection and familiarity is a matter for debate, since this depends on the nature of the relationship between recollection and familiarity (i.e. whether the two processes are redundant, exclusive or independent). This issue will be explored in more detail in Chapter 4, along with a discussion of the advantages of this method over two alternative process-estimation methods described briefly below.

The first of these alternative methods is the receiver operating characteristic (ROC) procedure (Yonelinas, 1994, 1997), in which subjects are asked to give confidence judgements using a linear scale for each recognition response. An ROC curve is then plotted which describes the relationship between the proportion of hits versus false alarms as a function of confidence. According to the dual-process signal detection model, familiarity in isolation will produce a

symmetrical, curvilinear ROC, whereas recollection will produce a linear ROC. Therefore, the ROC will be curvilinear and asymmetrical in cases where recollection and familiarity both contribute to performance (since the recollection component pushes the curve up at the high-end of the confidence scale, see Figure 1.6). An equation describes the expected ROC if performance is supported by recollection and familiarity (which are modelled independently of one-another and then combined). This equation is then fitted to the empirical ROC giving parameter estimates of recollection and familiarity.

Another popular alternative to the remember/know procedure is the process-dissociation procedure (Jacoby, 1991), which is related to the source memory method described earlier. There are two study lists, one visual and one spoken, for example, followed by two test blocks. In one test block, the "inclusion" block, subjects must endorse any item which they recognise, as "old", regardless of which study list it appeared in. In the "exclusion" block, subjects must only endorse items which they remember from one of the lists, e.g. the spoken list. Performance in the inclusion block gives an additive measure of recollection plus familiarity. Items from the visual list which are incorrectly accepted in the exclusion condition give a measure of familiarity in the absence of recollection. This gives the researcher enough information to calculate estimates of both recollection and familiarity.

**Behavioural evidence for dual-process models**

Although dual-process models of recognition memory are widely accepted, some researchers maintain that the extant data from recognition memory studies can be adequately described by a single-process model (e.g. Dunn, 2004). In addition to studies which have investigated the neuroanatomical basis of dual-process models, discussed in detail below, support for the existence of two distinct processes, ie. recollection and familiarity, comes from studies analysing ROCs and event-related brain potentials (ERPs, see below). Considering ROCs, in brief, different experimental manipulations have been shown to have dissociable effects on ROCs which cannot be explained in terms of a single process (Eichenbaum et al., 2007). For example, allowing subjects to study a list of items twice increases the sensitivity/height of the ROC relative to a single study session, whilst the level of asymmetry of the curve is unaffected (Ratcliff, McKoon, & Tindall, 1994). Deep versus shallow encoding, on the other hand, increases both the overall performance as well as the asymmetry of the ROC (Glanzer, Hilford, Kim, & Adams, 1999). These dissociable effects are indicative of the contribution of two independent processes to performance.

Few researchers deny that these effects provide compelling support for dual-process models of recognition memory. Findings from ROC curves are also important, however, in comparing the validity of the Yonelinas model with that of alternative dual-process models of recognition memory, and it has been suggested that the Yonelinas model may not provide the best account of the data. Wixted (2007) argues that an unequal-variance signal-detection (UVSD) model provides a more accurate, parsimonious explanation. This model is based on standard signal-detection theory, but it makes the additional assumption that the variance of the target distribution is larger than that of the foil distribution. According to this model, recognition decisions are made on the basis of the strength of a single memory signal. The influence of two independent processes, i.e. recollection and familiarity, can be incorporated by assuming that both processes can be described using separate UVSD models. The signals produced by the two processes are added together producing a single measure of memory strength. The model assumes that no single recognition decision is ever process-pure; rather there will always be some influence from both processes.

The Yonelinas model and the UVSD model are both able to explain a large proportion of the findings to date from studies of recognition memory. On the other hand, both models have encountered various challenges, and neither can claim to provide a complete explanation of the extant data. (See Wixted, 2007 and Parks & Yonelinas, 2007 for detailed discussion). A key finding which supports the Yonelinas model over the UVSD model, however, is the observation of *linear* ROC curves obtained in tests of source memory or associative memory, which are both thought to rely mainly on recollection (Rotello, Macmillan, & Van Tassel, 2000; Yonelinas, 1997; Yonelinas et al., 1999). When transformed into z-space, they are u-shaped. This cannot be explained by a model which assumes that recollection represents a signal detection process (Parks & Yonelinas, 2007), as even Wixted (2007) concedes. Of all the evidence which is able to adjudicate between the two models, this finding is perhaps the most compelling at present.

**ERP evidence for dual-process models**

ERP studies have identified correlates of recollection and familiarity at retrieval which differ in terms of their functional, temporal and topographical characteristics (Eichenbaum et al., 2007; Rugg & Yonelinas, 2003). An early frontal negativity (known as the FN 400) is associated with familiarity. The amplitude of this effect is negatively correlated with confidence and does not distinguish between items according to whether they are recollected

(Woodruff, Hayama, & Rugg, 2006). A slightly later, left-lateralised parietal positivity is associated with recollection. This effect is correlated with correct versus incorrect source memory (for example, (Wilding & Rugg, 1997) and with remember vs. know responses (e.g. Duarte, Ranganath, Trujillo, & Knight, 2006; Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997).

Together, these studies provide persuasive evidence for dual-process accounts of recognition memory. They only provide some hints, however, as to the neuroanatomical regions which support recollection and familiarity. The following section discusses studies which have attempted to investigate this issue directly.

**Neuroanatomy of dual-process models**

There are three key methodological approaches to the investigation of the neuroanatomical underpinnings of dual-process models of recognition memory: the study of patients with amnesia; functional neuroimaging; and lesion studies in animals, although the processes of "remembering" and "knowing" or "recollection" and "familiarity" are unlikely to be experienced in quite the same way in animals as they are in humans. On the whole, evidence from these techniques supports the view that recollection and familiarity rely on distinct neural circuits. In terms of the MTL, much of the evidence points to a role for the hippocampus in recollection, and the surrounding cortex, in particular the perirhinal cortex, in familiarity. The role of the parahippocampal cortex is less clear.

Some early dual-process models presumed that recollection relied on the MTL, whereas familiarity was supported by reactivation of representations in the neocortex (Mandler, 1980). This idea followed on from the work of Huppert and Piercy (1978), who characterised the strategy used by amnesic patients in tests of recognition memory as predominantly relying on familiarity. The patients seemed to focus on perceptual characteristics of stimuli and often confused recency of presentation with frequency (ie. they tended to incorrectly accept new words if they happened to also be highly frequent in language). They did not appear able to use the retrieval of contextual details (ie. recollection) to aid recognition. This led to the prediction that amnesia will result in impaired recollection combined with intact familiarity. Support for this view comes from studies which have observed greater impairments in memory for temporal source (Downes, Mayes, MacDonald, & Hunkin, 2002; Huppert & Piercy, 1976, 1978; Kopelman, 1989; Squire, 1982); spatial source (Chalfonte, Verfaellie,

Johnson, & Reiss, 1996; Hirst & Volpe, 1984); modality of presentation (Pickering, Mayes, & Fairbairn, 1989) and recall (Hirst, Phelps, Johnson, & Volpe, 1988; Huppert & Piercy, 1976; Isaac & Mayes, 1999; Johnson & Kim, 1985; Volpe, Holtzman, & Hirst, 1986) compared with item recognition in amnesia.

The studies mentioned above include amnesic patients with a mixture of aetiologies and thus a variety of different profiles of lesion locations and sizes. They cannot, therefore, reveal anything about the contribution of specific brain regions to recollection and familiarity. Studies of patients with more selective lesions are required to investigate the contribution of subregions of the MTL to these processes. For example, several groups examining performance in patients with apparently selective hippocampal damage have reported disproportionately large deficits in recall (Aggleton et al., 2005; Baddeley, Vargha-Khadem, & Mishkin, 2001; Barbeau et al., 2005; Bastin et al., 2004; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Vargha-Khadem et al., 1997; Yonelinas et al., 2002) and memory for associations (in some cases limited to cross modal associations, Aggleton et al., 2005; Baddeley et al., 2001; Barbeau et al., 2005; Bastin et al., 2004; Holdstock et al., 2005; Mayes et al., 2002; Mayes et al., 2004; Turriziani et al., 2004; Vargha-Khadem et al., 1997) compared with item recognition. This would appear to support the view that damage to the hippocampus impairs recollection whilst leaving familiarity relatively intact. As discussed in the previous section and by Rugg and Yonelinas (2003), however, such "task-dissociation" methods only provide an indirect comparison of recollection and familiarity, since these tasks are unlikely to all be process-pure. Although recall, and possibly memory for associations, might be exclusively supported by recollection, item recognition will most likely be supported be recollection and familiarity. One can only infer, therefore, that the reason for the preservation of item recognition is that, unlike recall and associative memory, it can be supported by familiarity which must therefore be intact in these patients.

Attempts to use process-estimation methods, which enable each process to be measured in isolation, have met with mixed success. Some researchers have had difficulty in training hippocampal amnesics to understand the remember/know procedure (Baddeley et al., 2001; Barbeau et al., 2005; Bastin et al., 2004). These researchers found that the patients used the

*remember* response with relatively high frequency but the justifications which they gave for selecting this response revealed that they did not understand the true concept of recollection. For example, patient Jon used the *remember* response whenever presentation of a test item produced an "immediate and clear image" of its prior occurrence (Baddeley et al., 2001). Bastin et al. reported that the hippocampal patient MR seemed to come closer to using the term correctly in that he used it whenever a test item brought to mind an associated word. He had trouble, however, deciding whether the associated word came to mind because he had also thought of it at study, or because he had created the association at test.

Mayes and colleagues reported testing the hippocampal amnesic YR on several recognition memory tests involving a remember/know procedure (Holdstock et al., 2002; Mayes et al., 2002). Details of these tests have not, however, been reported, and the results have only been used to confirm YR's intact familiarity, with her impairments on tests of recall being used as the key evidence of her impaired recollection. Successful training of the remember/know procedure has been documented in an amnesic patient, KN (Aggleton et al., 2005), who has bilateral hippocampal loss as well as some changes in the occipital lobes and amygdala shrinkage. Results from this task as well as from ROC curves provided evidence of preserved familiarity but not recollection in KN. Intact familiarity combined with impaired recollection, as measured by both remember/know and ROC curves, has also been reported in a small group of hypoxic amnesic patients (Yonelinas et al., 2002, Figure 1.6). These patients were assumed to have sustained bilateral selective hippocampal damage, as has frequently been observed following similar anoxic incidents (Cummings et al., 1984; Rempel-Clower et al., 1996; Zola-Morgan et al., 1986), although it was not possible to perform structural MRI in these cases to confirm this.

A recent study provided evidence to compliment the above findings and complete the double dissociation between the effects of damage to the hippocampus and perirhinal cortex on recollection and familiarity. Bowles and colleagues (2007) tested patient NB, who underwent partial surgical removal of her right temporal lobe, including a portion of her perirhinal cortex but not her hippocampus or parahippocampal cortex, on a series of recognition memory tests for words. Estimates of familiarity obtained using the remember/know, ROC and speeded-response procedures, were all reduced relative to those of healthy controls, whereas estimates of recollection were in the normal range. These findings are consistent

with the view that the perirhinal cortex supports familiarity, although it should be noted that the resection included the left amygdala and also caused partial damage to the entorhinal cortex. Replication of this finding, ideally in a patient with more circumscribed, and preferably bilateral damage to the perirhinal cortex would help to bolster this conclusion.

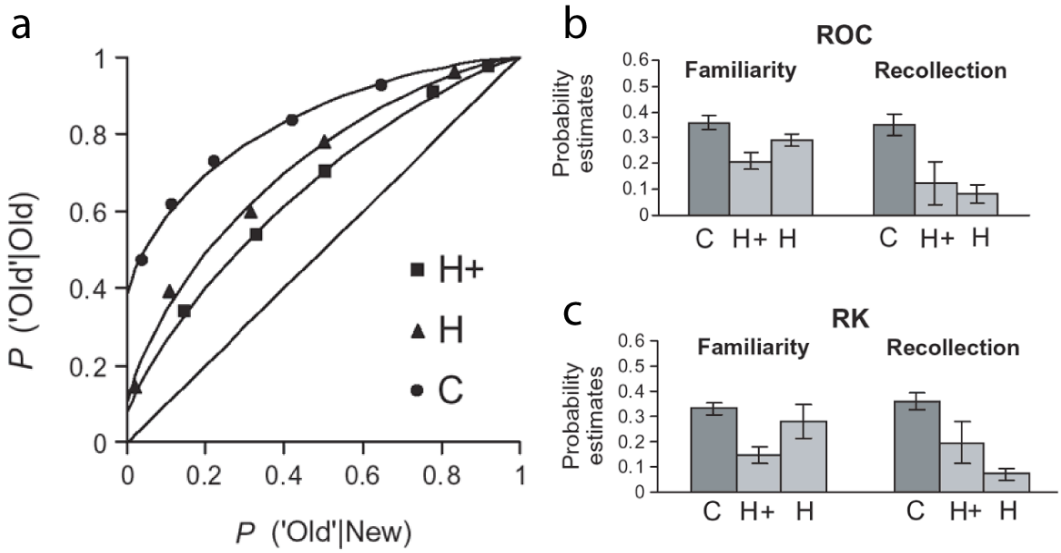


***Figure 1.6 (a) ROC curves for control (C), hypoxic (H) and hippocampal plus (H+) groups from Yonelinas et al. (2002). The leftmost data points correspond to the highest confidence responses with each subsequent point representing decreasing levels of confidence. The asymmetry of the control curve indicates that performance benefitted from the contribution of recollection and familiarity. The symmetry of the patients' curves indicates a reliance on familiarity in the absence of recollection. The points are fitted using a least squares method which produces the estimates of recollection and familiarity plotted in (b). (c) Estimates of recollection and familiarity derived from the Remember/Know procedure.***

In contrast to the focal hippocampal amnesic cases noted above who consistently present with selective impairments in recollection, Squire and colleagues consistently report equivalent impairments on tests of recall and recognition of items and associations in focal hippocampal amnesic patients (Gold et al., 2006; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Stark & Squire, 2003). Moreover, they found no evidence for a disproportionate reduction in the recollective component of recognition memory in patients with hippocampal damage as indexed by ROC curves (Wais, Wixted, Hopkins, & Squire, 2006). The reasons for these discrepant findings are unclear; one possible explanation is that they could be due to differences in the extent of damage to different MTL regions across different studies. On the one hand, it has been suggested that additional deficits in item recognition could be the result of damage outside the hippocampus in the patients reported by Squire and colleagues

(Yonelinas et al., 2004). On the other hand, it could be argued that the intact familiarity observed in some patients reported by other groups might be due to sub-total hippocampal damage.

On the whole, these studies support the view that the hippocampus is necessary for recollective but not familiarity-based processing. This evidence is strengthened by the variety of methodologies employed across the studies. The additional deficits observed on measures of familiarity in patients with more extensive MTL damage provide support for the view that familiarity relies on cortical regions outside the hippocampus. This conclusion is strengthened by the findings in patient NB, discussed above, who showed impaired familiarity combined with intact recollection following unilateral removal of her perirhinal cortex (Bowles et al., 2007). The removal of the perirhinal cortex in patient NB was incomplete, however, and extended into neighbouring MTL structures, making other potential explanations of her performance difficult to rule out. Converging data from functional magnetic resonance imaging (fMRI) therefore provides valuable support for a dual-process division of labour in the MTL, since this method enables both processes to be measured simultaneously.

Over the last five or so years, there has been a dramatic increase in the number of studies aiming to elucidate the neural correlates of recollection and familiarity, with activations in the MTL being a key focus of interest in many of these studies. Unfortunately, the precise localisation of activations in the MTL using fMRI is difficult, at present, since the region is small, relative to the current typical resolution of fMRI scanners, and its subregions are closely packed and highly interconnected. Not surprisingly, given these technical limitations and the difficulty in operationalising recollection and familiarity, the results of these studies have been somewhat inconsistent (Eichenbaum et al., 2007; Henson, 2005). It is therefore advisable to look for replication across studies and to bear in mind potential inaccuracies in the localisation of activations. Taking these caveats into account, several trends have emerged, as illustrated by some recent reviews and meta-analyses (Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007; Henson, 2005; Rugg & Yonelinas, 2003; Skinner & Fernandes, 2007). Two of the most consistent findings from these meta-analyses are: (i) activity in the hippocampus is higher during both encoding and retrieval of items which are associated with recollection relative to items associated with familiarity in

the absence of recollection. This includes trials endorsed with a remember rather than a know response, as well as correctly recognised items which are associated with correct rather than incorrect source or associative retrieval; (ii) familiarity-based retrieval leads to decreased activation in some MTL regions, particularly the perirhinal cortex, although the precise location of this effect is variable. In addition, activity in the parahippocampal cortex is frequently associated with recollection although this effect is less consistent than that observed in the hippocampus.

Of the evidence examined by the meta-analyses mentioned above, the most persuasive comes from demonstrations of dissociations within a single study. For example, two recent studies revealed double dissociations within the MTL associated with encoding activity which led to subsequent recollection or familiarity of words (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004). Both studies used a source memory task to assess levels of recollection. Measurements of familiarity were based either on item recognition (Davachi et al., 2003); or a positive linear correlation between neural activity and recognition confidence using a 6 point scale (levels 1-3 correspond to new and levels 4-6 correspond to old (Ranganath et al., 2004). In both cases, activity in the hippocampus and posterior parahippocampal cortex selectively predicted subsequent recollection but not familiarity, whereas activity in the rhinal cortex predicted subsequent familiarity but not recollection.

Further evidence comes from two additional studies, this time investigating neural activity associated with different components of retrieval. One study deliberately targeted familiarity by utilising an encoding task which has been shown to lead to low subsequent levels of recollection (Figure 1.7), and by requesting that subjects make no effort to recollect items during retrieval (Montaldi, Spencer, Roberts, & Mayes, 2006). At test, subjects were asked to rate the level of familiarity they felt for each item using a 3-point scale. In addition, they were requested to report recollection if and when it did occur. This study also differed from those mentioned so far in that it involved memory for visual scenes rather than words. Despite these differences, Montaldi et al. also observed hippocampal activity associated with recollection but not familiarity, together with a negative, linear correlation between activity in the perirhinal cortex and levels of familiarity. Finally, Daselaar et al. (2006) demonstrated a double dissociation in the MTL between regions supporting recollection and familiarity/novelty for words. These processes were modelled using oldness functions based

***Figure 1.7 Example trials from the match-to-sample (MTS) encoding task used in Montaldi et al. (2006). In each case, subjects were required to select which of the two scenes at the bottom matched the scene at the top. One of the lower scenes was identical to the top scene, whereas the second scene was shifted slightly either vertically or horizontally. Note that this task may have focussed subjects' attention to small details at the edges of the scenes, therefore potentially reducing holistic processing.***

on a recognition confidence scale, similar to that used by Ranganath et al. (2004). Recollection was operationalised using a non-linear function which was flat in the range 1-5 and rose steeply to level 6. This was based on the assumption that recollection is associated with high confidence recognition (Yonelinas, 2002). Familiarity and novelty were operationalised using positive and negative linear functions respectively, across the full range of the confidence scale. Within the MTL, activity in the posterior hippocampus was associated with recollection; activity in the posterior parahippocampal gyrus was associated with familiarity; and activity in the anterior hippocampus and rhinal cortex was associated with novelty (Figure 1.8). Note that since novelty is simply the inverse of familiarity, the claim made by the authors of a triple dissociation between familiarity, novelty and recollection is somewhat overstated.

To summarise these findings, each of the studies discussed above revealed activity in the hippocampus associated with recollection but not familiarity, with the exception of the anterior hippocampus in the study by Daselaar et al, activity in which was associated with novelty detection. This could perhaps be explained by the differential afferentation of the anterior and posterior portions of the hippocampus (Burwell & Amaral, 1998; Witter, Van Hoesen, & Amaral, 1989). Activity in the rhinal cortex during encoding was positively

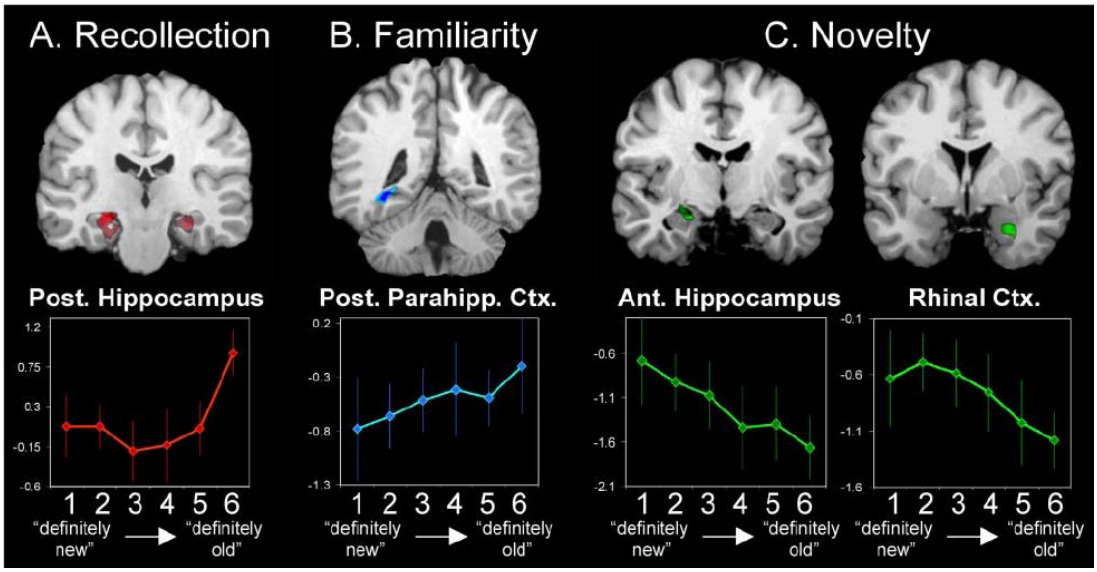


***Figure 1.8 Coronal sections illustrating the brain regions whose activity correlated with oldness functions which modelled (A) recollection; (B) familiarity; and (C) novelty. The line graphs represent peak effect sizes as a function of a 6-point confidence scale, with standard errors (vertical bars). Figure from Daselaar et al. (2006).***

correlated with subsequent familiarity, whereas at retrieval, there was a negative correlation between familiarity and rhinal cortex activity. This may seem confusing at first; however, it is in keeping with the idea that the perirhinal cortex supports novelty detection, so high levels of activity should lead to better encoding, which will be signalled during retrieval by low levels of activity. This is also consistent with electrophysiological recording studies which are discussed later. The patterns of activity observed in the posterior parahippocampal gyrus were inconsistent, as discussed in the broader reviews mentioned above. Further investigation is therefore required to establish the role of this region in recognition memory.

It is important to note that not all studies examining the fMRI correlates of recollection and familiarity fit with the pattern described above. For example, Yonelinas et al. (2005) scanned the test phase of a word recognition memory test in which participants were asked to rate items as recollected (R), or on a scale from 4-1 with 4 indicating confident recognition in the absence of recollection, and 1 indicating high confidence that an item had not been presented previously. Greater activity in response to items receiving R relative to those receiving 4 responses was observed in the bilateral hippocampus and the left parahippocampal cortex, which is in keeping with the proposed role for these structures in recollective processing. Activity in the left portion of the hippocampal region which showed a recollection effect was also correlated with decreasing levels of familiarity (i.e. 1 > 2 > 3 > 4), however, with a trend

for the same effect in the right hemisphere also. Activity in no other MTL region was found to correlate with familiarity. In addition, Gold, Smith, Bayley, Shrager, Brewer, Stark, et al. (2006) found that whereas activity in the hippocampus, perirhinal and parahippocampal cortices predicted subsequent item, but not source memory, activity in the entorhinal cortex predicted subsequent source but not item memory. These results conflict with the idea that the hippocampus and perirhinal cortex can be differentiated according to their involvement in recollection versus familiarity.

Few studies in animals have directly addressed dual-process models of MTL function, since the concepts of recollection and familiarity are difficult to relate to animal behaviour. One study in animals which is of particular relevance, however, investigated ROC curves in rats. Hippocampal lesions had a similar effect in rats as they do in humans, resulting in a symmetrical ROC curve, which, if interpreted according to the Yonelinas dual-process model, indicates that performance relied exclusively on familiarity in these animals (Fortin, Wright, & Eichenbaum, 2004), thus providing a rare example of direct support for the dual-process view in animals (although see later for discussion of stimulus-specific effects in animals and how these may relate to recollection and familiarity). This pattern of performance can also be accommodated by the unequal-variance signal detection model (Wixted, 2007), however, since more symmetrical ROC curves often result when memory strength is reduced, as would likely be the case following hippocampal damage.

Put together, the evidence from all the methodologies mentioned above provide fairly consistent, though not universal support for a functional dissociation in the MTL, contrary to a unitary model of MTL function (Squire et al., 2004). Whereas several studies suggest a role for the hippocampus in recollective aspects of memory, in particular associating items with their contexts, the perirhinal cortex often seems particularly crucial for familiarity. There is also some evidence supporting a role for the parahippocampal cortex in recollective aspects of memory, perhaps through supplying the hippocampus with contextual representations. Most of these studies, however have failed to take into account alternative stimulus categories, with the majority of studies focussing of verbal memoranda. This may lead to an incomplete picture of the division of labour within the MTL, as shall be discussed in a later section which looks at the evidence in support of domain-specific processing in the MTL.

**Associative memory and the hippocampus**

Another proposal which is closely related to dual-process theories of MTL function is that MTL subregions can be distinguished by the extent to which they contribute to the formation and storage of different types of associations. A formulation of this view, referred to as the domain dichotomy (DD) view, has recently been described by Mayes and colleagues (2007). Similarly to many dual-process models (e.g. Aggleton & Brown, 1999; Eichenbaum et al., 2007), this view assumes that due to the particular processing algorithms which are supported by the hippocampus and perirhinal cortex, these regions support recollection and familiarity respectively. This assumption is guided by a neural-network model (Norman & O'Reilly, 2003) which suggests that the hippocampus is able to support recall of associated information (ie. pattern completion), when given a retrieval cue, by nature of its pattern-separation algorithm. The perirhinal cortex, on the other hand, is better equipped to support familiarity due to its pattern-generalising algorithm.

Where the DD view diverges from alternative dual-process models, however, is in its proposition that the ability of particular MTL structures to support the formation of an association is dependent on the degree to which the information contained within that association converges within those structures. The DD view is in agreement with many dual-process views of the MTL in suggesting a key role for the perirhinal cortex in supporting familiarity for individual objects. Unlike many of these models, however, it also suggests that if two items are encoded in such a way so as to encourage a link to form between them, the perirhinal cortex may be able to support familiarity for a non-unitised representation of the association. This is most likely to happen if the two items are from the same domain, for example, two words or two faces, since these items are likely to be processed in close proximity to one-another within the perirhinal cortex. In cases where the information does not converge sufficiently in the perirhinal cortex, such as for between-domain associations and associations between items and context, these associations will be formed in the hippocampus (Figure 1.9).

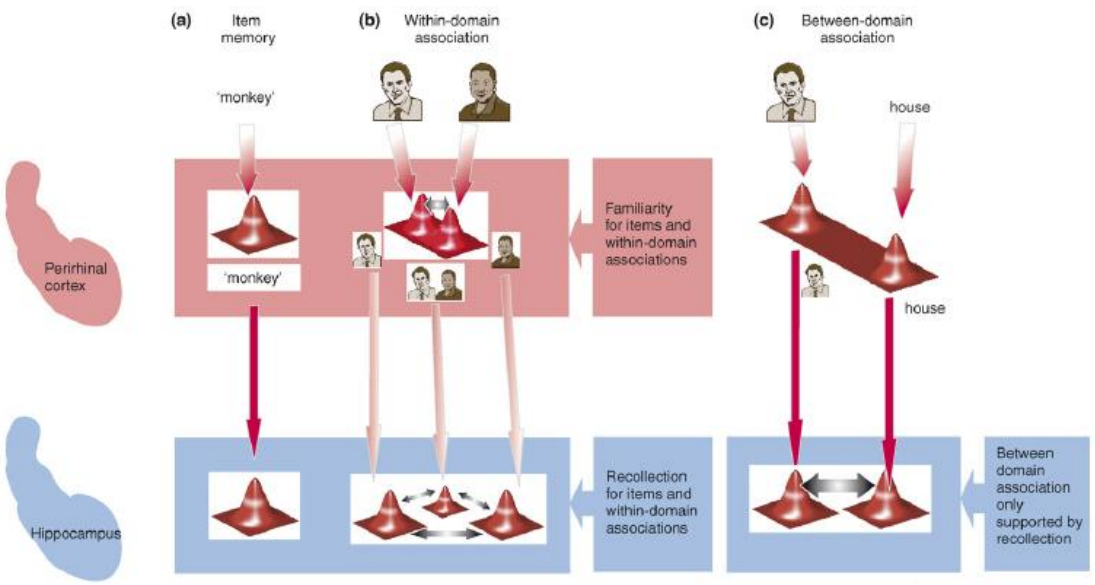


***Figure 1.9 Illustration of the domain dichotomy (DD) view as proposed by Mayes et al. (2007). (a) Representations of unitised items are strengthened in the perirhinal cortex, thus increasing their familiarity. (b) Representations of pairs of items from the same domain, which are encoded together directly, are bound together in the perirhinal cortex increasing familiarity for non-unitised associations. (c) Representations of pairs of items from different domains are not sufficiently close for the perirhinal cortex to support familiarity for associations between them. These associations are supported by hippocampally-mediated recollection. In each case, perirhinal representations feed into the hippocampus which combines them with contextual information to support recollection.***

It has previously been suggested that the familiarity signal in the perirhinal cortex may be able to support memory for associations (Yonelinas et al., 1999). These authors proposed, however, that such associations must be "unitised" to enable familiarity to support successful recognition. For example, if associations are formed between the elements of upright (as opposed to inverted) faces, the elements of the association become unitised, thus being treated as a single entity. As such, memory for the unitised pair can be supported by familiarity. The DD view does not make such an assumption, since it allows within-domain associations between, for example two faces, to be supported by the familiarity signal in the perirhinal cortex, despite the fact that the two faces will retain separate, albeit linked representations (Mayes et al., 2007).

The most compelling evidence in support of this particular aspect of the DD view (ie. the ability for familiarity to support non-unitised, within-domain but not between-domain associations), comes from the study of the amnesic patient YR who is thought to have selective bilateral hippocampal lesions. Whereas YR's item, intra-item and within-domain

(for example, face-face) recognition is intact, her memory for between-domain associations is impaired (Holdstock et al., 2002; Mayes et al., 2002; Mayes et al., 2004). In addition, the three developmental amnesic cases described earlier (Vargha-Khadem et al., 1997) also exhibited a pattern of intact recognition of within-domain associations combined with impaired recognition of between-domain associations. Furthermore, a recent study revealed intact memory for word-pairs in three hypoxic patients with presumed selective hippocampal damage in cases where the pairs were combined to form compounds, but not when they were integrated separately into a sentence (Quamme et al., 2007). Mayes and colleagues (2007) cite this as further support for the DD view; however, Quamme et al. argue that the compound task results in unitised associations. Therefore, although this interpretation does not contradict the DD view, this task fails to investigate the more controversial issue of whether regions outside the hippocampus are able to support memory for non-unitised, within-domain associations as predicted by the DD view. The failure to observe intact memory for within-domain associations which has occurred in some studies of hippocampal amnesics is attributed by Mayes et al. to generalised impairments of familiarity (Stark, Bayley, & Squire, 2002; Stark & Squire, 2003).

To date, no published functional imaging studies have directly contrasted activation patterns associated with memory for within- and between-domain associations. The findings in the previous section discussing evidence for dual-process models, although broadly consistent with the DD view, are unable to adjudicate between this view and closely related dual-process models of MTL function.

## *Domain specificity and the MTL*

An alternative, though not necessarily mutually-exclusive view of the division of labour in the MTL switches the focus from the types of *processes* performed by different subregions to the kinds of *representations* they contain (Bussey & Saksida, 2007; see also Davachi, 2006). More specifically, many researchers have proposed that the hippocampus supports spatial representations (Bilkey, 2007; Buckley, Charles, Browning, & Gaffan, 2004; Burgess & O'Keefe, 2003; Eichenbaum et al., 1999; Lee, Buckley et al., 2005; Maguire, Frackowiak, & Frith, 1997; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978), although a similar function has also been attributed to parahippocampal cortex (Burgess & O'Keefe, 2003; Epstein & Kanwisher, 1998), whereas the perirhinal cortex supports object

representations (Buckley & Gaffan, 2006; Lee, Barense et al., 2005; Lee, Buckley et al., 2005; Mumby, Glenn, Nesbitt, & Kyriazis, 2002; Murray & Bussey, 1999; K. I. Taylor, Moss, Stamatakis, & Tyler, 2006). This idea makes sense if one considers the anatomical connectivity and neuronal characteristics of these regions. Furthermore, it is supported by lesion and gene imaging studies in animals and in studies in humans with memory problems and fMRI.

Much of this evidence points to a role for the hippocampus and perirhinal cortex in long-term memory for scenes and objects respectively, but more controversially, some evidence also points to a role for these structures in working memory and perception. Many proponents of such modality-specific views of the function of the MTL are in agreement that the boundaries between short- and long-term memory and perception are a grey area and that the widespread adoption of a sharp division between these cognitive processes in the literature has hindered theoretical progress (Buckley & Gaffan, 2006; Bussey & Saksida, 2007; Gaffan, 2002; Murray, Graham, & Gaffan, 2005; Murray & Wise, 2004). As a result, although this thesis is concerned primarily with the contribution of MTL structures to long-term memory, this section will also contain a discussion of some of the findings implicating MTL regions in perception, or very short-term memory, since this will help to broaden our understanding of the properties of these regions.

**Perirhinal cortex**

The perirhinal cortex is located at the junction between the MTL and the ventral visual stream, which is responsible for the perception and discrimination of objects (Ungerleider & Mishkin, 1982). Traditionally, the line which marks the transition from the ventral visual stream into the MTL is drawn immediately prior to the perirhinal cortex, thus this region is thought of as an element of the "MTL memory system" (Squire & Zola-Morgan, 1991). Murray and Bussey (1999) have suggested, however, that the region should equally be considered as the apex of the ventral visual stream, and as such, it also plays a vital role in perception.

In keeping with its pivotal location in the brain, the anatomical connections of the perirhinal cortex make it ideally equipped for a role supporting the memory and perception of objects. Approximately 60% of the cortical input to the perirhinal cortex comes from adjacent visual stream regions, areas TE and TEO (Suzuki & Amaral, 1994). The perirhinal cortex is,

however, unique in the ventral stream in that it also receives inputs from cortical regions which supply it with information regarding additional sensory modalities. These include inputs from the posterior two-thirds of the insula which processes somatosensory information (Friedman, Murray, O'Neill, & Mishkin, 1986; Suzuki & Amaral, 1994); regions of the superior temporal gyrus which processes auditory information (Suzuki & Amaral, 1994) and the parahippocampal, orbitofrontal and cingulate cortices which process multimodal information (Carmichael & Price, 1995; Suzuki & Amaral, 1994). The perirhinal cortex is therefore ideally suited to combining its polymodal inputs and creating complex, multimodal representations of objects in the environment (Murray & Bussey, 1999).

Evidence from electrophysiological recording studies supports this idea, and has provided valuable insight into the neuronal mechanisms which could support both the identification of and familiarity for objects in the perirhinal cortex. Firstly, the vast majority of neurons in the perirhinal cortex exhibit stimulus specificity, for example, some only respond to faces, others to objects of particular colours. In some cases, these neurons do not appear to serve any additional (e.g. mnemonic) function (Xiang & Brown, 1998) but rather appear to exclusively aid stimulus identification. Others exhibit response decrements upon re-presentation of stimuli relative to initial presentation (Brown, Wilson, & Riches, 1987; Li, Miller, & Desimone, 1993; Sobotka & Ringo, 1993). In addition to the initial category selectivity of these neurons, their response decrements are also stimulus specific such that the prior occurrence of a particular stimulus from a given category will produce a decrease in firing rate upon re-presentation of that stimulus, whereas the firing rate to other stimuli in the category will remain unaltered (see Brown, 1996, for a review focussed on decremental responses properties of perirhinal neurons). A given neuron might therefore fire upon presentation of any red object, for example, and the *rate* of firing would signal the prior occurrence of a *particular* red object. These various firing characteristics together may form the basis of many of the mnemonic and perceptual mechanisms of the perirhinal cortex, and are consistent with a role for the perirhinal cortex in supporting familiarity for single objects, as proposed by the dual-process models discussed earlier (e.g. Aggleton & Brown, 1999). It is conceivable that rather than performing its mnemonic function independently, however, the perirhinal cortex is merely responding to the top-down influence of the hippocampus which may assess the prior occurrence of stimuli. The speed with which these neuronal responses are made, however, and the failure of neuronal recording studies to observe any appropriate

signals from the hippocampus, would appear to preclude this possibility (Brown & Aggleton, 2001).

To summarise, the evidence above suggests that the perirhinal cortex, rather than simply acting as a gateway for information flowing from the neocortex to the hippocampus, is well equipped to perform some important perceptual and mnemonic computations independently of the hippocampus. Experimental evidence discussed earlier indicates that, in animals at least, the perirhinal cortex can support object recognition memory in the absence of the hippocampus (e.g. Meunier et al., 1993). This leaves the question of the role played by the hippocampus and the circumstances under which its involvement is necessary for the successful performance on a task.

**Hippocampus**

Studies in non-human primates and rats have revealed that the hippocampus receives information from a wide range of neocortical regions spanning all sensory modalities. The majority of this information reaches the hippocampus indirectly, however, having been "pre-processed" by intermediate cortical regions, including the perirhinal cortex. Parallel processing pathways converge in the hippocampus, which acts as the apex of these various streams of information, performing what can be viewed as the "ultimate level of integration" (Lavenex & Amaral, 2000; see also Bussey & Saksida, 2007; Cohen & Eichenbaum, 1993; Squire, 1992). This would appear, at first, to provide support for the view that the hippocampus is essential to declarative memory for all perceptual categories (Squire et al., 2004). It is also consistent with the role for the hippocampus in recollective processing proposed by dual-process models (e.g. Aggleton & Brown, 1999).

Despite this, it seems reasonable to suppose that this high level of integration may not be necessary for the performance of all tasks. Indeed, as discussed above, there is a wealth of evidence which suggests that the hippocampus is not necessary for object recognition memory, since this can be adequately supported by the perirhinal cortex. There are, however, several a priori reasons to assume that the hippocampus is particularly involved in mnemonic, and perhaps perceptual tasks, which include a spatial component.

First, the anatomical inputs to the hippocampus provide it with an extensive array of spatially relevant sensory information. The entorhinal cortex provides the main direct cortical input to

the hippocampus via the perforant path (Suzuki & Amaral, 1990; Van Hoesen & Pandya, 1975; Witter, Groenewegen, Lopes da Silva, & Lohman, 1989). This region receives the majority of its input from the perirhinal and parahippocampal cortices which project predominantly into the lateral and medial aspects of the entorhinal cortex (the LEC and MEC) respectively. These processing streams remain relatively segregated as they enter the hippocampus, where they eventually converge. As discussed above, the perirhinal cortex plays a key role in processing sensory information about objects. The parahippocampal cortex, on the other hand, receives most of its input from the dorsal visual stream or "where" pathway (Ungerleider & Mishkin, 1982). This includes input from the retrosplenial cortex which has been implicated in spatial tasks (Vann, Kristina Wilton, Muir, & Aggleton, 2003) and which also projects directly to the MEC (Aggleton, Vann, Oswald, & Good, 2000). There are, therefore, two fairly separate streams of information entering the hippocampus, one via the perirhinal cortex and LEC processing item-related information, and the other, via the parahippocampal cortex and MEC processing spatial information (Burwell, 2000; Knierim, Lee, & Hargreaves, 2006; Figure 1.10). C-*fos* gene imaging has been used to assess the involvement of the various cortical inputs to the hippocampus in spatial memory tasks. This technique measures the expression of the immediate early gene c-*fos*, known to control the expression of other genes, some of which are thought to be involved in neuronal plasticity. As such, this gene imaging method provides a measure of neuronal processing thought to be linked to the learning process. These studies indicate that inputs into the hippocampus from retrosplenial, entorhinal and parahippocampal but not perirhinal cortices are of vital importance during spatial tasks. Lesion studies have indicated, however, some redundancy in these inputs since impairments following lesions to these regions individually have only partial effects on performance compared with lesions to the hippocampus itself (Aggleton et al., 2000).

Second, the electrophysiological properties of hippocampal neurons distinguish them from those of the perirhinal cortex and demonstrate a variety of space-related properties. Unlike perirhinal neurons, there is little evidence that hippocampal neurons provide any information regarding the prior occurrence of isolated items (Brown & Aggleton, 2001), although they do signal the familiarity of specific item-position associations (Eichenbaum, 2000). Furthermore, neuronal recording studies in rats have revealed the presence of "place cells", which fire selectively when the animal is located in particular positions within their

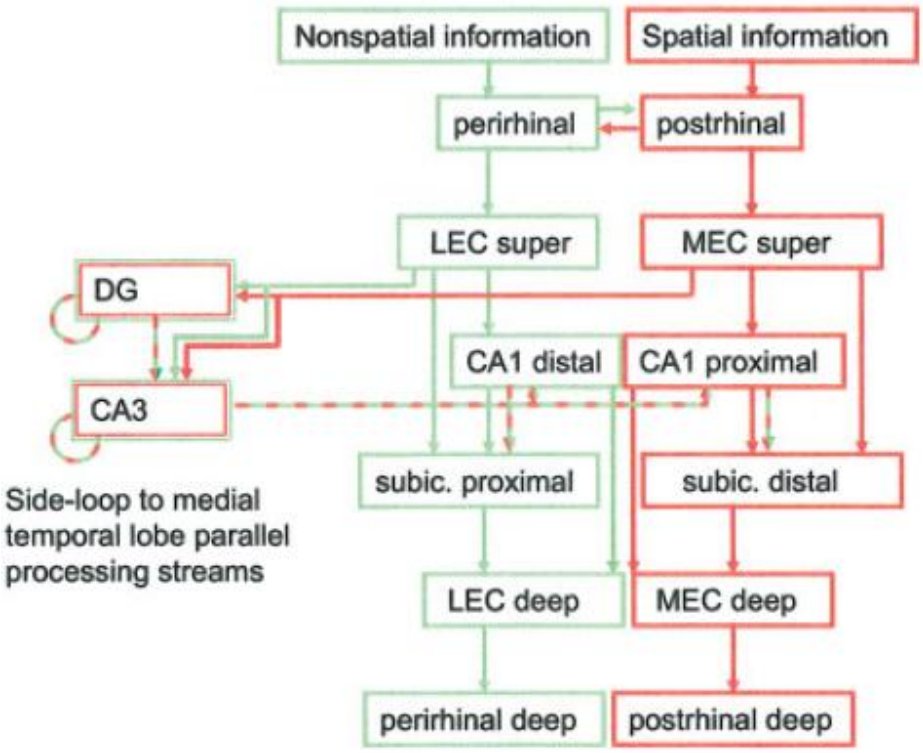


***Figure 1.10 Schematic illustration of partially segregated, parallel processing streams in the MTL as proposed by Burwell (2000). Non-spatial, item related information enters the hippocampus via the perirhinal cortex and LEC, whereas spatial information enters via the postrhinal/parahippocampal cortex and MEC. The two streams converge in the dentate gyrus (DG) and CA3 side-loop which creates an item + location representation. Figure from Knierim et al. (2006) adapted from Burwell (2000).***

environment, enabling the formation of a context-dependent map (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). The spatial map provided by place cells has the capacity to remain stable over extended periods (over several months) if the rat's environment does not change (L. T. Thompson & Best, 1990). The map is also flexible, however, and upon entering a novel environment, the cells will be rapidly remapped to create a representation of the new environment (Muller & Kubie, 1987). Ekstrom et al. (2003) recently provided evidence for a similar spatial map in humans based on neuronal recording studies in patients with intractable epilepsy. Recordings were made whilst the patients explored a virtual town using computer game software during an invasive procedure which was designed to search for potential seizure foci. Whereas a large proportion of neurons in the hippocampus responded to spatial locations, clusters of cells, predominantly located in the parahippocampal region responded to specific landmarks. Furthermore, neuronal recordings from a similar group of patients during the presentation of images from various categories (for example, faces, cars, patterns) revealed a high degree of selectivity in the hippocampus

in response to images of spatial layouts such as houses and scenes relative to the entorhinal cortex and amygdala (Kreiman, Koch, & Fried, 2000).

In keeping with the above findings regarding the anatomical connections and electrophysiological properties of neurons in the hippocampus, impairments on DNMS tests in rats following hippocampal lesions are generally modest or non-existent (Aggleton, Hunt, & Rawlins, 1986; Mumby & Pinel, 1994). Findings in monkeys are mixed, but generally, significant impairments following isolated hippocampal lesions are dependent on extended delays, and even then they are sometimes non-existent (Alvarez, Zola-Morgan, & Squire, 1995; Beason-Held, Rosene, Killiany, & Moss, 1999; Murray & Mishkin, 1998; Zola-Morgan, Squire, Rempel, Clower, & Amaral, 1992; Zola et al., 2000). Baxter and Murray (2001) performed a meta-analysis on a sub-set of these studies and observed an inverse relationship between extent of hippocampal damage and degree of impairment on the DNMS. One possibility, therefore, is that that partial lesions may lead to disruptive, pathological firing in the hippocampus which may affect functioning in neighbouring regions. This may explain the contradictory findings across these studies and highlights the need for complete removals of structures during lesion studies.

When tests involve a spatial component, however, lesion studies have consistently demonstrated a necessary role for the hippocampus (Buckley et al., 2004; Gaffan, 1994; Hampton, Hampstead, & Murray, 2004; Murray, Davidson, Gaffan, Olton, & Suomi, 1989). For example, Gaffan (1994) observed that impairments following fornix transection in monkeys were most severe on tests of object-in-place learning and least severe in object discrimination learning when the background became irrelevant. Learning to select a particular place in the absence of discrete objects produced an intermediate level of impairment. He proposed that a network involving the hippocampus, fornix and mamillary bodies is essential for associating the representations of the elements of complex scenes.

According to the cognitive map theory (O'Keefe & Nadel, 1978), the function of the hippocampus can be further narrowed down to allocentric or view-invariant spatial processing. This is in keeping with the observation that the firing patterns of hippocampal place cells in rats are not affected by the animal's orientation (O'Keefe, 1976). Support for this view from studies in humans comes from the finding that impairments on tests of object

location recognition following hippocampal damage are more severe for shifted than for same viewpoints (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). In contrast, the parahippocampal cortex is thought to support less flexible spatial representations (Burgess, Maguire, & O'Keefe, 2002). This is supported by imaging findings in which activity in the so-called "parahippocampal place area" has been associated with the perception of landmarks and spatial scenes (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998). The experiments in the current thesis involve memory for same and shifted view scenes which will enable this issue to be investigated further.

To summarise, there is a wealth of evidence which supports a role for the hippocampus as well as the parahippocampal cortex in supporting spatial representations, and for the perirhinal cortex in supporting object representations. The most compelling evidence for a division of labour in the MTL along these lines comes from studies which have directly compared perception or memory for these two categories of stimuli.

**Studies in Animals**

Working with animals has provided a unique opportunity to investigate the function of the hippocampus and perirhinal cortex independently of one another through the use of precise lesions to each structure in isolation. A recent paper by Winters et al. (2004) provided the first demonstration of a functional double dissociation following lesions to the perirhinal cortex and hippocampus in rats within a single study. Rats with perirhinal lesions but not those with hippocampal lesions were impaired on a spontaneous object recognition task which was designed to minimise the involvement of spatial and contextual factors. Conversely, rats with hippocampal, but not those with perirhinal lesions, were impaired on a spatially taxing radial maze task. A subsequent study confirmed that even when the delay between study and test was increased to 48 hours, hippocampal lesions did not produce any impairment on the object recognition task (Forwood, Winters, & Bussey, 2005). These studies therefore provide strong evidence that, provided the influence of spatial and contextual factors is excluded, the perirhinal cortex, but not the hippocampus, is necessary for the performance of object recognition memory.

Whilst providing a crucial tool for studying the precise role of different MTL structures, lesion studies do have their limitations. For instance, as discussed by Aggleton and Brown (2005), lesions to the perirhinal cortex may result in the recruitment, by the hippocampus, of

alternative cortical afferent information during spatial tasks, which is received via pathways parallel to those linking it to the perirhinal cortex (Burwell & Amaral, 1998; Burwell, Witter, & Amaral, 1995). Thus, although the perirhinal cortex may normally play a role in spatial processing, by providing the hippocampus with sensory information, this role may be masked in lesion studies due to the redundancy of the information it provides. Some researchers have therefore utilised c-*fos* imaging to address this issue. Aggleton and Brown (2005) recently reviewed several studies from their laboratory which utilised this technique in rats. They found that activation of c-*fos* increased in the hippocampus, but not the perirhinal cortex, during spatial memory tasks, and during the presentation of novel scenes consisting of rearrangements of familiar objects. The presentation of novel vs. familiar objects, on the other hand, produced increased c-*fos* activity in the perirhinal cortex but not the hippocampus. These results are therefore consistent with a role for the hippocampus and perirhinal cortex in spatial and object processing respectively. They also indicate that the perirhinal cortex does not provide the main route for sensory information to the hippocampus required for spatial tasks (as mentioned earlier in this section).

**Studies in humans**

Studies of recognition memory in humans have rarely attempted to systematically compare the involvement of MTL structures in the performance of recognition memory for different categories of visual stimuli. Three cases studies have, however, documented impairments in recognition memory for topographical material in the context of preserved recognition memory for faces following selective hippocampal damage (Bird, Shallice, & Cipolotti, 2007; Carlesimo, Fadda, Turriziani, Tomaiuolo, & Caltagirone, 2001; Cipolotti et al., 2006). Interestingly, levels of recollection and familiarity were estimated using ROC curves in two of these cases, and not only did these patients demonstrate a sparing of familiarity for faces, their recollection for faces was also spared (see Figure 1.11 for an illustration from one of these studies). Both recollection and familiarity for topographical stimuli (buildings and landscapes) were, however, impaired in both cases (Bird et al., 2007; Cipolotti et al., 2006). Furthermore, the third case study demonstrated intact memory for associations between faces in addition to intact memory for individual faces (Carlesimo et al., 2001). It seems difficult, therefore, to reconcile these findings with most dual-process models of MTL function (although see the section discussing associative memory, above, for a possible explanation of this latter finding). In contrast to these findings, the inverse pattern of performance has also been reported, ie. a sparing of recognition memory for topographical material, combined with

impaired memory for faces, in patients with semantic dementia (Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998), a condition known to affect anterior temporal lobe regions, including the perirhinal cortex (Davies, Graham, Xuereb, Williams, & Hodges, 2004). The above findings are therefore consistent with the view that the hippocampus and perirhinal cortex support spatial and object representations respectively. One of the aims of Chapters 2 and 3 of this thesis is to replicate these findings in larger groups of patients with hippocampal damage and semantic dementia, and to make more direct statistical comparisons between different stimulus categories using an equivalent experimental set-up.

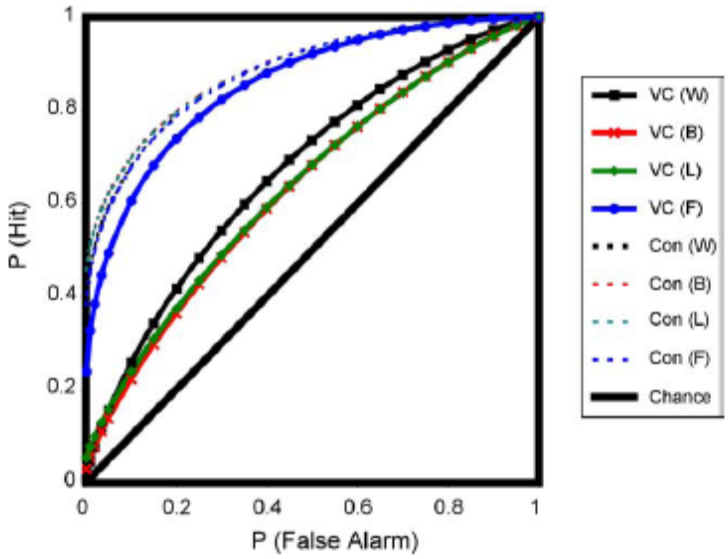


***Figure 1.11 ROC curves illustrating the performance of the hippocampal amnesic VC and controls on recognition memory tests involving words (W), buildings (B), landscapes (L), and faces (F) from Cipolotti et al. (2006). Note that the ROC curve corresponding to VC's performance on recognition memory for faces is asymmetrical, indicating that performance was supported by intact recollection and as well as familiarity.***

Several recent functional neuroimaging studies are also consistent with the idea that regions within the MTL can be dissociated according to the kinds of stimuli they process. Whereas networks of regions including the hippocampus, particularly at its posterior extent, are activated by spatial tasks such as navigation and memory for spatial locations (Burgess, Maguire, Spiers, & O'Keefe, 2001; Maguire et al., 1998; Parslow et al., 2004), networks including the perirhinal cortex are activated during memory and discrimination of objects (Devlin & Price, 2007; Kohler, Danckert, Gati, & Menon, 2005; Lee, Bandelow, Schwarzbauer, Henson, & Graham, 2006; Lee, Scahill, & Graham, 2008; Tyler et al., 2004). One study of particular interest revealed a double dissociation within a single experiment,

with activation being observed in the perirhinal cortex during presentation of novel objects, whereas the posterior hippocampus was activated in response to novel *rearrangements* of familiar objects (Pihlajamaki et al., 2004). Chapter 5 of the current thesis will investigate whether a similar dissociation can be observed when comparing activation patterns associated with recognition memory for faces and scenes.

**Evidence for MTL involvement in perception**

As discussed in the introduction to this section, there is increasing support for the idea that the role of the MTL extends into non-mnemonic processes, with the perirhinal cortex supporting object perception and the hippocampus supporting spatial perception (Buckley & Gaffan, 2006; Bussey & Saksida, 2007; Gaffan, 2002; Lee, Barense et al., 2005). The earliest report of perceptual deficits following perirhinal lesions came from a study by Eacott et al (1994), who observed deficits on a zero second delay version of the object match-to-sample-task (MTS) in macaques. Notably, deficits were only observed on the zero-delay condition in cases where the stimuli were designed to be particularly difficult to discriminate. Subsequent experiments revealed deficits on concurrent visual discrimination learning, again in monkeys with perirhinal lesions, but only when "object identification" was sufficiently taxed, either through increasing the number of trials or foils, or by requiring recognition of alternative views of stimuli (Buckley & Gaffan, 1997, 1998).

In order to more directly assess visual perception, Buckley et al. (2001) designed a series of "oddity" tasks which varied in their level of complexity. On each trial, monkeys were simultaneously presented with six visual stimuli, five of which were the same, and a fifth which was different, and were required to choose the odd-one-out. Perirhinal lesions had no effect on the simplest conditions which involved the discrimination of colours, differently sized objects, and simple shapes. This is not surprising given that simple features are thought to be represented by more caudal portions of the ventral visual stream (Desimone & Ungerleider, 1989). There were two conditions which required the discrimination of complex objects. In the "same-view" condition, five identical views of an object were presented alongside a single image of a different object. In the "different-view" condition, five different views of a single object were presented alongside a single view of a different object. Of these two conditions, only the latter, different-view condition was impaired following perirhinal lesions. The authors suggested that whilst the same-view condition could be solved on the basis of a single feature, the different-view condition could not, and instead

depended on the formation of a view-invariant, configural representation of the objects.

Lee, Buckley et al. (2005) have recently adapted the oddity paradigm for use in human subjects. This included the development of an additional condition involving virtual reality scenes in order to examine spatial perception. The authors observed deficits in patients with focal hippocampal lesions in the perceptual discrimination of virtual-reality scenes, but not faces (see also Hartley et al., 2007). A second group of patients with broader MTL damage that included the hippocampus and perirhinal cortex were impaired on both face and scene conditions, suggesting a role for human perirhinal cortex in the discrimination of faces (Figure 1.12). Similarly to Buckley et al (2001), these deficits were limited to trials where stimuli were presented from different, but not same, viewpoints, suggesting that view-invariant but not view-specific representations were impaired in these patients. In the case of the scene stimuli, this adds support to the view that the hippocampus is crucial for the processing of allocentric, but perhaps not egocentric spatial representations (Burgess et al., 2002; O'Keefe & Nadel, 1978). This is not, however, the only possible explanation for this dissociation as will be discussed in Chapter 2. It appears, therefore, that configural object-level representations depend on the perirhinal cortex, whereas (allocentric) spatial representations depend on the hippocampus, and as such, both regions contribute to memory and perception.

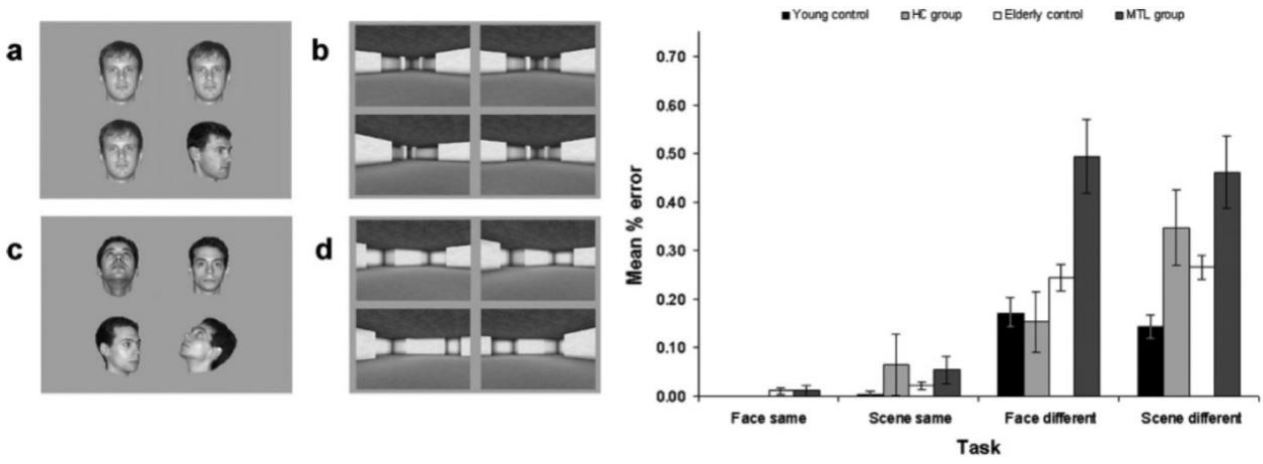


***Figure 1.12 Examples of a trial from each condition in Lee, Buckley et al. (2005): (a) Same-view faces; (b) Same-view scenes; (c) Different-view faces; (d) Different-view scenes; and corresponding performance (% error ± standard error) in each subject group (young controls matched to the HC group; elderly controls matched to MTL group).***

Bussey and Saksida (2002) described a role for the perirhinal cortex in both memory and perception of objects in their "Perceptual-Mnemonic/Feature-Conjunction" (PMFC) neural network model of processing in the ventral visual stream (VVS). According to this model, visual representations of increasing complexity are located from the caudal to the rostral extent of the VVS, with the perirhinal cortex housing object representations of the highest level of complexity. These high-level object representations comprise conjunctions of features which are represented individually by more caudal sections of the VVS. A prediction of this model is that when tasks which require the discrimination of objects can be solved on the basis of simple, non-overlapping features, they will not require the involvement of the perirhinal cortex. The authors would describe such a task as having low "feature ambiguity", since there are no features which are present in both sample and foil stimuli. If a task can only be solved on the basis of conjunctions of features, however, such that each individual feature appears in both target and foil stimuli, then such a task is described as having high feature ambiguity.

The PMFC model has been used to explain a variety of experimental findings in animals, in which feature-ambiguity has been explicitly manipulated. These include the presence of impairments following perirhinal lesions on tests of concurrent and single-pair object discrimination which were limited to conditions with high but not low feature ambiguity (Bussey, Saksida, & Murray, 2002, 2003). These findings have recently been replicated in humans: patients with damage to the perirhinal cortex (including patients with broad MTL damage as well as patients with semantic dementia) were impaired on object discrimination and object oddity tasks involving a high- but not low degree of feature ambiguity. Patients with lesions limited to the hippocampus, however, performed normally on all conditions. (Barense, Bussey, Lee, Rogers, Davies et al., 2005; Barense, Bussey, Lee, Rogers, Hodges et al., 2005; Barense, Gaffan, & Graham, 2007). Furthermore, patients with broad MTL lesions but not those with selective lesions to the hippocampus were impaired at discriminating pairs of morphed faces (Lee, Bussey et al., 2005). Both patient groups were, however, impaired at discriminating morphed scenes.

In addition, the PMFC model has been used to explain additional findings and discrepancies from studies which have not explicitly manipulated feature ambiguity. For example, the findings that deficits following perirhinal lesions can depend on (i) the adoption of large set

sizes in concurrent discrimination (for example, Buckley & Gaffan, 1997); (ii) increasing delay lengths in recognition memory tests (Buffalo et al., 1999; Buffalo, Reber, & Squire, 1998; Holdstock, Shaw, & Aggleton, 1995), (iii) the use of different- rather than same-view conditions in oddity tasks and, (iv) high levels of perceptual similarity between targets and foils in tests of recognition memory and perceptual oddity discrimination (Bartko, Winters, Cowell, Saksida, & Bussey, 2007) have all been explained as being the result of the need for high levels of feature ambiguity to elicit an impairment following perirhinal lesions (Bussey & Saksida, 2007; Bussey, Saksida, & Murray, 2005). This may explain why several studies have failed to observe perceptual deficits following perirhinal lesions (Buffalo et al., 1999; Buffalo et al., 1998; Holdstock et al., 1995; Stark & Squire, 2000). There is perhaps a danger of circularity in this explanation, however, and therefore further studies must be undertaken to rigorously test the predictions of the PMFC model directly.

Together, these findings provide support for the view that the hippocampus and perirhinal cortex are involved in both memory and perception. Crucially, their contributions to tests of both memory and perception can be distinguished according to the category of stimulus involved, with the perirhinal cortex supporting representations of complex objects, and the hippocampus supporting spatial representations. An interesting question is whether damage to MTL regions affects the same types of stimuli in mnemonic tasks as those that are affected in perceptual tasks. For example, in addition to the effects of broad stimulus categories (such as faces versus scenes) are there any effects of viewpoint in the pattern of memory impairments as there seems to be in the pattern of perceptual impairments? This issue will be explored in Chapters 2 and 3 of the current thesis which investigate recognition memory for faces and scenes from same- and different-views in groups of patients with damage to different MTL regions.

## *Summary and comparison of theories of MTL function*

The domain-specific and dual-process models of MTL function described above are in agreement in proposing functional subdivisions between components of the MTL. Both groups of theories are therefore incompatible with Squire's model of the MTL (Squire et al., 2004; Squire & Zola-Morgan, 1991), which posits that all the subregions of the MTL work together in the support of long-term declarative memory. What is less clear is whether the functional divisions proposed by domain-specific and dual-process models are compatible

with each other.

On the one hand, domain-specific and dual-process models of MTL function share many assumptions, and much of the evidence used as support for one division of labour could equally be taken as support for the other. Indeed, in a recent description of one dual-process model, Eichenbaum et al. (2007) discussed several findings from animal lesion studies which revealed roles for the perirhinal cortex and the hippocampus in object and spatial memory respectively. These findings were taken as support for a dual-process division of labour in the MTL. For example, the observation that the perirhinal cortex, but not the hippocampus, plays a crucial role in object DNMS (Meunier et al., 1993; Murray & Mishkin, 1998) is consistent with the proposal that the perirhinal cortex supports familiarity for objects. Similarly, impairments on tests such as object-in-place learning following hippocampal damage (Gaffan, 1994), are consistent both with a role for this regions in supporting spatial representations, and also for a role in supporting recollection (i.e. retrieval of spatial source). Moreover, it has been suggested that spatial memory is a special case of relational memory (e.g. Eichenbaum et al., 1999) and therefore requires hippocampally-mediated recollection.

There are situations, however, where dual-process models and domain-specific models would seem to lead to conflicting predictions. Perhaps the most obvious example is the case of recognition memory for different categories of visual stimuli. To summarise the findings discussed above, a plethora of studies in both humans and animals have indicated that the hippocampus and perirhinal cortex are specialised for spatial and object processing respectively. These findings would therefore lead to the prediction that selective damage to MTL structures may cause stimulus-specific dissociations on tests of recognition memory. Dual-process models, on the other hand, propose that the hippocampus and perirhinal cortex are specialised for recollective and familiarity-based processing respectively. Stimulus specific effects would not seem to be an obvious prediction of this view. Instead, selective damage to MTL regions might cause impairments on one process or the other, but such impairments should be common to all stimulus categories.

The implicit assumption in this latter prediction is that dual-process models would predict that the hippocampus supports recollection of both objects and scenes, whereas the perirhinal cortex would support familiarity for both categories. Proponents of dual-process views have

not explicitly specified whether this would, in fact, be their prediction, although it seems reasonable to assume this as the default position. The existing literature provide little evidence as to whether this might be the case, however, particularly since the overwhelming majority of evidence supporting dual-process models comes from tasks involving verbal memoranda. Nevertheless, one imaging study (Montaldi et al., 2006) would appear to provide some support for this possibility, at least regarding recollection and familiarity for scenes, which were associated with activity in the hippocampus and perirhinal cortex respectively (although the encoding method used in this study may have caused subjects to focus on isolated components of the scenes, which may have prevented the formation of complex representations; see Figure 1.7).

It is difficult to see, however, how such a model could explain all of the stimulus-specific effects observed in imaging and neuropsychological studies which were outlined earlier. One possibility is that memory for faces and scenes disproportionately depends on familiarity and recollection respectively. In favour of this option is the idea that spatial stimuli are inherently associative, requiring the integration of various elements and their relative positions. Since memory for associations is often assumed to require recollection, this may explain why damage to the hippocampus, which is assumed to be specialised for recollective processing, tends to impair spatial processing. Memory for items such as faces, however, can perhaps be adequately supported by familiarity signals in the perirhinal cortex.

An alternative possibility, which has gained support from three recent case studies (Bird et al., 2007; Carlesimo et al., 2001; Cipolotti et al., 2006), is that both recollection and familiarity for scenes are supported by the hippocampus, whereas recollection and familiarity for objects are supported by regions outside the hippocampus, for example, the perirhinal cortex. All three case studies revealed a sparing of recollection and familiarity for faces combined with impairments of both processes for scene stimuli following hippocampal damage. This data clearly favours a stimulus-specific account of the division of labour in the MTL over a dual-process account, at least in the case of visual stimuli.

## Overview of thesis

The experiments reported in the present thesis are designed to address these issues, and provide the first systematic test of the conflicting predictions which follow from domain-specific and dual-process theories of MTL function, on tests of recognition memory for different categories of stimulus.

Chapters 2 and 3 report the performance of patients with either focal or progressive damage to different MTL structures on a recognition memory test for faces and scenes. The results reveal that damage to the hippocampus is associated with impaired recognition memory for scenes, whereas deficits in recognition memory for faces are commonly observed in patients whose lesions involve the perirhinal cortex.

Chapter 4 describes the results of a modified version of the face and scene recognition memory test used in Chapters 2 and 3, that incorporates a remember/familiar judgement to estimate levels of recollection and familiarity, in young and older healthy adults. The findings suggest that recognition memory for scenes may disproportionately rely on recollection rather than familiarity, when compared with face recognition memory. This supports the possibility that the stimulus-specific deficits reported in Chapters 2 and 3 could potentially be explained by dual-process models of MTL function.

Chapter 5, which reports the results of two fMRI investigations of recognition memory, is not consistent with this possibility, however, and provides clear evidence of stimulus-specific, but not process-specific activation patterns in different MTL regions.

Chapter 6 contains a general discussion of these findings and concludes that in the case of visual recognition memory, the functional roles of different MTL structures depend on the category of stimuli involved, and not necessarily on the kind of processing that is performed.

# Chapter 2

# Recognition memory for faces and scenes in amnesia: Dissociable roles of medial temporal lobe structures

## Introduction

As discussed in Chapter 1, impairments in recognition memory are widely believed to be a key feature of medial temporal lobe amnesia. Whether the hippocampus and perirhinal cortex make different contributions to this type of memory, however, remains controversial. One prominent theory proposes that both structures form part of a unitary declarative memory system supporting conscious recall of past experiences, and therefore, both are essential for intact recognition memory (Squire et al., 2004; Squire & Zola-Morgan, 1991). An alternative view predicts that a network involving perirhinal cortex may be sufficient to support familiarity-based recognition memory for single items, in the absence of the hippocampus (Aggleton & Brown, 1999; Brown & Aggleton, 2001; Eichenbaum et al., 2007; Holdstock, 2005). According to this view, tasks requiring contextual information about the learning episode are dependent on the hippocampus, and perhaps also the parahippocampal cortex, and consequently damage to these structures will impair performance on such tests.

In support of the latter theory, studies in hippocampal patients have reported intact recognition memory for single items coupled with impaired recall and/or impaired recognition memory for (cross-modal) associations (Aggleton et al., 2005; Baddeley et al., 2001; Barbeau et al., 2005; Bastin et al., 2004; Holdstock et al., 2005; Mayes et al., 2002; Mayes et al., 2004; Turriziani et al., 2004; Vargha-Khadem et al., 1997). Conversely, Squire and colleagues consistently find impaired recall and recognition memory for both single items and associations in their focal hippocampal patients (Manns et al., 2003; Manns & Squire, 1999; Stark et al., 2002; Stark & Squire, 2003; Wais et al., 2006). For example, Gold et al. (2006) report deficits in item and source memory for words in patients with damage limited to the hippocampus. In addition, use of a similar task in functional magnetic resonance imaging (fMRI) revealed activation of the hippocampus and perirhinal cortex in healthy participants.

An alternative view that may partially explain this controversy is that different regions within

the MTL may be involved in the processing of different stimulus categories, with the hippocampus and perirhinal cortex playing a critical role in spatial and object processing, even when there is minimal demand for declarative memory. Much of the evidence in support of this view has come from investigations in rats and monkeys that have focused on object perception after perirhinal lesions (Buckley et al., 2001; Buckley & Gaffan, 2006; Bussey et al., 2002, 2003; Eacott & Gaffan, 2005). For example, monkeys with perirhinal lesions were found to be impaired on concurrent object discriminations with a high, but not low, degree of 'feature ambiguity', a property of visual discrimination problems that emerges when discriminating between objects with a large number of features in common (Bussey et al., 2002). In contrast, monkeys with hippocampal lesions performed normally on such tasks (Saksida, Bussey, Buckmaster, & Murray, 2006), a pattern also true of human amnesics with selective hippocampal damage (Barense, Bussey, Lee, Rogers, Davies et al., 2005).

The findings from these experiments have been interpreted as support for a view of visual processing in which the perirhinal cortex functions as the apex of the ventral visual processing stream, with perirhinal cortex containing representations of complex conjunctions of stimulus features, whereas more caudal regions (e.g., V4, TEO) house the components from which these conjunctions are formed (Bussey & Saksida, 2005). Lee and colleagues (Lee, Buckley et al., 2005; Lee, Levi, Davies, Hodges, & Graham, 2007) have recently proposed a similar role for the hippocampus in the processing of complex spatial scenes or spatial configurations based on data using a four-choice odd-one-out paradigm adapted from animal studies (Buckley et al., 2001). Lee et al. (Lee, Buckley et al., 2005) observed deficits in patients with focal hippocampal lesions in the perceptual discrimination of virtual-reality scenes, but not faces. A second group of patients with broader MTL damage that included the hippocampus and perirhinal cortex were impaired on both face and scene conditions, confirming a role for human perirhinal cortex in the discrimination of faces (see Buckley, 2005, for a review of similar experiments in monkeys with perirhinal lesions). These deficits were limited to trials where stimuli were presented from different, but not same, viewpoints, suggesting that view-invariant but not view-specific representations were impaired in these patients. These studies, when considered alongside other investigations revealing double dissociations in the involvement of MTL structures in object and spatial processing (e.g., early gene imaging, Aggleton & Brown, 1999, 2005; and lesion studies, Winters et al., 2004, in rats), highlight a key difference between stimulus categories that may be particularly

important for understanding human recognition memory.

The current Chapter reports the results of an experiment designed to test whether the stimulus specific effects seen on perceptual tasks in amnesic patients extend into the memory domain. Patients with amnesia were tested on a novel recognition memory test for faces and scenes (existing standardised tests do not allow direct comparison of performance on these two stimulus categories), which also incorporated same- and different-view conditions to test whether deficits in the memory domain are limited to tasks requiring view-invariant representations. It was predicted that hippocampal patients would show normal recognition memory for faces, but not scenes, whereas individuals with broader MTL lesions involving perirhinal cortex would show poor recognition memory regardless of stimulus type.

# Materials and Methods

## *Participants*

Six amnesic patients with focal brain lesions participated in this study. Structural magnetic resonance imaging (Grundman et al., 2004) scans in five of the patients were evaluated (see Scan Rating Method, below), and on the basis of these evaluations, patients were categorised into the following two groups: (1) individuals with selective hippocampal damage (HC group, n = 3) and (2) participants with broader MTL damage, including perirhinal cortex, in addition to the hippocampus (MTL group, n = 3). Of the three patients included in the MTL group (age = 69.7yrs; education = 10.3yrs; one female, two male), two had been diagnosed with viral encephalitis and the third had experienced traumatic intracerebral bleeding. Of the three patients categorised in the hippocampal group (age = 48.7yrs; education = 13yrs; all female), one had a diagnosis of viral encephalitis, another had cerebral anoxia in the context of suspected encephalitis, and the third had carbon monoxide induced hypoxia. One patient from the HC group (referred to as HC5) did not wish to undergo further scanning. It was not possible to retrieve her previous scan, but the radiological report indicated selective hippocampal damage and her performance on standard neuropsychological tests was indistinguishable from the other cases with selective hippocampal damage. Exclusion of this patient from the analyses did not significantly alter the experimental findings.

Since the two patient groups were not matched in terms age ($p < 0.05$) or sex, for the

experimental tests, two groups of twelve healthy controls were recruited to match the two patient groups in terms of age, education and sex: HC controls: age = 48.8yrs; education = 14.7yrs; all female; MTL controls: age = 69.0yrs; education = 11.6yrs; 4 female, 8 male (all $p > 0.19$).

All participants gave informed consent before undertaking the study. This investigation received ethical approval from the Cambridge and Southampton Health Authority Local Research Ethics Committees (UK).

## *Scan rating method*

The MRI scans from the patients were assessed using (a) detailed rating of a number of temporal lobe brain regions, based on a rating scale that focused on MTL regions (Barense, Bussey, Lee, Rogers, Davies et al., 2005; Galton, Gomez-Anson et al., 2001; Lee, Bussey et al., 2005) and (b) MRIcro (Rorden & Brett, 2000) to delineate which brain regions highlighted from the rating scale were damaged in the two groups. The results of these evaluations are shown in Table 2.1 and Figure 2.1. One hippocampal patient was not included in either analysis for the reasons given above. A further patient, referred to as MTL2, was not included in the second analysis since an electronic version of his scan was not available. Exclusion of either, or both, of these patients did not significantly alter the experimental findings.

The visual rating method assesses a total of nine regions, including (1) anterior hippocampus, which was rated on the anterior most pontine slice and based on the widths of the choroid fissure and temporal horn and the height of the hippocampal formation; (2) anterior temporal lobe, which was based on the cerebral spinal fluid space between the back of the orbit and temporal pole; (3) amygdala, which was rated on the scan-slice anterior to the tip of the temporal horn; (4) lateral temporal lobe, which was rated on the same slice as the anterior hippocampus and was based on the cortical thickness of the superior and middle temporal gyri; (5) posterior hippocampus, which was rated on the anteriormost slice through the cerebral aqueduct in parallel with the anterior measure and according to the width of the temporal horn and the height of the hippocampal formation; and finally (6) anterior parahippocampal gyrus; (7) medial bank of the collateral sulcus; (8) lateral bank of the collateral sulcus; and (9) occipitotemporal suclus, which were all rated on the slice showing

***Table 2.1. Structural MRI scan ratings for various brain regions (ordered from anterior to posterior), averaged across both hemispheres, for each individual patient.***

| | AntTemp | Amyg | PHG | MBCS | LBCS | MBOS | Ant-HC | LatTemp | PostHC |
|---|---|---|---|---|---|---|---|---|---|
| HC2 | 0 | 0.5 | 0.25 | 0.5 | 0.25 | 0 | 2* | 0 | 0.25 |
| HC3 | 0 | 0 | 0.75* | 0.75 | 0.5 | 0.25 | 1.25* | 0.5 | 1 |
| MTL1 | 2* | 2.25* | 1.5* | 1* | 1.25* | 2* | 1.75* | 1.75* | 1.75* |
| MTL2 | 2* | 3* | 2.5* | 2.75* | 2.5* | 2* | 3* | 1 | 2.75* |
| MTL3 | 1.75* | 2.75* | 2.75* | 2.75* | 2.5* | 2.5* | 2* | 0.5 | 2* |
| HC group | 0 | 0.250 | 0.500 | 0.625 | 0.375 | 0.125 | 1.625* | 0.250 | 0.625 |
| | (0) | (0.354) | (0.354) | (0.177) | (0.177) | (0.177) | (0.530) | (0.354) | (0.530) |
| MTL group | 1.917* | 2.667* | 2.250* | 2.167* | 2.083* | 2.167* | 2.25* | 1.083 | 2.167* |
| | (0.144) | (0.382) | (0.661) | (1.01) | (0.722) | (0.289) | (0.661) | (0.629) | (0.520) |
| Control group | 0.313 | 0.375 | 0.188 | 0.521 | 0.271 | 0.333 | 0.458 | 0.458 | 0.271 |
| | (0.284) | (0.483) | (0.188) | (0.291) | (0.310) | (0.289) | (0.382) | (0.411) | (0.361) |

***As a comparison, the mean ratings for the control group (with standard deviations) are also shown. An asterisk signifies significant atrophy ($p < 0.05$). A range of 0-3 (0-4 for the anterior hippocampus) was used where 0 = no visible damage and 3/4 = complete absence of area. The mean ratings and standard deviations of both patient groups and the control group are also shown. HC5 does not appear since her scan was not available for rating. Patient labels refer to those used in Lee et al (2005b) where applicable. HC: hippocampal; MTL: medial temporal lobe; AntTemp: anterior temporal cortex; Amyg: Amygdala; PHG: parahippocampal gyrus (corresponding to entorhinal cortex); MBCS: medial bank of collateral sulcus (corresponding to the transition between entorhinal and perirhinal cortex); LBCS: lateral bank of collateral sulcus (corresponding to perirhinal cortex); MBOS: medial bank of occipitotemporal sulcus (corresponding to the transition between perirhinal and isocortex); AntHC: anterior hippocampus; LatTemp: lateral temporal cortex (likely to correspond to TE); PostHC: posterior hippocampus.***

the collateral sulcus at its longest. Other than the anterior hippocampus, which was rated on a five point scale (normal=0, severe atrophy=4) based on Scheltens et al. (Scheltens et al., 1992), all regions were assessed using a four point scale (normal=0, severe atrophy=3), with ratings for each area averaged across both hemispheres.

Table 2.1 displays the ratings for each individual patient and the mean scores for each of the three subject groups (HC, MTL and control). A repeated measures ANOVA with a within-group factor of 'region' and a between-group factor of 'subject group' revealed a significant difference in scores across the 9 brain areas rated (Greenhouse-Geisser corrected $F_{(3.6, 50.7)} = 4.78$, $p < 0.01$). One-way ANOVAs confirmed a significant group difference on all brain areas (all $F_{(2,14)} > 15.4$, $p < 0.001$) other than the lateral temporal lobe measure which was not significant ($p > 0.1$). Post-hoc analyses comparing the HC group with their matched controls, on the regions in which there was a significant overall group difference, indicated significantly greater atrophy of the anterior hippocampus ($p < 0.01$) but no other significant differences. In contrast, the MTL group received significantly greater rating scores compared to the control group on all measures (all $p < 0.001$) for which the one-way ANOVAs revealed significant group differences.

In addition to this rating scale, regions of atrophy within the temporal lobe were delineated for the two patients from each group for whom appropriate scans were available using MRIcro (Rorden & Brett, 2000). The structural scans were first warped into Montreal Neurological Institute (MNI) space in SPM99 (Wellcome Department of Functional Neuroscience, London, UK) using a standard procedure for brain images with focal lesions (Brett, Leff, Rorden, & Ashburner, 2001). To do this, a mask was created in MRIcro for each of the subjects' lesions, by delineating regions of cerebral spinal fluid in the middle cranial fossae, including the inferior horn and choroidal fissure, up to a posterior limit of the end of the hippocampus. These masks were then used for cost function masked normalisation of each brain to a standard T1 MNI template. Following warping, the lesions of each patient were then redrawn, and finally overlaid onto an average brain T1 MNI template using MRIcro. Overlapping regions of damage within the temporal lobe are shown for each patient group in Figure 2.1. The results of this process were consistent with those of the rating scale. The region of overlapping damage across the two patients classified in the hippocampal group was focussed primarily in the hippocampus bilaterally. It should be noted, however,

that the possibility of damage to the parahippocampal gyrus, posterior to the region assessed by the rating scale, cannot be conclusively ruled out based on the present analyses. By contrast, the MTL patients had broader MTL damage encompassing the hippocampus and perirhinal cortex. Figure 2.1b shows an increased amount of cerebral spinal fluid in the region of the collateral sulcus and corresponding to the ventromedial aspect of the temporal pole, in line with recent descriptions of the perirhinal cortex (Davies et al., 2004; Insausti et al., 1998; Suzuki & Amaral, 1994).

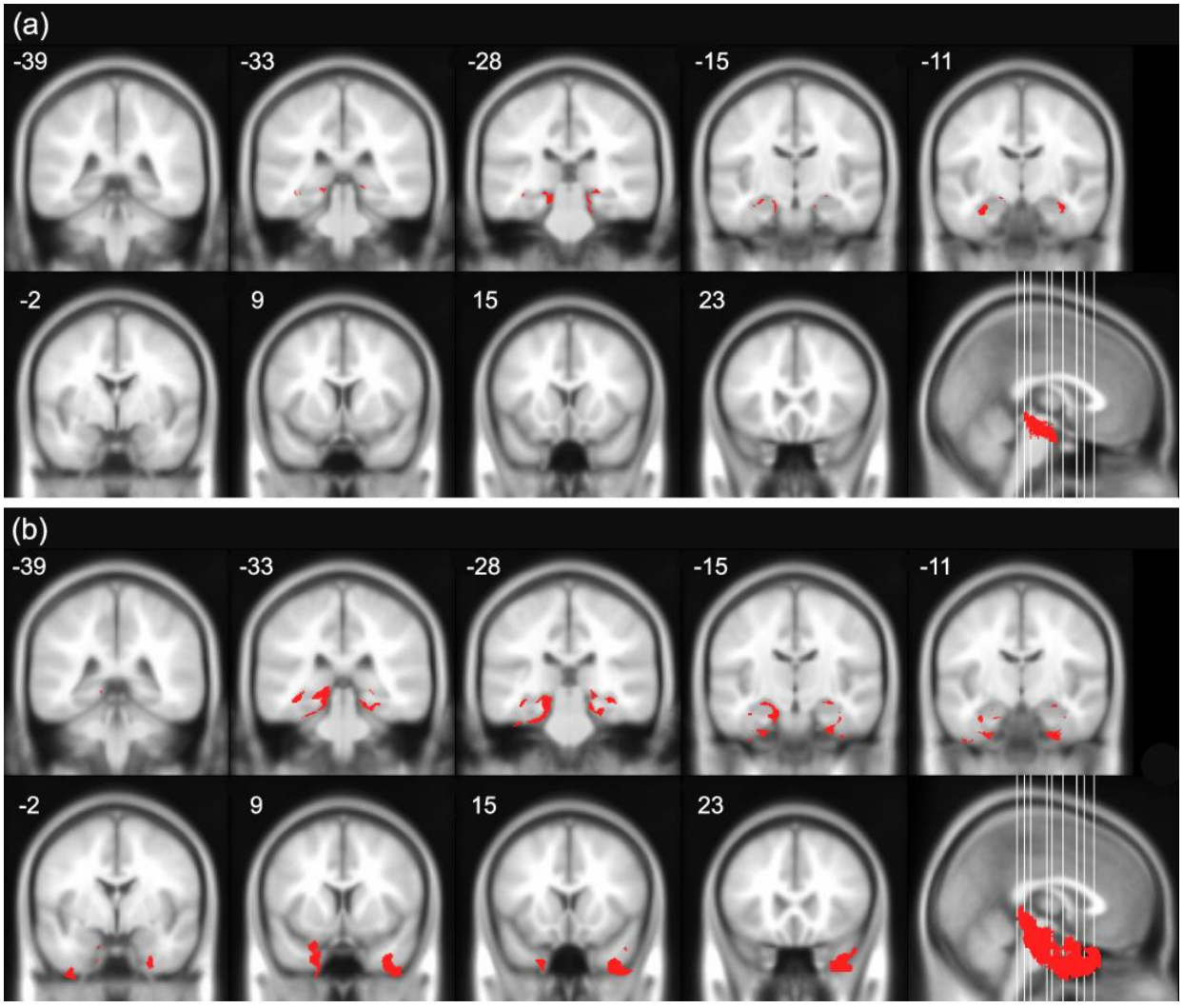


***Figure 2.1 Overlapping regions of atrophy within the temporal lobe are shown (in red) for (a) HC (n = 2) and (b) MTL (n = 2) patients with structural MRI scans, superimposed on a Montreal Neurological Institute average brain template.***

## *Neuropsychological Battery*

The cognitive abilities of the patients were assessed using a series of standardised neuropsychological tests, the results of which can be found in Table 2.2. Performance was evaluated by comparison with standard published norms where available. Both patient groups performed poorly on tests of recall (Logical Memory Stories 1 and 2, immediate and delayed recall; Rey Complex Figure delayed recall, Ostterrieth, 1944). Similarly, recognition memory, as assessed by both the Logical Memory Test and the words subtest of the Warrington Recognition Memory Test (Warrington, 1984), was impaired in both groups, with the exception of the patient HC2 who performed between the 10th and 25th percentile on the RMT words subtest. Scores on the face subtest of Warrington's RMT however, were of particular interest: whereas the MTL group was impaired, the HC group performed in the normal range. Visuoperceptual processing was within the normal range in both groups across all tasks (Benton Face Test, Benton, Hamsher, Varney, & Spreen, 1983; Visual Object Space Perception battery, Warrington & James, 1991; Rey Complex Figure copy, Ostterrieth, 1944). It should be noted, however, that these tasks are not sufficiently taxing to reveal the perceptual deficits of the type previously observed in these patients (Lee, Buckley et al., 2005; Lee, Bussey et al., 2005). Tests of semantic memory revealed mild impairments in the MTL group but not the HC group as measured by Category Comprehension; the Pyramids and Palm Trees Test (Howard & Patterson, 1992) and Naming. Both groups performed in the normal range on executive tasks (Wisconsin card sorting, Nelson, 1976; forwards and backwards digit span; Tower of London Test, Shallice, 1982; Raven's Coloured Progressive Matrices, Raven, 1962), with the exception of MTL3 who showed an impairment in backwards digit span.

***Table 2.2 The six patients' individual and group performance on a brief neuropsychological battery.***

| | HC5 | HC2 | HC3 | HC Mean | HC Mean % Score | MTL1 | MTL2 | MTL3 | MTL Mean | MTL Mean % Score |
|---|---|---|---|---|---|---|---|---|---|---|
| **Recall** | | | | | | | | | | |
| LM Immediate Recall (75) | 6 | 31 | 22 | 19.7 | 26.2 | 12 | 29 | 13 | 18.0 | 24.0 |
| LM Delayed Recall (50) | 0 | 24 | 4 | 9.3 | 18.7 | 3 | 0 | 4 | 2.3 | 4.7 |
| Rey Delayed Recall (36) | 1 | 18 | 3 | 7.3 | 20.4 | 7 | 0 | 4.5 | 3.8 | 10.6 |
| **Recognition** | | | | | | | | | | |
| LM Recognition (30) | 16 | 24 | 19 | 19.7 | 65.6 | 19 | 19 | 23 | 20.3 | 67.8 |
| WRMT – Words (50) | 37 | 42 | 33 | 37.3 | 74.7 | 19 | 31 | 31 | 27.0 | 54.0 |
| WRMT – Faces (50) | 42 | 48 | 44 | 44.7 | 89.3 | 32 | 32 | 30 | 31.3 | 62.7 |
| **Visuoperceptual** | | | | | | | | | | |
| Rey Copy (36) | 36 | 36 | 35 | 35.7 | 99.1 | 33 | 36 | 30.5 | 33.2 | 92.1 |
| VOSP (all sub-tests) | P | P | P | - | - | P | P | P | - | - |
| Benton Face Recognition (54) | 48 | 46 | 47 | 47.0 | 87.0 | 41 | 45 | 42 | 42.7 | 79.0 |
| **Semantic** | | | | | | | | | | |
| Picture Naming (64) | 62 | 62 | 64 | 62.7 | 97.9 | 28 | 55 | 46 | 43.0 | 67.2 |
| Category Comprehension (64) | 63 | 64 | 64 | 63.7 | 99.5 | 57 | 59 | 54 | 56.7 | 88.5 |
| Pyramid and Palmtrees (52) | 52 | 51 | 52 | 51.7 | 99.4 | 45 | 49 | 46 | 46.7 | 89.7 |
| **Executive** | | | | | | | | | | |
| WCST (categories, 6) | 6 | 6 | 6 | 6.0 | 100.0 | n.t. | 6 | 6 | 6.0 | 100.0 |
| Digit Span – Forwards | 5 | 6 | 6 | 5.7 | - | 7 | 8 | 6 | 7.0 | - |
| Digit Span – Backwards | 4 | 4 | 6 | 4.7 | - | 4 | 7 | 2 | 4.3 | - |
| TOL (correct solutions, 16) | 16 | 16 | 16 | 16.0 | 100.0 | 11 | 13 | n.t. | 12.0 | 75.0 |
| RCP (36) | 34 | 34 | 34 | 34.0 | 94.4 | 19 | 33 | 22 | 24.7 | 68.5 |

***Maximum scores are given in brackets where applicable. LM: Logical Memory; Rey: Rey Complex Figure; WRMT: Warrington Recognition Memory Test; VOSP: Visual Object and Space Perception Battery; WCST: Wisconsin Card Sorting Test; TOL: Tower of London; RCP: Raven's Coloured Matrices; n.t.: not tested.***

## *Behavioural Procedure*

The stimuli consisted of 256 photographs of faces and 256 photographs of scenes. The pictures were grouped into 64 sets of four for each stimulus type. Each set contained two similar faces or scenes, each shown from two different views. In the case of the faces, pairs were selected from the Facial Recognition Technology (Feret) Database (Phillips, Moon, Rizvi, & Rauss, 2000; Phillips, Wechsler, Huang, & Rauss, 1998) that were judged to look as similar as possible. For each subject, a frontal view, and a second view with the subject facing to their left by approximately 40° were used. In the case of the scenes, pairs of locations were found around Cambridge and London that shared the same general form but that differed in the shape and/or configuration of some features. These included pictures of both the inside and outside of buildings, as well as gardens and fields etc. Pictures from a range of angles were initially taken, and for each pair, two views were subsequently chosen. The difference in viewing angle between the two views ranged from approximately 30-90° across different sets, but was kept as similar as possible between pairs within each set.

Testing was conducted using an LCD touchscreen. Before testing began, subjects were given the opportunity to make themselves comfortable and to familiarise themselves with the touchscreen. A short practice block was administered prior to each encoding block to ensure subjects understood the instructions and to give them experience of the view manipulation.

There were two study blocks, one for each stimulus set. For each of these study blocks, subjects were required to view a series of 64 pictures on the touchscreen and indicate whether they found each picture pleasant or unpleasant by pressing the appropriate button on the screen. Each picture was presented for 5 seconds regardless of when the pleasant/unpleasant response was made. On trials where no response had been made within this time, subjects were shown a brief message asking them to try to respond more quickly on subsequent trials. Two test blocks, one same-view, and one different-view followed each study block, after a short delay (approximately 1 minute).

There were four test conditions, assigned to separate blocks: *same-view faces; different-view faces; same-view scenes* and *different-view scenes.* For each of these blocks, subjects were presented with a series of 32 matched pairs of stimuli, one of which they had seen at study, and one of which was new, presented side by side. They were instructed to indicate which

stimulus had been presented previously by touching that picture on the screen. The next pair was then presented. There was no time limit for making a response but subjects were encouraged not to spend too long and to "go with their gut feeling" if they were unsure. For the *same-view* test blocks, the target stimulus was shown from the same view as it was presented at study. For the *different-view* test blocks, the target stimulus was shown from a different view to that seen at study. In both cases, where applicable, the foil was presented from the same orientation as the target picture. Examples of a trial from each condition are shown in Figure 2.2.

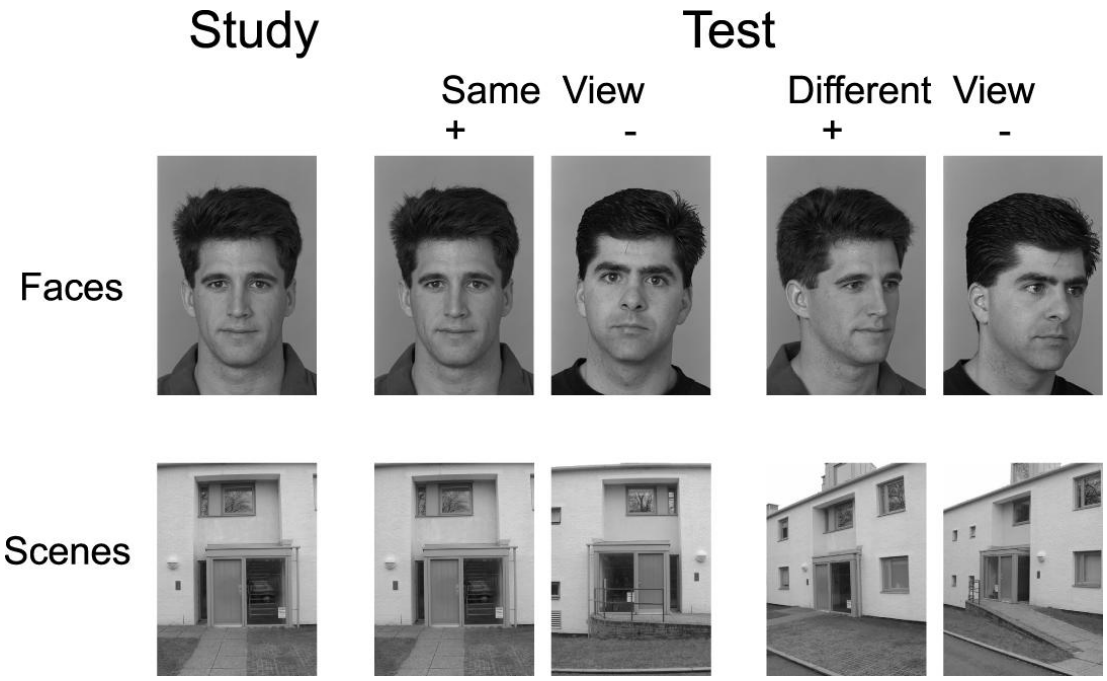


***Figure 2.2 Examples of one trial from each condition in the experiment. (+) Indicates correct stimulus; (−) indicates incorrect stimulus. NB. The same items appear in the same- and different-view conditions presented here for illustrative purposes only. All items in the experiment were trial unique and assigned to a single condition only.***

The assignment of stimuli to conditions and the presentation order of the two tasks (faces and scenes) were counterbalanced across subjects. Given that pilot studies showed that the different-view conditions were more difficult than the same-view conditions, subjects were tested on the different-view block before the same-view block in an attempt to better match performance.

### *Statistics*

A repeated measures analysis of variance (ANOVA) was conducted on all the performance

data1. Two within-subject factors each with two levels were included: "stimulus", with the levels face and scene, and "view" with the levels same and different. In addition, two between-subject factors each with two levels were included: "health", with the levels control and patient, and "lesion type" with the levels HC and MTL (used to classify both patients and their matched controls). As noted earlier, the two patient groups were not matched in terms of age or sex so direct comparisons of performance should not be made between the two groups of patients across the various tasks. The statistical design described enables us, however, to compare the two groups of patients with respect to their individual matched control groups, in other words, it enables us to contrast the relative levels of impairment between the two groups of patients. An interaction between "health" and "lesion" indicates that the level of impairment on a given condition or set of conditions differs between the two groups of patients. An interaction between "health", "lesion" and either "stimulus" and/or "view" indicates that the magnitude and/or direction of the difference in impairment between the two patient groups differs across the various conditions in the experiment. A four-way interaction was, in fact, observed and investigated in two ways. First, the data from the two sets of patients and matched controls were subjected to two separate 3-way ANOVAs in order to investigate whether the pattern of impairment differed across the various conditions within each patient group. Significant interactions between health and either "stimulus" and/or "view" indicated that the level of impairment differed between conditions; such interactions were examined further using independent-sample t-tests. Second, in order to directly compare the level of impairment between the two patient groups on each condition, a further 4 univariate ANOVAs were performed, each with the same two between subject factors "health" and "lesion". Since the predictions regarding the performance of the patients compared with their respective control groups were directional, all quoted p values are one-tailed.

## Results

The mean performance level of all control and patient groups can be found in Table 2.3. For illustration purposes, difference scores between each patient group and its corresponding control group can be found in Figure 2.3(a). Statistical analyses revealed a significant

[1] The use of parametric statistics was deemed appropriate since an analysis of the distribution of the residuals of the data revealed no outliers or departures from normality, and therefore the underlying assumptions of the general linear model were met.

"stimulus" x "view" x "health" x "lesion" interaction ($F_{(1,26)} = 4.12$; $p < 0.05$) indicating that the difference in performance between the two patient groups relative to their matched controls varied across the four conditions.

***Table 2.3 Mean % correct (with standard deviations) for each group on each of the four conditions (chance performance = 50%).***

| | HC Controls | HC Patients | MTL Controls | MTL Patients |
|---|---|---|---|---|
| **Same View Faces** | 92.7 (7.9) | 88.5 (6.5) | 89.8 (7.1) | 72.9* (1.8) |
| **Different View Faces** | 83.6 (8.5) | 81.3 (0.0) | 78.6 (8.8) | 53.1* (20.5) |
| **Same View Scenes** | 84.1 (11.9) | 61.5* (1.8) | 82.2 (7.5) | 52.1* (9.0) |
| **Different View Scenes** | 75.5 (9.7) | 60.4* (4.8) | 68.0 (10.4) | 55.2* (4.8) |

***An asterisk indicates significant impairment relative to the matched control group (p < 0.05). HC: hippocampal; MTL: medial temporal lobe.***

As described above, two separate 3-way ANOVAs were then performed, one for each set of patients plus their matched controls. In the HC group analysis, there was a significant 2-way interaction between "stimulus" and "health" ($F_{(1, 13)} = 21.18$; $p < 0.001$). This interaction reflects poorer performance in the HC group in the scene compared with the face conditions. T-tests revealed that whereas the HC group performed in the normal range on both face conditions (both $p > 0.22$), they were significantly impaired on both scene conditions (same-view: $t = 4.66$; $p < 0.001$; different-view: $t = 3.05$; $p < 0.01$). In the MTL group analysis, there was a significant 3-way interaction between "stimulus", "health" and "view" ($F_{(1, 13)} = 11.53$; $p < 0.01$), which is likely to be the result of floor effects. More importantly, T-tests revealed that the MTL group was significantly impaired on all four conditions compared to their control group (all $t > 2.0$, $p < 0.05$).

Further analyses were then performed on each condition in turn in order to contrast the level of impairment between the two patient groups on each condition. The analyses of both the *same-view* and *different-view faces* conditions revealed a significant "health" x "lesion" interaction (same-view: $F_{(1, 26)} = 3.66$; $p < 0.05$; different-view: $F_{(1, 26)} = 6.23$; $p < 0.01$) indicating that the MTL group were significantly more impaired than the HC group on both

face conditions. In the analyses of both scene conditions, no such interactions were observed ( both $p > 0.15$), indicating that the level of impairment did not significantly differ between the two groups on either of the scene conditions.

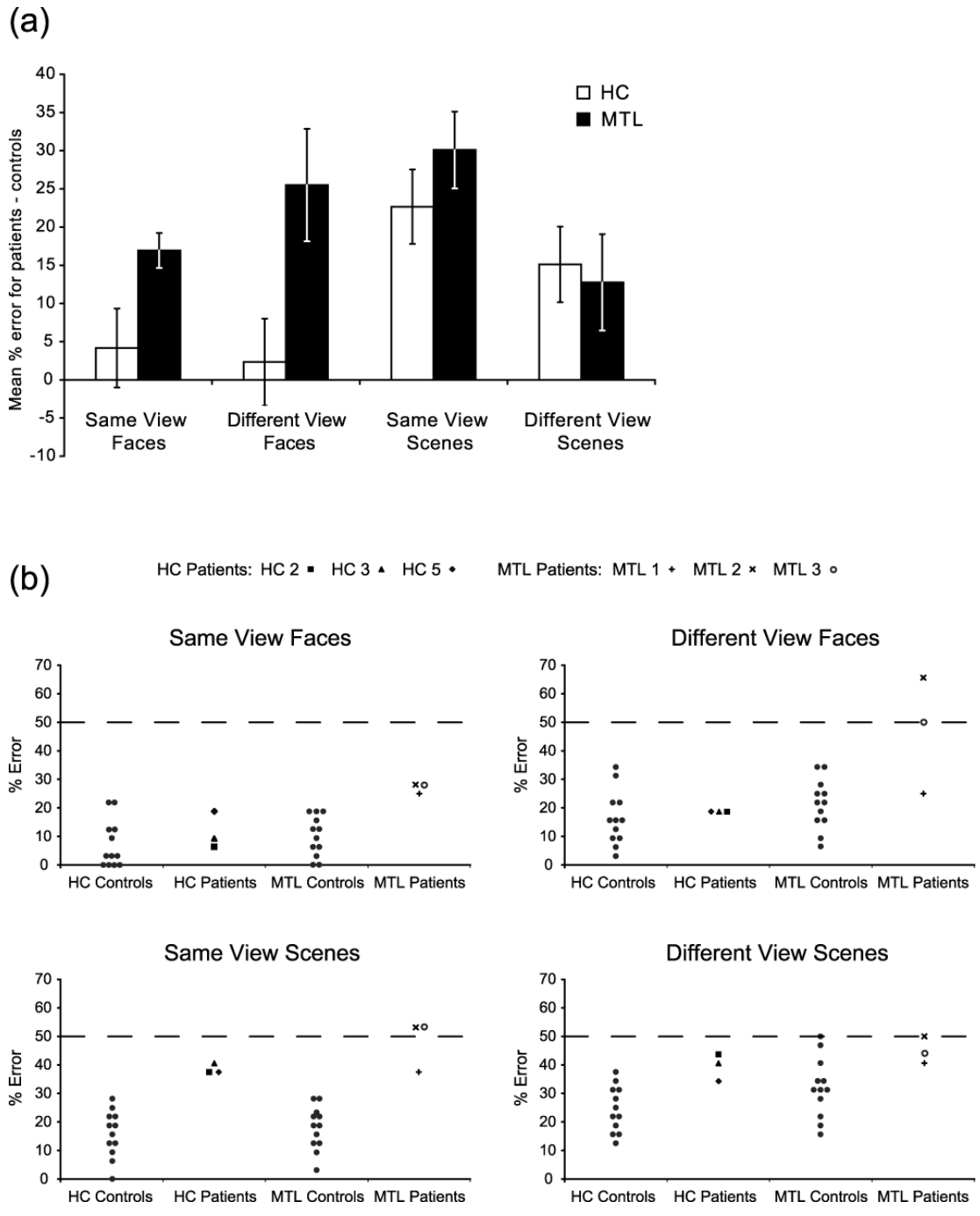


***Figure 2.3 Performance on the task illustrated as (a) mean % error (±S.E.) for each patient group minus its matched control group and (b) individual scores (errors) for each of the four conditions (chance performance = 50%).***

Individual scores for each subject are provided for each condition in Figure2.3 (b). Both groups are clearly impaired on the two scene conditions, as found in the analyses above, although floor effects limit the observable levels of impairment on the *different-view scenes* condition. One could argue that a slight ceiling effect in controls is masking a significant impairment in the HC group on the *same-view faces* condition. The same cannot be said of the *different-view faces* condition, however, since no controls performed without error, and scores were well distributed. In the MTL group, one patient scored within the control range on the *different-view faces* task, but in general, memory for faces and scenes in this group was impaired.

# Discussion

Contrary to most theoretical accounts of recognition memory, amnesic individuals with either selective hippocampal damage or more extensive injury that included perirhinal cortex showed distinct patterns of performance on a novel recognition memory test that contrasted faces and spatial scenes. Patients with broad MTL lesions were impaired on recognition memory for faces and scenes regardless of view. By contrast, cases with bilateral hippocampal damage performed within the normal range on both same- and different-view faces, but had poor memory for same- and different-view scenes. These results challenge current conceptualisations of recognition memory by suggesting that although both the hippocampus and perirhinal cortex are critical to recognition memory, the role played by these two regions appears to be limited to particular stimulus categories.

Consistent with the present findings, in a brief review of published cases, Aggleton and Shaw (1996) noted normal face recognition memory in some patients with focal hippocampal damage. A similar large scale study of recognition memory in patients with unilateral temporal lobe pathology revealed that damage in non-hippocampal MTL regions, but not the hippocampus, was a good predictor of impairment on the same test (Baxendale, 1997). In addition, three case studies have shown impaired recognition memory for topographical stimuli in the context of preserved recognition memory for unfamiliar faces following hippocampal damage (Bird et al., 2007; Carlesimo et al., 2001; Cipolotti et al., 2006), although no direct statistical comparisons between performance on these two stimulus categories were provided. The present study, therefore, which is the first to directly contrast recognition memory for faces and scenes in the same experimental paradigm, extends these

preliminary investigations and confirms that recognition memory is not a single process that can be easily mapped onto a single MTL structure.

A direct prediction from the view that the MTL functions as a single declarative memory system, is that all types of recognition memory should be deficient in amnesic individuals with MTL damage, regardless of their specific lesion site. Furthermore, a direct relationship should be evident between extent of lesion and degree of deficit (Gold et al., 2006). Although the two patient groups examined here differed by the additional involvement of non-hippocampal MTL structures (in the MTL group), and it is this extra lesion that is assumed to be causing the poor face recognition memory, it is important to note that the size of the hippocampal lesion was also predictably bigger in the MTL participants. It is possible, therefore, that this difference in lesion size explains the patterns seen in the two patients groups, in particular the normal performance of the HC group on the face compared to scene tasks, which were not matched for overall difficulty. Such an explanation may also seem intuitively appealing given our expertise, as humans, at recognising faces, which may render this skill more robust in the context of memory impairment.

There are a number of reasons this explanation seems unlikely to be underlying the effects observed. First, although the face conditions were easier than the scene conditions overall, a comparison of the *different-view face* and *same-view scene* conditions reveals that control performance was matched across these two conditions (see Table 2.3 and Figure 2.3(b)). Despite this, the HC group was significantly impaired on the *same-view scene* but not the *different-view face* condition, a pattern inconsistent with an explanation based on differences in difficulty across conditions. Second, there is increasing converging evidence of dissociations in performance along similar lines to those reported here from both human and animal studies, including observations of the reverse dissociation, in other words, impaired memory for faces in the context of preserved memory for scenes. For example, good scene recognition memory in the context of poor face recognition memory (albeit on recognition memory tasks that were not as well-matched) has been documented in patients with semantic dementia (Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998). This finding is particularly interesting as it suggests that not all patients with memory problems show an advantage for faces over scenes. The performance of patients with semantic dementia on the present task will be explored in Chapter 3 in an attempt to replicate these findings. Further support comes from double dissociations that have been demonstrated in both the imaging

and animal literature. In a recent functional neuroimaging study, Pihlajamaki et al. (2004) found activation in perirhinal cortex when a novel object was presented (see also Lee, Bandelow et al., 2006), whereas the posterior hippocampus was activated in response to novel *rearrangements* of familiar objects. Chapter 5 will attempt to replicate these findings in a modified version of the recognition memory paradigm used in the present chapter. In addition, rat lesion and early gene imaging studies have also highlighted critical roles for perirhinal cortex and hippocampus in object and spatial memory, respectively, including documenting double dissociations in performance (Aggleton & Brown, 2005; Winters et al., 2004). There is increasing convergent evidence, therefore, that the MTL, across species, may be functionally specialised according to spatial and object processing.

The impairment seen in both patient groups on same-view scenes seems, at first glance, inconsistent with some theoretical accounts of the hippocampus, such as the cognitive map theory (O'Keefe & Nadel, 1978), in which the hippocampus is involved in allocentric but not egocentric spatial processing. Using novel virtual reality environments, large deficits in recognition memory for shifted-view scenes has been documented in a patient with bilateral hippocampal damage (King et al., 2002). Strikingly, the patient's memory for same-view scenes was normal, except in conditions where participants were required to remember 10 or more items. The authors propose that greater list lengths may force an increasing reliance upon allocentric processing, and consequently hippocampal function. If true, individuals with hippocampal damage may perform more poorly on same-view scene recognition memory when larger sets of stimuli are presented. The data reported here are consistent with this hypothesis: patients showed poor memory for same-view scenes when asked to remember 64 consecutively presented images. Notably, however, the effects seen on recognition memory performance by increasing stimuli set size may not necessarily be due to increased allocentric processing. Such a manipulation is also likely to increase the need for discriminating between spatially ambiguous scenes, a process that may require increasing access to conjunctions of spatial features stored within the hippocampus (Buckley et al., 2004; Lee, Buckley et al., 2006).

Another potential explanation for the presence of impairments on both the same- and different-view scene conditions in the HC group is possible damage to the parahippocampal cortex, the presence of which could not be conclusively ruled out on the basis of the rating methods used in the present study. An examination of Figure 2.1, which shows the lesion

overlap for the two hippocampal patients for whom scans were available, reveals a small area of damage which may correspond to the parahippocampal cortex, particularly at y = 28. This structure is known to support processing of scenes, perhaps in a more view-invariant manner than the processing performed by the hippocampus (Burgess & O'Keefe, 2003; Epstein & Kanwisher, 1998). Notably, the portion of the lesion which could correspond to parahippocampal cortex is small relative to the amount of damage in the hippocampus, and also appears to be located more anteriorly than the region commonly found to be activated during scene processing, which is referred to as the parahippocampal place area (PPA, Epstein & Kanwisher, 1998). It seems unlikely, therefore, that damage to this region can completely explain the impairments on scene recognition memory observed in these patients. Moreover, some contribution of damage to the parahippocampal cortex to the deficits observed in the HC group does not invalidate the crucial finding of the present chapter, which is that subregions of the MTL can be dissociated according to stimulus category.

The finding that different structures in the MTL may be differentially involved in accurate recognition memory for complex scenes and faces does not necessarily invalidate dual-process theories of recognition memory, in which the hippocampus is thought to play a key role in recollective aspects of recognition, and perirhinal cortex in familiarity for previously studied items (irrespective of type, Aggleton & Brown, 1999; Brown & Aggleton, 2001). If it was found that recognition memory for scenes relies more on recollection, whereas recognition memory for faces relies more on familiarity, this could potentially explain why damage to the hippocampus had a disproportionate effect on the former relative to the latter stimulus category. Recent evidence, however, suggests that both recollection and familiarity for scenes, but not faces, relies on the hippocampus, as evidenced by the observation of intact recollection and familiarity for faces but not scenes in two focal hippocampal cases, VC and RH (Bird et al., 2007; Cipolotti et al., 2006). The division of labour proposed by dual-process models of MTL function may therefore not apply to visual memoranda such as those used in the present chapter. These issues will be explored further in Chapter 4 which examines levels of recollection and familiarity for faces and scenes in young and older healthy participants, and in Chapter 5 which explores the neural correlates of these processes within the MTL.

The profiles of performance seen in the recognition task across different-view scene and face conditions have been shown to extend to tasks that do not contain an overt long-term memory

demand. Lee Buckley et al. (2005) found that the hippocampal group were unable to discriminate between different-view virtual reality scenes, whereas the MTL group, with more extensive lesions that included perirhinal cortex, were additionally impaired on different-view oddity judgement for faces. In contrast to the current study, deficits in same-view conditions were not observed. This could have been due to the precise nature of the stimuli used in each study (for example Lee at al. utilised virtual reality rather than real world scenes), or a reflection of the increased demands of mnemonic versus perceptual tasks. Notably, in the arrays used for the same-view face conditions in the study by Lee et al., the target stimulus (odd-one-out) was always presented from a different orientation to the three images of the same face, e.g. on some trials, there were three views of one face looking straight ahead, and an image of a different face turned to one side. This meant that this condition could be solved by simply comparing the outline of each face, which may explain the lack of any impairment in the MTL group. Even without this extra complication, it is not entirely clear how the deficits in recognition memory relate to the perceptual impairments seen in the patients. One plausible account is that the memory deficits are a consequence of poor perception (Gaffan, 2001). More specifically, that the hippocampus and perirhinal cortex store conjunctions of spatial and object information, respectively, and that incomplete representations, present after brain damage, inevitably result in deficient and erroneous memory. Another possibility is that functionally distinct neuronal populations may underlie mnemonic and perceptual processing. For example, electrophysiological recordings from perirhinal cortex have revealed neurons that show decreased firing rates in response to previously seen objects, whereas other neurons show stimulus specific effects in the absence of familiarity- or repetition-related response changes (Xiang & Brown, 1998).

The current findings provide strong evidence against the view that all structures within the MTL play an essential role in recognition memory (Manns et al., 2003). What explanation can be given, then, for the observation of poor recognition memory in hippocampal patients in previous studies (Gold et al., 2006; Manns et al., 2003; Manns & Squire, 1999; Stark et al., 2002; Stark & Squire, 2003; Wais et al., 2006)? It seems most likely that contradictory findings across published articles stem from differences in the stimuli and procedures used in these experiments. For example, recognition of verbal material may well be hippocampally-dependent: not only do a number of studies report poor verbal recognition memory (Gold et al., 2006; Manns et al., 2003; Wais et al., 2006), but all the hippocampal patients reported here also present with deficient memory for words. Impairments have also been

demonstrated using nonverbal material but these tests typically involve memory for scenes and associations (Manns & Squire, 1999; Stark & Squire, 2003), incorporate a yes/no test format (Stark et al., 2002) and/or long delays between study and test (Manns et al., 2003) making these results incomparable to those reported here. When immediate forced choice recognition memory for faces has been tested (Reed & Squire, 1997), it is notable that hippocampal patients were not significantly impaired.

In summary, the experiment described in the present chapter represents the first systematic comparison of recognition memory for faces and spatial scenes following MTL lesions in humans. Whereas both hippocampal and non-hippocampal MTL lesions affect recognition memory, the present findings provide strong evidence to suggest that different MTL structures play unique roles in processing information about different stimulus categories (scenes and faces). These results complement recent neuropsychological studies of visual discrimination in amnesia, and taken together, these investigations suggest a radical revision to models of MTL function, taking into account the role played by the hippocampus and perirhinal cortex is space and object processing. These conclusions would be strengthened, however, if it could be shown that disproportionate damage to the perirhinal cortex, relative to the hippocampus, affects recognition memory for faces relative to scenes. This possibility was investigated in the following chapter in patients with the neurodegenerative disease semantic dementia.

# Chapter 3

# Recognition Memory for Faces and Scenes in Semantic Dementia

## Introduction

The findings of the previous chapter challenged the long-standing view that the MTL functions as a unitary declarative memory system (Manns et al., 2003; Squire et al., 2004; Squire & Zola-Morgan, 1991). Patients with damage thought to be restricted to the hippocampus showed a specific deficit in recognition memory for scenes but not faces, whereas damage which extended beyond the hippocampus, including the perirhinal cortex, impaired memory for both categories. This single dissociation is also difficult to accommodate in a popular alternative account of MTL function which proposes that the hippocampus is crucial for recollective-processes, whereas the perirhinal cortex supports familiarity (Aggleton & Brown, 1999; Brown & Aggleton, 2001; Eichenbaum et al., 2007). The findings of the previous chapter can only be explained by this theory if it can be shown that recognition memory for scenes relies more on recollection whereas recognition memory for faces can be adequately supported by familiarity. This possibility will be explored in Chapter 4.

The conclusions drawn in the previous chapter were limited for the following reasons: (i) the patient sample sizes were small which makes replication of the observed effects particularly desirable; and (ii) an explanation of the data in terms of the combined effects of lesion size and difficulty cannot be definitively ruled out. The patient group with the smaller lesion size (the HC group) were impaired on the stimulus category which the control group found most difficult (scenes) but not on the easier stimulus category (faces). Larger MTL lesions, however, impaired both categories. An interesting question, therefore, is whether an alternative pattern of damage to the MTL might produce the reverse pattern of performance to that found in the focal hippocampal cases, in other words, impaired face recognition memory combined with intact spatial recognition memory. Such a double dissociation in MTL function would challenge an account based on lesion size and would instead provide support for models which propose specialisation of subregions of the MTL according to stimulus category (Buckley et al., 2004; Lee, Barense et al., 2005; Murray et al., 2007). These issues are explored in the current chapter which examines the performance of patients with semantic dementia on the recognition memory test for faces and scenes described in the

previous chapter.

## *Semantic Dementia*

The term semantic dementia (SD) refers to the temporal lobe variant of fronto-temporal dementia and was coined to capture the selective and progressive loss of conceptual knowledge observed in these patients, whilst other cognitive domains such as phonology, syntax, visuospatial abilities and non-verbal episodic memory (at least for some stimulus categories) remain relatively intact (Hodges & Patterson, 2007; Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989; Warrington, 1975). Early studies revealed profound anomia and progressive loss of comprehension, not only of words (Warrington, 1975) but also of objects, people and concepts (Hodges et al., 1992; Snowden et al., 1989). Subsequent studies have confirmed the cross-modal nature of the breakdown of semantic knowledge, with impairments being observed on a wide range of tasks, regardless of modality, including many which are exclusively non-verbal in nature. For example, SD patients perform poorly when asked to match spoken words or environmental sounds to pictures (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000); to sort words or pictures into categories (Rogers, Lambon Ralph et al., 2004); to demonstrate the use of everyday objects (Hodges, Bozeat, Lambon Ralph, Patterson, & Spatt, 2000); or to choose the appropriate colour with which to fill in line drawings of objects (Rogers, Patterson, & Graham, 2007).

This pervasive loss of conceptual knowledge across all modalities is thought to be the result of damage to a unitary semantic network (Patterson et al., 2006; Rogers, Lambon Ralph et al., 2004), which provides links between unimodal representations of perceptual features and verbal concepts stored in disparate cortical regions. For example, the concept of a dog is represented by the co-joint activation of disparate cortical regions which code the visual (e.g. "has eyes"), auditory (e.g. barks), tactile and olfactory attributes and verbal descriptors of dogs, as co-ordinated by the semantic network. In early stages of the disease, infrequent and uncommon concepts are the most affected, whereas broader concepts remain intact (Patterson et al., 2006; Rogers, Lambon Ralph et al., 2004). This causes a tendency to produce over-generalised and over-regularised responses, for example super-ordinate or highly familiar names are often given for infrequent exemplars on semantic tests such as naming (e.g. animal or dog instead of horse, Hodges, Graham, & Patterson, 1995; Warrington, 1975). A recent

study revealed similar patterns of errors on tasks which are not generally considered to involve the semantic system (Patterson et al., 2006). In tests involving production (as opposed to forced-choice tasks), such as reading aloud and delayed copy drawing, patients tended to neglect distinguishing features of unusual items and produced more "regular" responses. For example, when asked to reproduce a picture of a duck following a delay of a few seconds, patients with SD sometimes include four legs in their picture (see also Bozeat et al., 2003), despite having produced an accurate picture when copying without a delay. In forced-choice paradigms, such as lexical decision and object decision, in low frequency irregular conditions, patients were more likely to select non-real items which conformed to the usual pattern for items of their class, in preference to real items which were atypical in structure; for example they would accept kackey over khaki since the former has a more typical orthographic structure (see also Rogers, Ralph, Hodges, & Patterson, 2004). Across all the tasks employed, there was a frequency-by-typicality interaction, such that performance was most impaired on items which had low frequency and were also atypical compared to other exemplars in their category. Patterson et al (2006) propose that these errors can all be understood as being the result of the impact of a degraded semantic network on perceptual or lexical representations, with particular consequences for atypical items.

Structural imaging studies examining the pattern of tissue loss in SD have consistently identified highly circumscribed atrophy (Chan et al., 2001; Davies et al., 2004; Galton, Patterson et al., 2001; Mummery et al., 2000; Noppeney et al., 2007; Rosen et al., 2002) and hypometabolism (Diehl et al., 2004; Nestor, Fryer, & Hodges, 2006) of the anterior temporal lobes. The extent of damage to this region has been shown to correlate with the degree of semantic impairment in patients with SD (Davies et al., 2004; Galton, Patterson et al., 2001; Mummery et al., 2000; Williams, Nestor, & Hodges, 2005) and as a result, this region is considered the most likely location of the semantic network described above (Patterson et al., 2006; Rogers, Lambon Ralph et al., 2004). The pattern of damage is normally asymmetrical, with greater atrophy observed in the left hemisphere in most cases, and a strong antero-posterior gradient such that anterior regions are most affected (Chan et al., 2001; Davies et al., 2004; Galton, Patterson et al., 2001; Mummery et al., 2000; Noppeney et al., 2007; Rosen et al., 2002). Of particular interest here is the extent to which this damage involves MTL structures. Two recent studies highlighted atrophy to the perirhinal cortex and neighbouring anterior entorhinal and temporopolar cortices (parts of which are often considered to be an

extension of the perirhinal cortex, Insausti et al., 1998) in patients with SD, relative to those with Alzheimer's disease and controls (Davies et al., 2004; Lee, Buckley et al., 2006). Furthermore, Nestor and colleagues (2006) observed that the full extent of the perirhinal cortex was contained within an area of metabolic underfunctioning in patients with SD. Damage is also frequently observed in the amygdala and/or anterior hippocampus (Chan et al., 2001; Davies et al., 2004; Galton, Patterson et al., 2001; Lee, Buckley et al., 2006; Noppeney et al., 2007; Rosen et al., 2002).

## *Recognition memory in SD*

Despite the devastating loss of semantic knowledge, and the well-established involvement of MTL structures in the disease pathology, many aspects of episodic memory in patients with SD remain remarkably normal. Intact recognition memory has been reported for a variety of visual stimuli, including line drawings and colour pictures of animals and objects (Graham, Becker, & Hodges, 1997; Graham, Simons, Pratt, Patterson, & Hodges, 2000; Simons, Graham, & Hodges, 2002); as well as paintings (Diesfeldt, 1992; Warrington, 1975), except in the most severe cases. This is provided, however, that target stimuli remain perceptually identical between study and test. For example, Graham et al. (2000) tested eight patients with SD on a 3-alternative forced-choice recognition memory test involving coloured pictures of objects and animals. There were two retrieval conditions: in one condition, target items were unaltered between study and test; in the other condition, target items at test depicted a different angle or alternative exemplar of the items depicted at study (e.g., at study, participants viewed a round-dial phone which was switched to a push button phone at test). Performance in the former, perceptually identical condition was within the normal range. Performance in the latter condition, however, was impaired. The authors suggested that whereas the perceptually identical condition could be performed on the basis of perceptual representations, which were presumed to be intact in the patients, performance in the condition involving perceptually different targets relied more on conceptual knowledge about the objects, and hence was impaired in SD.

In contrast to the above findings, impaired recognition memory for faces has frequently been reported in SD (Lee, Buckley et al., 2006; Lee et al., 2007; Simons, Graham, Galton, Patterson, & Hodges, 2001; S. A. Thompson et al., 2004; Cipolotti & Maguire, 2003; Evans, Heggs, Antoun, & Hodges, 1995; Maguire & Cipolotti, 1998; Scahill, Hodges, & Graham,

2005; Warrington, 1975). In several cases, this impairment has been observed together with a relative sparing of recognition memory for topographical stimuli in the same patients (Cipolotti & Maguire, 2003; Evans et al., 1995; Lee, Buckley et al., 2006; Maguire & Cipolotti, 1998). For example, Cipolotti and Maguire (2003) recently reported a single case study of an SD patient, OI, who showed the classic pattern of anterior temporal atrophy, which was more pronounced in the left hemisphere. When tested on a combination of standard and novel experimental tests of recognition memory, OI exhibited a striking dissociation, with impaired recognition memory for unfamiliar faces (from the Warrington RMT, and both the short and the easy Camden RMTs), motorbikes, dogs and cat faces, combined with preserved recognition memory for buildings, landscapes and leaves. In addition, a similar dissociation has also been reported in SD on performance of the four-choice face and scene oddity tasks described in the previous chapter. In this case, Lee Buckley et al. (2006) reported a selective impairment on the face but not the scene conditions in patients with SD, a pattern which mirrored their performance on standard tests of recognition memory. As discussed previously, these tasks are designed to tax perceptual rather than mnemonic processes; how these impairments relate to memory is therefore unclear.

The studies described above suggest that SD may indeed produce the reverse pattern of performance to that of the HC group on the recognition memory task described in the previous chapter, i.e. impaired recognition memory for faces but not scenes. This outcome is far from certain, however, for the following reasons. First, the majority of the studies described above were not specifically designed to directly contrast performance on these two stimulus categories. As a result, the procedures used were not always well matched (e.g. the standard RMT for faces involves black and white stimuli, whereas the topographical scene test is given in colour). Furthermore, direct statistical comparisons between performance on the two categories relative to controls have not been reported. Second, the majority of the evidence for this dissociation comes from single-case studies and so replication in a larger group of patients would help to establish the reliability of the dissociation.

### *Effects of laterality and disease progression*

To summarise the findings discussed above, single case studies show that SD can result in impairments in recognition memory for faces combined with intact recognition memory for

objects (provided they are perceptually unaltered between study and test) and topographical stimuli, such as scenes. There are, however, reports of some exceptions to this general pattern. Two inter-related factors which appear to influence performance are disease progression and laterality. A common method used to investigate the effects of laterality in SD is to divide patients into two, or sometimes three groups, according to whether atrophy is predominantly left-lateralised, right-lateralised or bilateral. Three studies which investigated the effect of laterality on face recognition memory used this technique and revealed intact performance in patients with predominantly left-lateralised damage, whereas bilateral or right-lateralised damage was consistently associated with impaired performance (Scahill et al., 2005; Simons et al., 2001; S. A. Thompson et al., 2004). These data suggest, therefore, that it is damage to the right rather than the left temporal lobe which causes face recognition memory impairments.

This method of dividing patients may produce misleading results, however, since left-dominant damage does not imply an intact right temporal lobe or vice-versa. In fact, a patient with predominantly left-lateralised atrophy who is at a more advanced stage of disease progression could potentially have more damage to the right temporal lobe than a patient with predominantly right-lateralised pathology, who is at an earlier stage. This is because atrophy is likely to spread to the non-dominant hemisphere at later stages of the disease (Brambati et al., 2007; Whitwell, Anderson, Scahill, Rossor, & Fox, 2004). This may explain why two single cases were impaired on face but not topographical recognition memory despite being reported as having predominantly left-lateralised atrophy (Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998). A more valid way to measure the relative effects of damage to each hemisphere is to correlate performance with the extent of damage to each hemisphere across all patients, regardless of which hemisphere is dominant in each case. This kind of analysis was performed by Simons et al. (2001), who measured the degree of correlation between performance on the face sub-test of Warrington's (1984) RMT and the extent of damage to the left and right temporal lobes (using the average of ratings for the hippocampus and the parahippocampal gyrus, with the latter region including the perirhinal cortex). The analysis revealed a highly significant correlation between performance and the extent of damage in the right hemisphere, but not the left. Further analyses revealed a significant correlation between performance and extent of damage to both the right hippocampus and the right parahippocampal gyrus, although the latter region had significantly greater predictive

power than the former. This provides more convincing evidence that damage to the right, but not necessarily the left temporal lobe, perhaps in particular the parahippocampal gyrus, is the cause of impaired recognition memory for faces in SD. This is in keeping with the established view of a dominance for processing of faces in the right hemisphere which is supported by investigations of patients with prosopagnosia (e.g. De Renzi, 1986; Landis, Cummings, & Christen, 1986); face processing using a divided visual field (Hillger & Koenig, 1991); the effects of early hemispheric visual deprivation on the development of face processing (Le Grand, Mondloch, Maurer, & Brent, 2003) and functional neuroimaging studies (e.g. Schiltz & Rossion, 2006).

The first aim of the current experiment was to replicate the dissociation observed in previous studies between impaired face and intact scene recognition memory in a group of patients with SD. Since SD is known to affect MTL regions, this result, together with the findings of Chapter 2 would provide evidence of a double dissociation in MTL contributions to recognition memory for faces and scenes. The experimental design was identical to that described in the previous chapter and therefore, unlike previous studies which have examined stimulus-specific recognition memory in SD, enabled direct comparison of performance across well-matched face and scene conditions. The second aim was to investigate the extent to which performance on the task correlated with the extent of damage to patients' left and right temporal lobes. These analyses provided insights into both stimulus-specific laterality of function in the temporal lobes as well as the relationship between disease progression and recognition memory performance. On the basis of previous studies, it was predicted that performance on the face conditions would correlate with the right but not the left temporal lobe measure. A novel aspect of the current experiment was investigation of the extent to which damage in the left and right temporal lobes correlated with performance on recognition memory for scenes, and how this compared with the pattern observed for faces.

# Materials and Methods

## *Participants*

Ten patients diagnosed with SD (age = 63yrs; education = 12.4yrs; all male) participated in this experiment. For the experimental tests, ten healthy subjects (age = 64.9yrs; education = 12.4yrs; all male) were age, education and sex-matched to the patients (all $p > 0.5$).

The patients presented through the Memory Clinic, Addenbrooke's Hospital, Cambridge, UK and have been assessed longitudinally on an extensive neuropsychological battery, the results of which were used by a senior neurologist to make a diagnosis. All patients fulfilled the Lund-Manchester consensus criteria for frontotemporal lobar degeneration (Neary et al., 1998): impaired receptive and expressive content-word vocabulary and impoverished semantic knowledge, with relative preservation of nonverbal reasoning, visuospatial abilities, phonology, syntax and day-to-day memory (see below for scores on standard neuropsychological tests).

## *Scan rating method*

Unfortunately, one patient was unable to undergo brain scanning due to the presence of a cardiac pacemaker. Structural magnetic resonance imaging (MRI) scans for the remaining nine patients were assessed by a senior neurologist using ImageJ software. In order to analyse the two hemispheres of each patient independently, one copy of each scan was reflected across the y-z plane (i.e. so that the left hemisphere appeared on the right and vice-versa), with a second copy being viewed in its original orientation. The right-hand side of each image was then discarded which effectively created a set of 18 hemispheres for assessment. These 18 images were ranked (non-parametrically) from most severe (1) to least severe (18) for overall temporal lobe atrophy. The neurologist was blind to the identity of each scan and the hemisphere from which each image was derived.

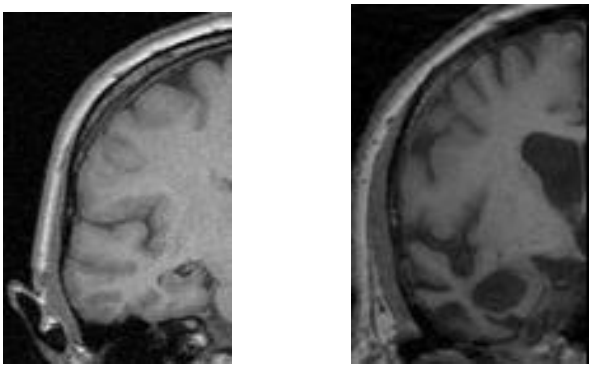

***Figure 3.1 Illustrations of the highest (left) and lowest ranked patient scans at the level of the amygdala.***

Potential sources of error come from between-subject qualitative differences in atrophy patterns and gyral anatomy. Nevertheless, there was a large range of atrophy across the patient group, as indicated in Figure 3.1, which illustrates the highest and lowest ranked images. The results of the rankings can be found in Table 3.1. It should be noted that in

some cases, the degree of atrophy across two or more images was indistinguishable, so in these cases, the same rank was given to each image. Testing sessions were all carried out within 10 months following the scanning session (mean = 6 months).

All participants gave informed consent before undertaking the study. This investigation received ethical approval from the Cambridgeshire Health Authority Local Research Ethics Committees (UK).

## *Neuropsychological Battery*

The cognitive abilities of the patients were assessed using a series of standardised neuropsychological tests, the results of which were compared with published normative data (Table 3.1). General cognitive ability as assessed by performance on the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) was relatively high, ranging from mild impairment to performance within the normal range. Semantic memory was assessed using four standardised tests: (i) category fluency, in which the participant must produce as many exemplars as possible from a given category in one minute, in this case animals; (ii) naming of 64 line drawings; (iii) category comprehension in which participants select which of ten pictures from a given category matches a spoken word; and (iv) the Camel and Cactus test (Bozeat et al., 2000), in which participants are asked which of four same-category items has an associative relationship with a fifth image; for example, when presented with a camel the subject should select the cactus rather than the tree, sunflower or rose. Unsurprisingly, the patients were impaired across all four semantic tasks. Performance on tests of visuoperceptual ability (Visual and Object Space Perception battery, Warrington & James, 1991; and Rey figure copy); and working memory (digit span) was relatively intact. Performance on tests of recall (immediate and delayed recall of the Rey complex figure, Ostterrieth, 1944) was mixed, however, with patients BH, GH, JM and AN obtaining low scores.

***Table 3.1 Background neuropsychology and temporal lobe ranks for the ten patients.***

| | AB | BC | JC | DG | BH | GH | MJ | JM | AN | PS | Patients Mean | Controls Mean (Std Dev) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MMSE (30) | 25 | 29 | nt | 23 | 25 | 29 | 29 | 23 | 22 | 28 | 25.9 | 28.8 (0.5) |
| **Semantic** | | | | | | | | | | | | |
| Picture Naming (64) | 23 | 47 | 26 | 20 | 21 | 42 | 36 | 19 | 15 | 35 | 28.4 | 62.3 (1.6) |
| Category Comprehension (64) | 38 | 61 | 56 | 45 | 40 | 55 | 49 | 54 | 28 | 58 | 48.4 | 63.7 (0.5) |
| Camel and Cactus (64) | 38 | 48 | 52 | 51 | nt | 42 | 32 | 52 | 32 | 50 | 44.1 | 56.9 (7.27) |
| Category fluency – animals § | 8 | 13 | 5 | 5 | 3 | 11 | 4 | 3 | 6 | 8 | 6.6 | 17.5 (3.9) |
| **Recall** | | | | | | | | | | | | |
| Rey immediate recall (36) | 22.5 | 15 | 20.5 | 25 | 7.5 | 8 | 18.5 | 5 | 9 | 22 | 15.3 | 18.3 (5.2) |
| Rey delayed recall (36) § | nt | nt | 18 | 16.5 | 8 | nt | 15.5 | 4.5 | nt | 21 | 13.9 | 15.3 (7.4) |
| **Visuoperceptual** | | | | | | | | | | | | |
| Rey Copy (36) | 36 | 32 | nt | 35 | 34 | 36 | 34 | 36 | 36 | 34 | 34.8 | 34.0 (2.9) |
| VOSP - dot count (10) | 10 | 10 | 9 | 10 | nt | 10 | 10 | 10 | 10 | 10 | 9.9 | 9.9 (0.3) |
| VOSP - position (20) | 20 | 20 | 20 | 20 | nt | 20 | 20 | 20 | 20 | 20 | 20 | 19.8 (0.6) |
| **Working memory** | | | | | | | | | | | | |
| Digit Span – Forwards | 5 | 8 | 7 | 7 | 7 | 5 | 7 | 6 | 6 | nt | 6.4 | 6.8 (0.9) |
| Digit Span – Backwards | 4 | 3 | 4 | 4 | 5 | 4 | 6 | 3 | 5 | nt | 4.2 | 4.7 (1.2) |
| **Temporal lobe ranks** | | | | | | | | | | | | |
| Left | 1.5 | 11.5 | 11.5 | 4 | - | 7.5 | 16 | 14 | 1.5 | 11.5 | - | - |
| Right | 9 | 4 | 18 | 15 | - | 7.5 | 4 | 17 | 11.5 | 6 | - | - |

***Maximum scores are given in brackets where applicable. MMSE: Mini-mental state examination; VOSP: Visual Object and Space Perception Battery; nt: not tested.***

***Controls from Bozeat et al. (2000), n = 31; age= 68.5 yrs, education= 11.2 yrs; except § controls from Hodges and Patterson(1995) n = 24; age =69.7yrs; education = 10.7yrs***

## *Behavioural Procedure*

The behavioural procedure was identical to that described in Chapter 2.

## *Statistics*

Statistical analyses were designed to address the two aims of the chapter. The first group of analyses investigated whether patients with SD were disproportionately impaired on recognition memory for faces compared with scenes. Analyses were performed both at the group level and the level of individual patients, since variability amongst the patients was high, as would be expected in patients with a progressive disease such as SD. For the group data, a repeated measures ANOVA was conducted in the same manner as described for Experiment 1 in the previous chapter, with the exclusion of the factor "lesion", since there was only a single patient group and a matched control group. The factors "stimulus", "view" and "health" remained, each with two levels. Observed interactions involving the factor "health" were examined further using independent-sample *t*-tests, and separate ANOVAs for each subject group, including the factors "stimulus" and "view".

Many researchers rely on transforming patient data using the *z*-distribution to establish the presence of impairments and dissociations in single patients relative to controls. These methods treat measures derived from the control sample as parameters, rather than sample statistics, which is not appropriate when sample sizes are small. The result is an increase in the Type I error rate, ie. patients' scores are more likely to be erroneously categorised as abnormal. Alternative methods developed by Crawford and colleagues[2], which were specifically designed to overcome these problems, were therefore used in the current chapter when making comparisons between individual patients and the control sample. Rather that relying on *z*-scores, these methods involve modified *t*-tests which produce much better control of the error rate. Crawford & Howell's (1998) modified *t*-test was used to test for significant impairments on a given task in individual patients, and dissociations were tested for using the results of these individual *t*-tests, together with Crawford and Garthwaite's (2005) Revised Standardised Difference Test (RSDT). Monte Carlo simulations have revealed that these methods provide good control of the Type I error rate over a range of control sample sizes and levels of correlation between conditions, and are also robust to

[2] Software to run Crawford and Howell's (1998) test and the RSDT can be downloaded from the following website: http://www.abdn.ac.uk/~psy086/dept/SingleCaseMethodsComputerPrograms.HTM

departures from normality in the distribution of the data (Crawford & Garthwaite, 2005).

Claims of a dissociation between the level of impairment of a patient on two tasks are frequently made on the basis of the presence of a significant impairment on one task but not the other. This method is flawed, however, since this pattern of performance may reflect a small difference in the extent of impairment on each task, with performance on one task just happening to fall within the normal range, whereas performance on the other task does not. Similarly, although a patient may be significantly impaired on two tasks, the degree of impairment may differ significantly between the two tasks. Crawford and Garthwaite (2005) have therefore extended the criteria, originally proposed by Shallice (1988), for identifying *classical* and *strong* dissociations, which can be tested using the RSDT. The requirements for a classical dissociation are (i) impaired performance ($p < 0.05$) on condition X, but not condition Y, as measured using Crawford and Howell's modified *t*-test (1998); and, (ii) a significant difference between the size of the standardised difference in performance of the patient on task X versus task Y compared to the size of this difference found in controls, measured using the RSDT. The requirements for a strong dissociation are equivalent to the requirements for a classical dissociation, with the exception that performance on both tasks is significantly impaired in the patient.

Since the previous, group-level analysis revealed an interaction between "health" and "view", modified *t*-tests and RSDT analyses were performed without collapsing across "view". The performance of each individual on each condition was subjected to a modified *t*-test to establish whether an impairment relative to controls was present. The RSDT was then used to test for significant dissociations between two pairs of conditions: (i) *same-view faces* and *same-view scenes*; (ii) *different-view faces* and *different-view scenes*.

The second aim of the experiment was to investigate the effects of disease progression and laterality on performance. Multiple linear regression analyses were therefore performed to explore the relationship between performance on each condition and the degree of atrophy in the left and right temporal lobes. More specifically, performance of each patient in each of the four conditions was regressed against (i) the temporal lobe rank for the left hemisphere; (ii) the temporal lobe rank for the right hemisphere; and (iii) age. These regressors, together with a constant term, were added for each condition separately, plus a grand mean across all

the data. Thus, there were 4 conditions x 9 subjects = 36 datapoints, and 4 conditions x 4 regressors (left, right, age, condition mean) + 1 grand mean = 17 regressors (with 16 degrees of freedom in the model). Note that since a high rank corresponded to a larger amount of remaining tissue and performance was measured as % correct, positive correlations were predicted between temporal lobe ranks and performance.

Two further multiple linear regression analyses were then performed on two variables of interest: performance on the face conditions and performance on the scene conditions, collapsed across view. The lack of any difference in the regression slopes for same- and different-views in the previous analysis justified collapsing across view. There was also no difference in the regression slopes for faces versus scenes, but it was of particular theoretical interest to explore the two conditions separately. In each case, performance of each patient on the condition of interest (i.e. faces or scenes, collapsed across view) was regressed against (i) the temporal lobe rank for the left hemisphere; (ii) the temporal lobe rank for the right hemisphere; and (iii) age. The model also incorporated a constant term (= mean performance). Thus, there were 4 regressors (left, right, age, mean). Since these analyses revealed a significant relationship between the right, but not the left hemisphere ranks, and performance, the two models were used to calculate partial correlations between performance on each condition, and the right hemisphere rank, corrected for the left hemisphere rank and age.

# Results

The mean performance level of the controls and all ten patients can be found in Table 3.2. For illustration purposes, difference scores between the patient and control groups can be found in Figure 3.2(a).

## *Comparisons between performance of patients and controls*

Statistical analyses contrasting control performance with that of the complete patient group revealed significant interactions between "stimulus" and "health" ($F_{(1, 18)} = 24.72$; $p < 0.001$) and between "view" and "health" ($F_{(1, 18)} = 8.92$; $p < 0.01$). These interactions were due to a significantly larger impairment in the patients on the face compared with the scene conditions, and also on the same-view compared with the different-view conditions. Both effects are made evident by examination of Figure 3.2(a). The latter interaction, between

"view" and "health" was not expected. One possibility is that it results from floor effects, perhaps particularly on the *different-view scene* condition. A series of single-sample *t*-tests revealed, however, that the performance of both groups was significantly better than chance across all conditions. Furthermore, the distributions of scores in each group on the *different-view scene* condition, as illustrated in Figure 3.2(b), indicate that performance was above floor in both groups. *T*-tests comparing performance in the two groups revealed that the patients were impaired on all conditions (all $t > 3.8$, $p < 0.001$) except for *different-view scenes* ($p > 0.3$).

***Table 3.2 Mean % correct (with standard deviations) for each group on each of the four conditions (chance performance = 50%).***

| | **Controls** | **Patients** |
|---|---|---|
| **Same View Faces** | 88.1 (5.9) | 61.9* (12.7) |
| **Different View Faces** | 80.3 (9.9) | 60.3* (9.2) |
| **Same View Scenes** | 82.5 (6.3) | 69.4* (9.1) |
| **Different View Scenes** | 65.6 (6.1) | 63.4 (10.0) |

***An asterisk indicates significant impairment relative to the matched control group (p < 0.05).***

The interaction between health and view was explored further by performing separate analyses on each group of participants in turn. The analysis of control performance revealed a significant "stimulus" x "view" interaction ($F_{(1, 9)} = 7.81$; $p < 0.05$). Paired-samples *t*-tests revealed a significant effect of view on both the face and scene conditions (faces: $t_{(9)} = 3.16$; $p < 0.05$; scenes: $t_{(9)} = 7.69$; $p < 0.001$). In contrast, in the analysis of the patient data, neither the main effect of "view" nor the interaction between "view" and "stimulus" were significant (both $p > 0.1$). This analysis did reveal, however, a main effect of stimulus ($F_{(1, 9)} = 6.92$; $p < 0.05$). These effects are made clear by examination of Table 3.2 and Figure 3.2(b). Indeed, as can be seen in the figure, one patient actually performs better than all the controls on the different-view scene conditions. These analyses suggest that for some reason, the controls

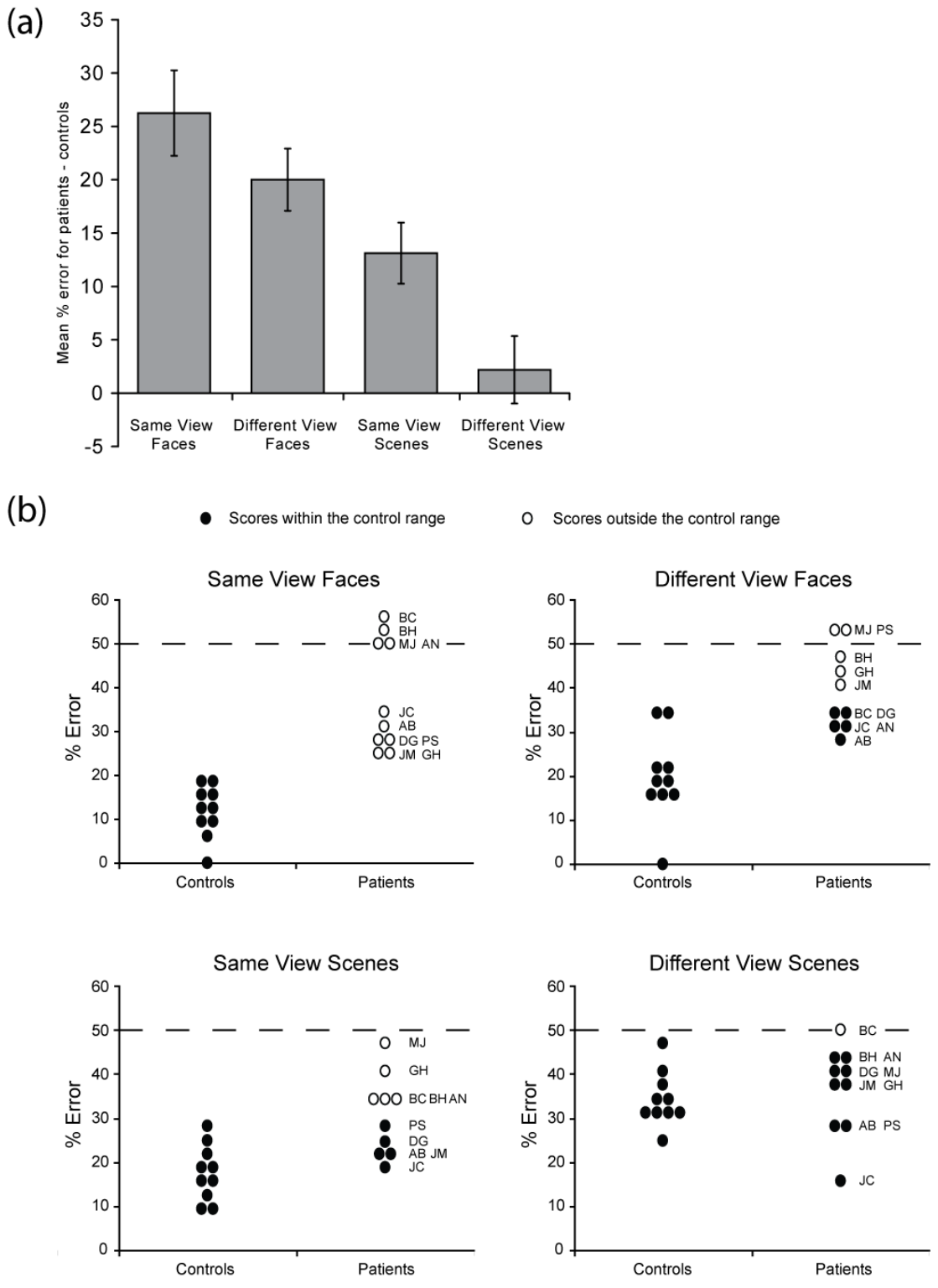


***Figure 3.2 Performance on the task illustrated as (a) mean % error (± S.E.) for the patient minus the control group and (b) individual scores (errors) for each of the four conditions (chance performance = 50%). For patients, scores inside the control range are identified as filled circles, whereas those outside the control range are depicted using empty circles as assessed using the Crawford and Howell (1998) method.***

may have been more affected by a change in view than the patients, causing the otherwise counter-intuitive effect that the patients were more impaired on the same-view than the different-view conditions. On the other hand, since the different-view conditions were always tested before the same-view conditions, this interaction may reflect a delay-dependent deficit in the patients. Unfortunately, it is not possible to tease these two possibilities apart based on the current data. Furthermore, a detailed exploration of this unexpected result is beyond the scope of the current thesis.

The results of the RSDT analyses (Crawford & Garthwaite, 2005) which examined the difference in the level of impairment between the face and scene conditions for individual patients can be found in Table 3.3. The results of Crawford and Howell's (1998) modified *t*-tests which assessed whether the scores for each patient should be classified as impaired are also illustrated in Figure 3.2(b). The RSDT analysis revealed that although five patients were impaired on the *same-view faces*, but not the *same-view scenes*, only one patient met Crawford and Garthwaite's (2005) criteria for a classical dissociation. The same was true for the different-view conditions, with five patients being impaired on faces but not the scenes, but only one patient meeting the criteria for a classical dissociation (notably this was not the same individual who showed a dissociation on the same-view conditions). Three patients met the requirements for a strong dissociation on the same-view conditions, indicating that although they were impaired on faces and scenes, the degree of impairment was greater for faces. In summary, five of the ten patients showed a significant dissociation, with superior performance on scenes compared to faces, relative to controls, on either the same- or different-view conditions. There were no cases of the reverse dissociation, i.e. superior face relative to scene recognition memory.

***Table 3.3 Results of Crawford and Howell's (1998) modified t-test which tested for significant impairments relative to controls on each condition, and the RSDT analyses which tested for significant stimulus-specific dissociations in each individual patient.***

| | Same View Faces | Different View Faces | Same View Scenes | Different View Scenes | Same View | *t,p* | Different View | *t,p* |
|---|---|---|---|---|---|---|---|---|
| AB | 68.8* | 71.9 | 78.1 | 71.9 | - | ns | - | ns |
| BC | 43.8* | 65.6 | 65.6* | 50.0* | Scenes > Faces$^{st}$ | $t_{(9)} = 3.69$, $p < 0.01$ | - | ns |
| JC | 65.6* | 68.8 | 81.3 | 84.4 | Scenes > Faces$^{cl}$ | $t_{(9)} = 2.78$, $p < 0.05$ | - | ns |
| DG | 71.9* | 65.6 | 75.0 | 59.4 | - | ns | - | ns |
| BH | 46.9* | 53.1* | 65.6* | 56.3 | Scenes > Faces$^{st}$ | $t_{(9)} = 3.30$, $p < 0.01$ | - | ns |
| GH | 75.0* | 56.3* | 59.4* | 62.5 | - | ns | - | ns |
| MJ | 50.0* | 46.9* | 53.1* | 59.4 | - | ns | - | ns |
| JM | 75.0* | 59.4* | 78.1 | 62.5 | - | ns | - | ns |
| AN | 50.0* | 68.8 | 65.6* | 56.3 | Scenes > Faces$^{st}$ | $t_{(9)} = 2.92$, $p < 0.05$ | - | ns |
| PS | 71.9* | 46.9* | 71.9 | 71.9 | - | ns | Scenes > Faces$^{cl}$ | $t_{(9)} = 2.96$, $p < 0.05$ |

****Signifies significant impairment (p < 0.05) as assessed using Crawford and Howell's (1998) modified t-test.***

***st: strong dissociation; cl: classical dissociation as assessed using Crawford and Garthwaite's (2005) RSDT procedure.***

## *Regression analyses*

The initial multiple regression analysis on the patients' data showed an overall model fit (after removing the grand mean) of $R^2 = 0.53$. Contrasts collapsing across condition revealed a significant difference in the regression slopes of performance as a function of right versus left hemisphere ranking ($t_{(20)} = 2.37$, $p < 0.05$). Individual contrasts showed a reliable positive relationship between performance and right hemisphere ranking ($t_{(20)} = 3.07$, $p < 0.005$), but no reliable relationship with left hemisphere ranking, ($p > 0.4$). There was also a reliable negative relationship with age ($t_{(20)} = -1.84$, $p < 0.05$), which was not expected, but note that an important aspect about the multiple regression is that the effect of right hemisphere rankings cannot be explained by any (linear effects) of age.

Further contrasts revealed no significant differences in the regression slopes of the relationships between right hemisphere ranking and performance for scene versus face conditions ($p > 0.3$), or for same- versus different-view conditions ($p > 0.2$). The same was true of the differences between the regression slopes of the relationships between left hemisphere ranking and performance (scenes versus faces: $p > 0.1$; same- versus different-views: $p > 0.2$). Overall, these results suggest that the right hemisphere ranking, but not the left hemisphere ranking predicted performance, irrespective of stimulus category or view.

Two further models examining performance on the face and scene conditions separately, collapsed across view, revealed significant partial correlations between right hemisphere rank and performance (faces: $r^2 = 0.66$, $p < 0.05$; scenes: $r^2 = 0.50$, $p < 0.05$), corrected for left hemisphere rank and age.

Performance of the individual patients is illustrated in Figure 3.3. Since the rank given to the right, but not the left hemisphere was found to be a significant predictor of performance on both stimulus conditions, the data are plotted as functions of the right temporal lobe ranks. Since the relationship between performance and right hemisphere ranking did not differ between same- and different-views, the data are plotted collapsed across this factor. Despite there also being a lack of any significant difference in the relationship between right hemisphere rank and performance on faces versus scenes, separate plots are provided to illustrate the interaction between stimulus category and the level of impairment relative to controls. In order to aid comparison between patients and mean control performance, the

figures represent the raw data and do not take into account age or the rank given to the left temporal lobe, and so they should not be viewed as an illustration of the linear regression analyses. Crawford and Howell's modified *t*-test (using a threshold of $p < 0.05$, as before) was performed on the data collapsed across view in order to illustrate which of the data points lie within the control range, and which do not. These analyses revealed impaired performance in all patients on the face conditions, whereas impairments on the scene conditions were only observed in four of the patients (equivalent analyses revealed impairments on both faces and scenes in the patient who was unable to undergo MRI scanning). These figures therefore provide a useful summary of the patient data in relation to both the control performance and the level of tissue remaining in the right temporal lobe, ignoring effects of view.

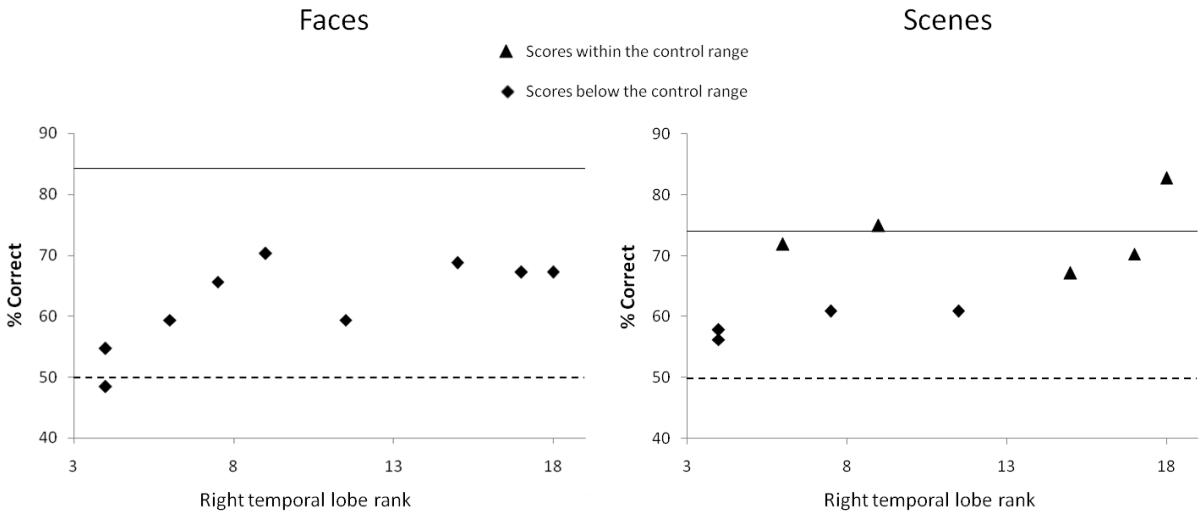


***Figure 3.3 Performance of the patients (% correct) on the face and scene conditions, collapsed across view, as a function of right temporal lobe rank. Note that high ranks indicate larger amounts of remaining tissue. Solid lines represent control means. Diamonds represent scores below the control range; triangles represent scores within the control range as assessed using the Crawford and Garthwaite (2002) method. Chance performance = 50%.***

# Discussion

Patients with SD, a neurodegenerative condition known to affect MTL regions, were disproportionately impaired on recognition memory for faces compared with scenes. This was true at both the group level, and in some cases, at the level of individual patients. Correlational analyses indicated that the degree of impairment on both stimulus categories was associated with the extent of damage to the right, but not the left temporal lobe. These

results complement previous findings of both the current thesis and the wider literature and provide additional support for a stimulus-specific division of labour in the MTL. They are also indicative of a greater dependence on the right hemisphere than the left hemisphere for visual recognition memory. The implications of these findings are discussed below, together with some tentative hypotheses regarding the specific anatomical causes of the recognition memory deficits observed in SD.

## *Sub-total damage to the MTL can be associated with disproportionate impairments in recognition memory for faces relative to scenes*

As a group, patients with SD, were disproportionately impaired on recognition memory for faces compared with scenes. At the individual patient level, a rigorous method used to analyse single cases relative to modest control samples revealed impairments on one or both scene conditions in only half of the patients, whereas all the patients showed some impairments on one or both of the face conditions, relative to healthy age, gender and education-matched controls. Strict criteria for a significant stimulus-specific dissociation were met in five of the ten patients, with superior performance being observed on scenes compared to faces, although in each case, this was limited either to the same-view conditions or the different-view conditions. There were no cases of the reverse dissociation, i.e. superior performance on faces compared to scenes. These findings replicate previous studies which have revealed disproportionate impairments on recognition memory for faces relative to topographical material in patients with SD (Cipolotti & Maguire, 2003; Evans et al., 1995; Lee, Buckley et al., 2006; Maguire & Cipolotti, 1998). The current study, however, represents the first report of direct statistical comparisons between performance on face and scene recognition memory, in a group of patients with SD, using an identical experimental paradigm.

Performance on the same task to that reported in the current chapter was previously shown to result in impairments on the scene but not the face conditions in patients with focal hippocampal damage, and on both stimulus categories in patients with broader MTL damage (K. J. Taylor, Henson, & Graham, 2007; see also Chapter 2). A possible explanation for these previous findings was that relatively restricted damage to the MTL impaired the scene but not the face conditions simply because the scene conditions, as measured by control performance, were the most difficult. The current findings cast doubt on this explanation by

revealing that sub-total damage to the MTL can, in some cases, impair recognition memory for faces whilst leaving recognition memory for scenes intact. The results of the current and previous chapters combined therefore provide support for a division of labour in the MTL according to stimulus category (Buckley et al., 2004; Lee, Barense et al., 2005; Murray et al., 2007).

### *Potential anatomical causes of recognition memory impairments*

Correlational analyses revealed a significant association between increasing levels of temporal lobe damage and decreasing levels of performance on both stimulus categories, an observation which has previously been made for face recognition memory in SD (Simons et al., 2001), but has not previously been investigated for recognition memory of scenes. These findings suggest that recognition memory for faces is particularly vulnerable to very early stages of disease pathology in SD, with a progressive loss of this ability as the disease develops. Recognition memory for scenes, on the other hand, appears to be relatively unaffected at early stages, but as the disease progresses, this ability also gradually deteriorates.

Although the precise contribution of particular MTL structures to performance on the task cannot be directly addressed in the current chapter, since individual ratings for different MTL structures were not available, some insight can be gained by considering the patterns of performance described above, in the light of studies which have examined the typical patterns of atrophy and underfunctioning observed in SD.

As described in the introduction, the focus of pathology in SD is the anterior temporal lobe. There is usually an asymmetric distribution of atrophy such that damage is more dominant in one hemisphere or the other, and there is an anteroposterior gradient such that the amount of damage decreases posteriorly along the temporal lobe (Chan et al., 2001; Davies et al., 2004; Galton, Patterson et al., 2001; Lee, Buckley et al., 2006; Noppeney et al., 2007; Rosen et al., 2002). Atrophy is thought to spread from this anterior temporal starting point, into more posterior sections of the temporal lobe and/or inferior posterior frontal lobes as the disease progresses (Hodges & Patterson, 2007), although this has only been formally confirmed by one group study using fluid registration (Whitwell et al., 2004) and an additional case study using an experimental inverse-consistent registration method (Leow et al., 2005). Increasing

involvement of the non-dominant hemisphere has also been observed (Brambati et al., 2007; Whitwell et al., 2004). It is noteworthy that there is a strong correlation between structural and functional loss in SD (unlike in Alzheimer's disease, for example), and so it is reasonable to assume that information from structural imaging studies provides an accurate picture of the underlying causes of cognitive impairments in the disease (Nestor et al., 2006). In other words, provided that structural imaging studies are not hampered by technical problems, such as signal dropout or low resolution, they are likely to reveal the majority of regions in the brain which are underfunctioning in SD.

One region which may have played a central role in the face recognition memory deficits observed in the current chapter is the perirhinal cortex. Two recent studies have highlighted significant atrophy to this region and adjacent temporopolar cortex (a portion of which is considered a part of total perirhinal cortex, Insausti et al., 1998) in SD relative to AD and controls (Davies et al., 2004; Lee, Buckley et al., 2006). Davies and colleagues examined the scans of eight patients with SD and found that of the regions which were assessed (temporopolar cortex, perirhinal cortex, entorhinal cortex and hippocampus, with the latter two regions being divided into anterior and posterior sections), the temporopolar/perirhinal region was numerically the most affected in terms of % tissue loss relative to controls. This was followed by anterior and then posterior entorhinal cortex and anterior and then posterior hippocampus. This pattern was particularly prominent in the left hemisphere, although the pattern on the right was similar. Lee Buckley et al. (2006) examined a broader range of temporal lobe structures in eight patients with SD, and looked for regions in which atrophy was observed across all patients. Areas of overlap across all patients were observed in the left temporal pole and bilateral perirhinal cortex and anterior hippocampus. Furthermore, in a recent analysis of SD using FDG-PET imaging (Nestor et al., 2006), the perirhinal cortex was found to be in the middle of a large area of hypometabolic tissue. Prior to these studies, few, if any, had specifically defined and examined the extent of damage to the perirhinal cortex in SD, which may explain why its involvement has not been highlighted previously.

These findings suggest that the perirhinal cortex is one of the most severely and consistently affected regions in SD, and damage to this regions is therefore a possible cause of the deficits observed in the current study in recognition memory for faces, which were observed across all patients. This would be in keeping with the proposed role for this structure in

processing complex, configural objects (Barense, Gaffan, & Graham, 2007; Buckley et al., 2001; Bussey et al., 2002; Lee, Buckley et al., 2005) and in supporting (familiarity-based) memory for individual items (Aggleton & Brown, 1999; Brown & Aggleton, 2001; Meunier et al., 1993; Winters et al., 2004).

Other structures which may have played a role in the face recognition memory deficit are the amygdala, anterior hippocampus and entorhinal cortex, and more lateral structures such as the fusiform gyrus, all of which have frequently been found to be atrophied in patients with SD (Chan et al., 2001; Davies et al., 2004; Galton, Patterson et al., 2001; Lee, Buckley et al., 2006; Noppeney et al., 2007; Rosen et al., 2002). The possible involvement of entorhinal cortex is difficult to rule out, particularly since this region receives the majority of its inputs from the perirhinal cortex and therefore the functioning of these two regions is likely to be tightly linked. A section of the fusiform gyrus, known as the fusiform face area (FFA, Kanwisher, McDermott, & Chun, 1997) has been consistently associated with face processing. Nestor and colleagues (2006) found, however, that the area of significant hypometabolism in a group of patients with SD only extended posteriorly as far as $y = -38$ on the left, and $y = -16$ on the right. Since the FFA is situated at the posterior end of the fusiform gyrus, with its location in the 12 subjects who participated in Kanwisher et al's original paper ranging from $y = -39$ to $y = -75$ in Talairach space, it is unlikely to be affected during early stages of SD.

The amygdala has been implicated in both mnemonic and perceptual processing of emotional stimuli, including faces (Breiter et al., 1996; Calder, Lawrence, & Young, 2001; Dolan, 2002). Moreover, this structure was also significantly damaged in the broader MTL patients in the previous chapter who also exhibited impaired recognition memory for faces. The role of this region in episodic memory, however, is thought to be limited to stimulating up-regulation of processing in perceptual, memory and attentional systems in response to emotionally significant stimuli, rather than providing a storage site for memories (Anderson & Phelps, 2001; Cahill & McGaugh, 1998; Hamann, Ely, Grafton, & Kilts, 1999; Packard, Cahill, & McGaugh, 1994; Paz, Pelletier, Bauer, & Pare, 2006). One might predict, therefore, that since the current experiment contained a single, continuous block of neutral faces at encoding, any amygdala-driven modulation of processing would not be a particularly significant factor affecting performance and therefore, damage to this structure would not be

expected to have such a devastating and consistent effect on performance. The role played by the amygdala in episodic memory is yet to be fully understood, however, and so some involvement of this structure in the recognition memory impairments found in SD cannot be ruled out on the basis of the current study.

Finally, it is important to consider whether damage to the anterior hippocampus could have been a factor in the face recognition memory impairments. Activity in this region has been associated with memory and perception of objects, including faces, in a number of recent functional imaging studies (Kohler et al., 2005; Lee et al., 2008; Pihlajamaki et al., 2004). A key argument against this possibility, however, is the observation of intact performance on the same task in patients with restricted damage to the hippocampus (K. J. Taylor et al., 2007; Chapter 2). Notably, for the two patients in the previous study whose scans were rated, the hippocampal damage was more prominent in the anterior portion of the hippocampus than the posterior portion.

Further support for the view that damage to the perirhinal, and perhaps entorhinal cortex are likely to have been the main cause of the impairment in recognition memory for faces comes from two studies which found a significant correlation between face or object recognition memory performance, and the extent of damage to the parahippocampal gyrus (in all cases, the region corresponded to portions of the perirhinal and entorhinal cortex) in SD (Simons et al., 2001; Simons, Graham et al., 2002) and Alzheimer's disease (Galton, Patterson et al., 2001). In each case, the correlation with the extent of damage to the hippocampus was either not significant or significantly smaller than that with the parahippocampal gyrus.

In contrast to the face conditions, significant impairments on the scene conditions were only observed in half of the patients. Since performance also correlated with the extent of damage to the right temporal lobe, it seems likely that the ability to perform the scene conditions depends on regions which tend not to be affected until later in disease progression. Given the relatively small number of studies which have looked at the progression of atrophy in SD, it is more difficult to infer which particular regions are most likely to be involved in the deficits observed on the scene conditions. It seems plausible, given the assumption that atrophy gradually spreads from the temporal pole into more posterior regions, that the involvement of the hippocampus would be minimal and limited to its anterior extent during the early stages

of the disease, and would then spread more posteriorly. Similarly the parahippocampal cortex may be affected at later stages. Given the impairments of patients with focal hippocampal pathology on the scene conditions in Chapter 2, and the wealth of evidence from several methodologies of a role for both structures, particularly the posterior hippocampus, in spatial processing (Aguirre et al., 1998; Buckley et al., 2004; Ekstrom et al., 2003; Epstein & Kanwisher, 1998; Lee et al., 2008; Maguire et al., 1998; O'Keefe & Nadel, 1978; Parslow et al., 2004; Pihlajamaki et al., 2004), it seems likely that damage to these regions was the cause of the impairments in the scene conditions in the current experiment, although this cannot be confirmed based on the current findings.

In summary, the current findings are consistent with the view that the perirhinal cortex supports recognition memory for faces, and the hippocampus, perhaps particularly the posterior hippocampus (although see Chapter 2), supports recognition memory for scenes, although in the context of the current experiment, strong conclusions regarding structure to function relationships cannot be made. What can be concluded with more certainty is that there seems to be an antero-posterior gradient in function across the temporal lobe such that recognition memory for faces relies on more anterior regions, whereas recognition memory relies on more posterior regions. This pattern will be explored further in Chapter 5 which examines functional activation of the MTL during encoding and retrieval of the face and scene stimuli used throughout this thesis. Of critical importance in terms of the thesis as a whole is the observation that limited damage to the MTL was associated with disproportionate impairments on recognition memory for faces compared with scenes. An explanation of the effects observed in the previous chapter as being based on an interaction between lesion size and difficulty is therefore difficult to maintain.

## *Effects of damage to the right, but not the left hemisphere on visual recognition memory*

The correlations between performance on both the face and scene conditions in the current experiment, and the amount of tissue remaining in the temporal lobe, were only significant for the right and not the left hemisphere, with the difference in the strength of correlation between hemispheres also being significant. This is consistent with previous findings in SD (Simons et al., 2001), and in Alzheimer's disease (Cahn et al., 1998). In both cases, performance on the face version of Warrington's RMT (1984) correlated more highly with

the amount of remaining tissue in the right hemisphere than the left hemisphere. It may also explain why intact face recognition memory has been reported in patients with predominantly left-lateralised damage, whereas bilateral or right-lateralised damage has been associated with impaired performance (Scahill et al., 2005; S. A. Thompson et al., 2004). Together, these findings are in keeping with the long-standing view that processing of visual (as opposed to verbal) material is often lateralised in the non-dominant (usually right) hemisphere. For example, prosopagnosia has frequently been observed in patients with brain lesions apparently restricted to the right hemisphere (De Renzi, 1986; Sergent & Signoret, 1992). and a recent meta-analysis found that the region most commonly affected in cases of prosopagnosia was located in the right inferior occipital gyrus (Bouvier & Engel, 2006). In terms of episodic memory, patients with unilateral damage to structures in the left MTL have been found to show disproportionate impairments on tests of verbal memory (Frisk & Milner, 1990). In contrast, patients who have undergone right temporal lobectomy show disproportionate impairments on topographical memory (Spiers et al., 2001), relative to controls and right temporal lobectomy patients. It is important to note, however, that studies which suggest lateralisation of function on the basis of lesion evidence can rarely rule out the potential knock-on effect of the original lesion on the contralateral hemisphere, which could result in underfunctioning, thus disguising the possibility that the process ordinarily relies, at least partially, on both hemispheres. This problem can be dealt with to some extent, however, by investigating the functionality of contralesional tissue using functional neuroimaging (Sorger, Goebel, Schiltz, & Rossion, 2007).

Very few imaging studies have formally compared the contribution of each hemisphere to performance on mnemonic tasks involving different stimulus categories. Claims have frequently made for lateralisation of function based on the discovery of suprathreshold activity in one hemisphere and not the other; but without statistically comparing the activity in each hemisphere, a claim for lateralisation is not strictly valid. A recent study which did directly contrast left and right hemisphere contributions to successful encoding (as measured by a subsequent recognition memory test) of line drawings of objects, faces and words revealed a significant interaction between subsequent memory, stimulus type (words versus faces) and laterality (Powell et al., 2005). Word encoding was left-lateralised whereas face encoding was right-lateralised. Object encoding did not show a laterality effect. These findings are therefore consistent with the view that visual recognition memory, at least for

some categories of stimulus, depends more on the right than the left hemisphere.

## *Are faces particularly vulnerable in SD?*

One limitation of the current findings is that it is unclear whether the devastating effect of SD on recognition memory for faces would extend to other kinds of objects, or whether faces pose a particular problem for patients with SD. As discussed in the introduction, intact recognition memory has been reported for line drawings and colour pictures of animals and objects in SD (Graham et al., 1997; Graham et al., 2000; Simons, Graham et al., 2002), in all but the most severe cases, provided that the items presented at study and test were perceptually identical. Recent evidence, however, suggests that performance on tests of object processing, including discrimination and recognition memory tasks, following damage to the perirhinal cortex, may depend on the extent to which stimulus features overlap, both within and across successive trials (Bussey et al., 2002). When features are repeated across both target and foil stimuli, the degree of "feature-ambiguity" is thought to increase, causing increasing reliance on the perirhinal cortex which is able to resolve this ambiguity. Consistent with this view, recent studies revealed that, when required to make discriminations between pictures of objects, including every-day objects such as cars, and novel "greeble" stimuli, patients with SD were impaired on trials containing items with a high, but not a low number of overlapping features. (Barense, Bussey, Lee, Rogers, Hodges et al., 2005; Barense & Graham, 2007). It is possible, therefore, that impairments were not generally observed on previous tests of object recognition memory in SD because the stimuli involved were easy to distinguish on the basis of simple features. Faces are an example of highly configural stimuli, with many features being shared across all exemplars, which may explain why they are particularly vulnerable to damage which includes the perirhinal cortex.

## *Recollection and familiarity in SD*

An important issue in the current thesis is whether behavioural dissociations observed following incomplete damage to the MTL, such as the stimulus-specific effects in the current chapter, and in Chapter 2, can be explained according to dual-process models of recognition memory. According to one prominent theory, recollection and familiarity depend on networks which include the hippocampus and perirhinal cortex respectively (Aggleton & Brown, 1999; Brown & Aggleton, 2001) see also (Eichenbaum et al., 1994; Eichenbaum et al., 2007). Since the perirhinal cortex is thought to be disproportionately damaged in SD,

relative to the hippocampus, one might predict disproportionate deficits in familiarity relative to recollection in patients with SD, a pattern of performance which was recently reported in a case study of a patient who had undergone unilateral temporal lobe surgery which removed a portion of the left perirhinal cortex whilst leaving the hippocampus intact (Bowles et al., 2007). If, as was suggested in the previous chapter, recognition memory for faces relies more on familiarity than recollection, this could potentially explain the pattern of impairments observed in the current chapter.

In what is possibly the only study which has investigated recollection and familiarity in SD, the relative levels of recollection and familiarity were very variable (Simons, Verfaellie et al., 2002). Two patients conformed to the pattern which would be predicted by the model described above, if the perirhinal cortex was indeed disproportionately affected relative to the hippocampus: they were impaired on recognition memory of line drawings but performed normally on a source monitoring task thought to tax recollective processing. A further two patients demonstrated the reverse dissociation, however, and the majority showed no dissociation between item and source-based tasks. The variability observed in this study make it difficult to predict to what extent familiarity and recollection are likely to have been impaired in the patients reported in the current chapter. It is therefore difficult to assess the validity of a dual-process explanation of the current findings.

## Summary

In summary, the findings of the current chapter, together with Chapter 2, indicate that different MTL structures make distinct contributions to recognition memory, according to the stimulus category involved. The evidence suggests that whereas anterior structures, perhaps in particular the perirhinal cortex, support recognition memory for faces, the hippocampus seems to be particularly important in recognition memory for scenes. There is also evidence that recognition memory for both categories of stimulus are particularly dependent on structures in the right, rather than the left temporal lobe. Since levels of recollection and familiarity were not assessed in either chapter, the possibility that these stimulus specific effects are attributable to a differing dependence of memory for faces and scenes on familiarity and recollection cannot be ruled out. The following chapter therefore examines the contribution of familiarity and recollection to recognition memory for these two stimulus categories in order to assess this possibility.

# Chapter 4
# Recollection and familiarity for faces and scenes in younger and older subjects

## Introduction

The findings of the previous two chapters are indicative of a functional double dissociation between the roles of different MTL structures in recognition memory for different stimulus categories. Patients with damage limited to the hippocampus were impaired on recognition memory for scenes, but not faces (Chapter 2; see also Bird et al., 2007; Carlesimo et al., 2001; Cipolotti et al., 2006). In contrast, when analysed as a group, patients with semantic dementia displayed significantly greater impairments on recognition memory for faces than for scenes (Chapter 3; see also Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998). This double dissociation is incompatible with the view that all components of the MTL make some contribution to recognition memory, regardless of stimulus type (Squire et al. 2004; Manns et al 2003). Instead, these findings provide support for the idea that the hippocampus and surrounding cortex build complex representations of spatial scenes and objects respectively (Buckley et al., 2004 & Gaffan, 2004; Lee, Barense et al., 2005; Murray et al., 2007).

Another prominent theory proposes that the contributions made by the hippocampus and perirhinal cortex to recognition memory can be distinguished according to the nature of the processes performed by each region. According to this view, the perirhinal cortex supports familiarity-based recognition of individual items, whereas the hippocampus supports episodic recollection (Aggleton & Brown, 1999; see also Eichenbaum et al., 1994), perhaps by providing links between perirhinal-based item representations and memory for contextual representations stored in the parahippocampal cortex (Diana et al., 2007; Eichenbaum et al., 2007). One formal model of the contribution of recollection and familiarity to recognition decisions is the "dual-process" signal-detection model developed by Yonelinas and colleagues (Yonelinas, 1994; Yonelinas et al., 2002).

As discussed in previous chapters, stimulus-specific dissociations are not directly predicted by dual-process theories of MTL function. An important question, therefore, is whether the effects reported in Chapters 2 and 3 can be accommodated by existing dual-process theories,

and if so, how. One possibility is that for some reason, recognition memory for scenes tends to be associated with disproportionately high levels of recollection, whereas recognition memory for faces is more associated with familiarity. Since the contributions made by recollection and familiarity to performance in the previous chapters were not assessed, one aim of the current chapter was to measure the levels of these two processes in a recognition memory test involving the face and scene stimuli used in those chapters. If levels of recollection were found to be disproportionately high for scene compared with face stimuli, this might suggest that controls ordinarily rely more on recollection in recognition memory for scenes than for faces, and therefore stimulus-specific effects could be more easily accommodated by dual-process theories of MTL function.

Irrespective of the outcome of these behavioural assessments, however, it is possible that whatever levels of recollection and familiarity there are for faces, regions outside the hippocampus support both processes during face recognition, whereas the hippocampus itself might support recollection and familiarity for scenes. This would suggest that although dual-process models may capture some aspects of the division of labour in the MTL, the particular processes performed by each region may differ according to the categories of stimuli involved. This possibility is supported by three cases studies in which hippocampal damage impaired both recollection and familiarity for scenes, whilst sparing recollection and familiarity for faces (Bird et al., 2007; Carlesimo et al., 2001; Cipolotti et al., 2006). Chapter 5 therefore examined MTL activity associated with recollection and familiarity for the same stimuli using functional magnetic resonance imaging (fMRI), in order to investigate these ideas. These imaging experiments were performed using healthy, young participants, and so Experiment 2 of the current chapter therefore investigates the behavioural performance of young participants on the recognition memory test.

## *Changes in behavioural procedure*

The behavioural and imaging experiments used in this and the following chapter were based on a common format. The experiments involved recognition memory for faces and scenes, and, as in the previous experiments, incorporated same- and different-view conditions to examine the effect of this manipulation on levels of recollection and familiarity. Study blocks proceeded in much the same way as in the previous two chapters. At test, however, participants were first asked to perform a yes/no recognition judgement for each item (as

opposed to the forced-choice decision required in Chapters 2 and 3). If they responded "yes", levels of recollection and familiarity were assessed using an adaptation of the remember/know paradigm. Finally, participants were asked to respond whether they thought the view being presented at test was the same or different to that shown during study. Performance on this "view discrimination" task gives an idea of how aware participants were of the view manipulation, and also of whether participants had access to a trace of the exact image as it appeared at study (akin to a verbatim trace of a verbal stimulus), or whether their recognition relied more on memory for the "gist" of what was shown.

The adoption of a yes/no paradigm, rather than the forced-choice paradigm that was used in the previous experiments, was crucial for both the behavioural and imaging experiments. In terms of the behavioural experiments, it would be difficult to establish the contribution of recollection and familiarity in a forced-choice paradigm, since participants may rely on information about both the target and foil stimuli when making their recognition decisions. Similarly, the imaging data would be more difficult to interpret, since it would be difficult to distinguish the relative contribution of the target and foil stimuli to the total activation associated with a trial (consider, for example, comparison of correct vs. incorrect two-alternative forced-choice trials: from a signal-detection perspective, a correct trial is likely to reflect high strength associated with the target and low strength associated with the foil, whereas an incorrect trial is likely to reflect similar and intermediate strengths associated with the target and the foil, and hence the summed strength associated with the two types of trial could be equivalent, resulting in indistinguishable fMRI activity).

This change in paradigm led to the need for a further alteration in experimental design, this time involving the kinds of foils used. In order to maximise difficulty, and thus avoid ceiling effects in controls in the previous, forced-choice design, target items were presented alongside visually similar foils. Behavioural pilot studies for the current experiment, however, which also used the visually similar items as foils, revealed unacceptably low levels of performance, for both faces and scenes, even in younger participants. It became apparent that in a yes/no testing format, participants were unable to distinguish these highly similar items. New items were therefore collected and were intermixed with one item from each matched pair from the previous experiments, in order improve performance on the yes/no version.

These changes in experimental design had the unfortunate consequence of reducing the comparability between the experiments in this (and the following) chapter and those in the previous chapters. It was assumed, however, that if the changes affected, for example, the contributions of recollection and familiarity to performance, that this effect would be equivalent across both stimulus categories, although this could not be experimentally verified. This issue will be explored in more detail in the discussion.

## *Measuring recollection and familiarity*

The remember/know procedure was used to estimate recollection and familiarity in the experiments reported in this and the following chapter. A crucial advantage of this method over alternative techniques for measuring recollection is that it is a very inclusive method. Some alternative paradigms, such as the process-dissociation procedure, or source memory, use a participant's ability to recall a particular aspect of the study event, e.g. the task performed at study, as a measure of recollection. This can lead to underestimation of levels of recollection, since participants may recall details which are not relevant to the task (i.e. non-criterial recollection). This problem is reduced in the remember/know paradigm, since participants are encouraged to endorse items as remembered provided recall of associated details occurs at test, regardless of the kind of information that is recollected. The disadvantage of this method is that it relies on a subject's ability to follow the instructions and to accurately introspect about the nature of their memory. Some researchers have argued, for example, that subjects simply map remember and know responses onto high and low confidence respectively (Donaldson, 1996). This claim has been questioned, however, by studies which have demonstrated that confidence and remember/know responses can be dissociated (Gardiner & Java, 1991; Parkin & Walter, 1992; Rajaram, 1993). Furthermore, the ability to accurately retrieve contextual details about a study event has been shown to be significantly higher for items receiving remember rather than know responses (Perfect, Mayes, Downes, & Van Eijk, 1996), supporting the view that remembering and knowing represent qualitatively rather than simply quantitatively different types of memory. As discussed in the Methods section, steps were taken in the current experiment to ensure that the instructions were followed accurately.

The most appropriate way to derive estimates of recollection and familiarity based on remember and know responses depends on the nature of the relationship which is assumed to

exist between recollection and familiarity. Building on the ideas of Jones (1987) three theoretically plausible relationships have been outlined: independence, redundancy and exclusivity (Knowlton & Squire, 1995). In the current thesis, the relationship is assumed to be independent and therefore, estimates of recollection and familiarity were obtained using a modified procedure as suggested by Yonelinas and Jacoby (1995), and described in the Methods section. This model assumes that a given item can be associated with a feeling of familiarity, recollection or both. One explanation for how this is supported by the brain is that the two processes are partially supported by common neural systems, but that additional processing is carried out by distinct systems which are specific to each process (e.g. Aggleton & Brown, 1999). This would lead to the prediction that functional double dissociations could theoretically be observed following isolated damage to the systems which specifically support the two processes. Until recently, neuropsychological investigations had only produced single dissociations, with selective hippocampal damage leading to impaired recollection combined with generally unimpaired familiarity (e.g. Aggleton et al., 2005; Holdstock et al., 2002; Mayes et al., 2002; Yonelinas et al., 2002; but see Gold et al., 2006; Wais et al., 2006). There is now evidence from a single patient that unilateral damage to the left perirhinal cortex, which does not affect the hippocampus, can produce the complementary dissociation, i.e. impaired familiarity combined with intact recollection of verbal memoranda (Bowles et al., 2007). This completion of the double dissociation provides evidence that in the case of verbal stimuli, recollection and familiarity are at least partially supported by distinct structures, although this does not necessarily prove that recollection and familiarity ordinarily act independently.

Models assuming a relationship of redundancy are based on the idea that all recognised items are accompanied by a feeling of familiarity, and a sub-set of these items are also recollected. Under this view, recollection and familiarity are thought to depend on a common neural system, with additional, specialised processing supporting recollection if and when it occurs. According to these models, double dissociations following isolated brain lesions are not theoretically possible, although a single dissociation could result from damage to regions which specifically support recollection.

The third possibility is that recollection and familiarity are mutually exclusive (Gardiner, 1988; Gardiner & Parkin, 1990). This relationship can be seen as the default when using the

remember/know paradigm since it underlies the use of uncorrected remember and know response rates as measures of recollection and familiarity, although this fact is rarely discussed in studies which calculate estimates in this way. Note that many researchers may consider the subjective experiences of recollection and familiarity to be mutually exclusive, i.e. it might be suggested that when recollection does occur, it overrides feelings of familiarity (although opinions relating to this point vary). What is more crucial, however, is the relationship which is assumed to exist between the neural correlates underlying the two processes. In a rare discussion of this issue, Gardiner and Parkin dismissed independence and redundancy and went on to conclude: "Exclusivity assumes that the underlying components have no relation with one another, so that the outcome of one component exerts no influence whatsoever over the other component. This type of relation is consistent with evidence that has identified a number of variables that affect the probability of 'remember' responses but have no influence on the level of 'know' responses." One example of this evidence is the observation that divided attention at study affects remember but not know responses (Gardiner & Parkin, 1990). The conclusion that this supports the exclusivity assumption is somewhat flawed, however, since a relationship of exclusivity actually implies dependence between recollection and familiarity in the form of mutual inhibition, which would be required to prevent the simultaneous occurrence of both processes (Montaldi et al., 2006). The exclusivity assumption would therefore predict that manipulations which have a direct effect on recollection but not familiarity should actually lead to indirect increases in familiarity (Yonelinas & Jacoby, 1995). Furthermore, Yonelinas and Jacoby found that interpretation of recognition memory data based on an exclusivity assumption can lead to highly improbable results. For example, in one experiment, the sizes of simple geometrical shapes were altered between study and test, and ROC curves were plotted based on rates of "know" responses as a function of confidence. Interpretation of the data according to an exclusivity assumption led to the seemingly implausible conclusion that, in cases where the response criterion was relatively relaxed, new shapes were more familiar than old shapes (Yonelinas & Jacoby, 1995).

Although data pertaining to this issue are limited and difficult to interpret, there is little, if any evidence in favour of the exclusivity assumption which can counter the paradoxical results described above and elsewhere in the literature. The weight of opinion currently supports the independence assumption and so although other options cannot be conclusively

ruled out, this seems a reasonable assumption to make at the present time.

## *Aims of the chapter*

Together, the two experiments reported in this chapter enabled analysis of the effects of stimulus category, view change and age on recognition accuracy, view discrimination and levels of recollection and familiarity. Experimental analyses were designed to answer the following questions:

**Do recollection and familiarity make disproportionate contributions to recognition memory for faces and scenes?**

As described at the beginning of the chapter, the main aim of Experiment 1 was to establish whether recollection and familiarity make disproportionate contributions to recognition memory for faces and scenes, in order to assess the ability of dual-process models to explain the stimulus-specific effects demonstrated in previous chapters. This experiment involved a group of older participants, designed to roughly match the participants in the previous two chapters in terms of age.

**Are there any differences in performance between older and younger participants?**

Scanning older participants could have been problematic, since the experimental paradigm is particularly lengthy and demanding. The imaging experiments in the following chapter were therefore performed using young, healthy participants. This also enabled the analysis of normal, healthy brain function, rather than analysing activity in older participants which may be affected by compensatory strategies recruited to counteract the effects of cognitive decline. Although a detailed investigation of aging effects is beyond the scope of the current thesis, it was important to explore the potential differences between the accuracy and quality of memory processing in younger and older participants, in order to establish to what extent the imaging experiments can be related to the neuropsychological experiments in the previous chapter, which involved older participants. Experiment 2 of the current chapter therefore involved a group of younger participants, for comparison with the older participants from Experiment 1. Studies which have investigated the effects of aging on recollection and familiarity generally report age-related impairments in recollection, whereas familiarity frequently appears to be unaffected (for reviews, see Spencer & Raz, 1995; Yonelinas, 2002). Experiment 2 was novel in enabling comparison of aging effects on recollection and familiarity for different stimulus categories. This experiment also constituted a behavioural

pre-trial for the imaging experiments in the following chapter.

These two issues constitute the main motivation for the experiments reported in this chapter. Two further issues, however, were explored in addition:

**Do changes in view affect levels of recollection and familiarity?**

It was predicted that recognition accuracy would be reduced for different-view items, as was the case in the previous experiments. The effect that changes in view would have on recollection and familiarity individually was difficult to predict, however. One possibility, which follows on from the Complementary Learning Systems model of recognition memory (Norman & O'Reilly, 2003), is that levels of familiarity might be less affected than recollection by such a shift in viewpoint. This might be the case since two views of a particular item are likely to produce highly overlapping representations in the neocortical system, which mediates familiarity, and therefore, the altered view might seem almost as familiar as the original view. Since recollection is thought to be mediated by a hippocampally-based system which supports pattern separation, on the other hand, a change of view may have a greater effect on levels of recollection.

**Which factors affect view discrimination performance?**

Finally, analyses were performed to establish whether participants' ability to detect changes in viewpoint differed according to stimulus category, or whether or not they recollected an item. Since this type of task has not been investigated previously, it was difficult to predict how participants would perform, although it seemed likely that recollection would be associated with more accurate view discrimination, whereas familiarity might not have provided enough information to decide whether a change in view had occurred.

# Experiment 1: Recollection and familiarity for faces and scenes in older subjects

## *Materials and Methods*

### Participants

24 participants were recruited from the MRC Cognition and Brain Sciences volunteer panel. The data for five of the subjects were excluded from the analyses due to a strong bias to

respond either *remember* or *familiar* (<1 *familiar* response for every 10 *remember* responses or vice versa). This left 19 participants (11 female, mean age 63.6 years). All participants gave informed consent before undertaking the study. The investigation received ethical approval from the Cambridge and Southampton Health Authority Local Research Ethics Committees (UK).

**Behavioural Procedure**

The stimuli consisted of photographs depicting 180 scenes and the faces of 180 individuals. There were two views of each individual and of each scene making 360 face and 360 scene items in total. As in previous chapters, the faces were selected from the Feret Database (Phillips et al., 2000; Phillips et al., 1998). For each subject, a frontal view, and a second view with the subject facing to their left by approximately 40° were used. There was some overlap between the stimuli used in this experiment and those used in the experiments reported in previous chapters. Pilot work revealed that in the current yes/no set-up, subjects frequently confused target items with the items which had served as their matched pairs in the forced-choice paradigm, and therefore performance in the more difficult, different-view conditions was close to floor. In order to minimise confusability between items, one individual or location was therefore selected from each pair of stimuli used in the previous experiments. The remaining stimuli from each set were then discarded. Additional faces were then selected from the database, and additional scene stimuli were photographed to increase the total stimulus set. As before, for the scene stimuli, pictures from a range of angles were initially taken, and for each pair, two views were subsequently chosen. The difference in viewing angle between the two views ranged from approximately 30-90° across different sets (see Figure 2.2, pp 58, for examples of items presented from same and different views, although note that, as mentioned above, only one item from each pair was used, to prevent high levels of visual overlap between items in the present experiment).

The experimental set-up was identical to that described in Chapter 2. The procedure, however, differed in a number of ways. Since the design of the current experiment was more complex, written instructions were provided for participants to read prior to testing (see Appendix for this chapter) and participants were encouraged to clarify these instructions with the experimenter before the experiment began.

There were four study blocks, two for faces and two for scenes, each consisting of 60 trials. Each study trial proceeded exactly as described in Chapter 2. Each study block was followed by a test block, after a short delay (approximately 1 minute).

Each item from the study blocks appeared in the following test block in one of two conditions: *same-view*, in which the item appeared from the same view to that shown at study; or *different-view*, in which the item appeared from a different view to that shown at study. The 60 items presented in each study block were split equally into these two conditions. An additional 30 *new* items which had never been seen before were also presented, making a total of 90 trials in each test block.

On each test trial, an item was presented on the touchscreen and participants were asked to respond to a series of questions which also appeared on the screen. First, participants were asked whether they thought they had seen the item before, to which they responded *Yes* or *No*. It was stressed that participants should respond *yes* both for items which they thought were identical to items viewed at study, as well as for items which they believed represented different views of items shown at study. If the participant responded *No*, the next item appeared following a short delay. If they responded *Yes*, they were then asked to make a *Remember/Familiar* (R/F) judgement adapted from the Remember/Know procedure (Gardiner, 1988; Rajaram, 1993; Tulving, 1985). Briefly, participants were instructed to respond R if they were able to recollect specific details of the study event, such as what they were thinking at the time when the item was presented, or the temporal position of the item in the study list. If they were unable to recollect any specific associations they were asked to respond F. This slight adjustment from the usual *know* response was made as pilot work revealed that many subjects found the original *remember/know* terminology counter-intuitive. Finally, participants performed a "view discrimination": they were asked to respond *Same* if they thought the viewing angle of the item had not altered from that shown during the study phase, or to respond *Different* if they believed the viewing angle had changed. For this final decision, subjects were also given the option of responding *Don't Know*, in order to reduce the rate of guessing. The next item then followed after a brief delay. All responses were made by pressing buttons on the touchscreen and trials were self-paced. A schematic of a sample scene trial at test is shown in Figure 4.1.

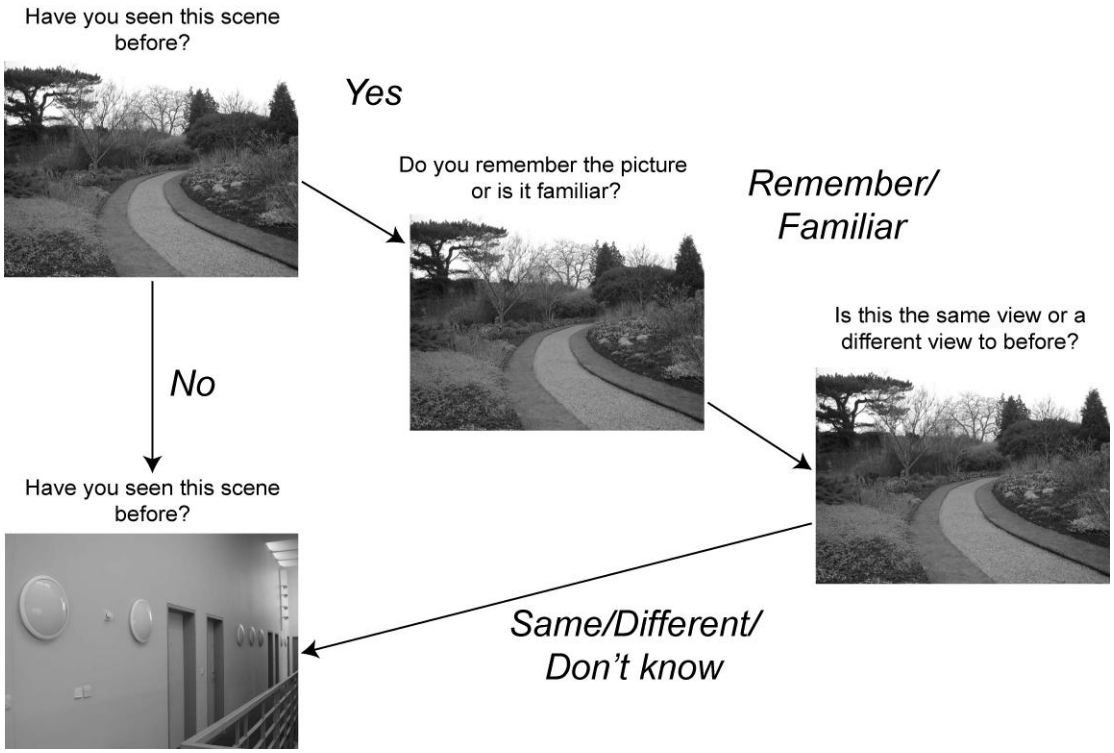


***Figure 4.1 Example of a scene trial at test. If the participant responded "Yes" to the first question, two further questions appeared on the screen, one after the other, and after a short delay, the next item was presented. If they responded "No", the next item appeared following a short delay. All questions in the test block were self-paced.***

As in previous experiments, a short practice session which included both an encoding and a retrieval block was administered prior to the initial encoding block for each stimulus category, to ensure subjects understood the instructions. Prior to commencement of the experiment proper, subjects were asked to give some examples of the reasoning behind their selection of R or F for the items presented in the practice test block to check that they were using the procedure correctly.

All items used in the experiment were trial-unique so there was no overlap between items across different test blocks. The presentation order of each study/test block pair alternated between faces (F) and scenes (S). The choice of faces or scenes as the first block, as well as the assignment of stimuli to conditions, was counterbalanced across subjects. The full experiment comprised four study/test blocks giving two possible run-orders: FSFS for half the participants and SFSF for the other half.

**Statistics**

The behavioural data were analysed in terms of (i) recognition accuracy; (ii) probability estimates of recollection and familiarity; and (iii) accuracy of the view judgement for each stimulus category.

(i) Recognition accuracy was assessed using the discrimination index *Pr*. This index provides one way to separate true discrimination from response bias (Snodgrass & Corwin, 1988). It is based on a two-high threshold model: one threshold for accepting old items as old (*P*o) and the other for accepting new items as new (*P*n). According to the model, an area of uncertainty lies in between the two thresholds, and items falling into this area produce guesses, which in some cases lead to misses and false alarms. For simplicity, it is assumed that *P*o and *P*n are equal and this common threshold is called *Pr* which is calculated using the formula *p*(hit)-*p*(false alarm), i.e. the proportion of old items to which participants correctly responded "yes" minus the proportion of new items to which participants incorrectly responded "yes". An alternative would have been to use d', derived from signal detection theory (SDT). SDT relies on the assumption of equal variance and normality for old and new distributions. This assumption, however, has recently been challenged in the recognition memory literature (Wixted, 2007). In practice, *Pr* and d' tend to yield similar results (Snodgrass & Corwin, 1988; in one experiment *Pr* was found to be slightly more sensitive) and so the decision was made to use *Pr*, with the additional advantage that it requires a simpler transformation of the data. Note that there is a single set of new items for each stimulus category and so the same value for false alarms was used to calculate *Pr* for both the same- and different-view conditions. The level of *Pr* for each stimulus category was entered into a repeated-measures analysis of variance (ANOVA) with two within-subjects factors, "stimulus" (faces or scenes) and "view" (same or different).

(ii) Probability estimates of the levels of recollection and familiarity were derived as follows. The uncorrected proportion of old items given R responses was used to measure recollection. The question of how best to assess levels of familiarity was more complex. In the original procedure, as described by Tulving (1985), the proportion of old items given *know* responses was used as a direct measure of familiarity. Since participants were required to only respond *know* in the absence of

recollection, this procedure therefore assumed that recollection and familiarity were mutually exclusive. As discussed earlier, it is unlikely that this is the most appropriate way to model the relationship between recollection and familiarity and furthermore, it would contradict all of the dual-process models described in Chapter 1. Most dual-process models assume a relationship of independence between the two processes. In the current chapter, therefore, estimates of recollection and familiarity were derived using an alternative method developed by Yonelinas and Jacoby (1995), which is in keeping with the independence assumption, known as the "independence remember/know method". This model assumes that, as stated above, the proportion of old items given R responses provides a direct measure of levels of recollection:

$$\text{Recollection} = p(\text{R}|\text{old})$$

The proportion of F responses will underestimate the true rate of familiarity, since some items receiving an R response will have also been familiar. F responses therefore only measure the probability that as item was familiar and it was not recollected:

$$p(\text{F}|\text{old}) = \text{Familiarity}(1 - p(\text{R}|\text{old}))$$

Rearranging this equation to calculate familiarity gives:

$$\text{Familiarity} = p(\text{F}|\text{old}) / (1 - p(\text{R}|\text{old}))$$

To obtain a measure of discriminability, these values were corrected for false alarm rates (analogous to *Pr* above), giving the following equations for recollection and familiarity:

$$\text{Recollection} = p(\text{R}|\text{old}) - p(\text{R}|\text{new})$$

$$\text{Familiarity} = p(\text{F}|\text{old}) / (1 - p(\text{R}|\text{old})) - p(\text{F}|\text{new})/(1 - p(\text{R}|\text{new}))$$

Note that, similarly to the calculations used for recognition accuracy, the same response rates for false alarms were used for both same- and different-view calculations. These measures were entered into a repeated-measures ANOVA incorporating the factor "memory category" (recollection or familiarity) in addition to

"stimulus" and "view". The inclusion of estimates of recollection and familiarity in a single ANOVA may seem unusual; however, this enabled the assessment of the relative effect of stimulus category on the level of these two processes (and the theoretical independence of the scores helps to justify the assumptions of the ANOVA).

The analyses described above were designed to compare the relative levels of recollection and familiarity associated with recognition memory for faces and scenes. An alternative way to estimate the relative reliance of recognition memory for each stimulus category on recollection is to simply measure the probability that an item is recollected given that it is a hit, i.e. *p*(R|Hit). This has the advantage of making no assumptions regarding the relationship between recollection and familiarity. This measure was derived for each stimulus category and entered into a repeated-measures analysis of variance (ANOVA) with two within-subjects factors, "stimulus" (faces or scenes) and "view" (same or different).

(iii) Performance on the view discrimination was calculated using a similar equation to that used for recognition accuracy (*Pr*): *p*("same"|same hit)-*p*("same"|different hit), i.e. the proportion of old items presented from the same view to which participants correctly responded "same" minus the proportion of old items presented from a different view to which participants incorrectly responded "same" (compare with calculation of *Pr* in point (i)). Trials on which participants responded "don't know" were excluded from the calculations. Two analyses were carried out. One examined the effect of stimulus category on performance of the view judgement, irrespective of whether participants responded R or F, using a paired-samples *t*-test with the single factor, "stimulus". For the second analysis, separate measures of performance on the view discrimination were derived for items to which subjects responded R or F, to assess whether the former were associated with improved accuracy compared with the latter. A 2-way ANOVA was performed with the factors "memory category" (which in this case corresponded to items receiving an R or F response, rather than measures of recollection or familiarity as before), and "stimulus". Note that since these analyses looked at view *discrimination*, a single value described the performance across the same- and different-view conditions combined, and therefore the factor "view" was not present in these analyses.

Finally, four single-sample *t*-tests were carried out, to assess whether performance on the view discrimination differed significantly from chance for items receiving an F response and those receiving an R response on each stimulus category.

Any interactions observed using the ANOVAs described above were examined further using appropriate ANOVAs or *t*-tests broken down by one of the interacting factors. All quoted *p* values are two-tailed.

## *Results*

A complete breakdown of the average proportion of responses in each category across the 19 subjects who were included in the analyses below is presented in Table 4.1.

***Table 4.1 Mean number of each response combination for each category of item in Experiment 1.***

| **Yes/No**<br>**R/F**<br>**View** | *Yes*<br>*R*<br>*Same* | *Yes*<br>*R*<br>*Different* | *Yes*<br>*R*<br>*DK* | *Yes*<br>*F*<br>*Same* | *Yes*<br>*F*<br>*Different* | *Yes*<br>*F*<br>*DK* | *No*<br>-<br>- |
|---|---|---|---|---|---|---|---|
| **Studied Items** | | | | | | | |
| *Same view faces* | 22.6 (8.7) | 7.6 (5.4) | 1.2 (1.9) | 6.8 (9.4) | 7.7 (5.3) | 3.8 (4.3) | 10.1 (4.2) |
| *Different view faces* | 5.6 (4.6) | 9.3 (6.3) | 0.8 (1.5) | 3.1 (4.4) | 13.0 (6.4) | 4.4 (4.7) | 23.8 (7.2) |
| *Same view scenes* | 34.0 (9.7) | 4.7 (3.3) | 0.7 (1.6) | 6.2 (9.8) | 6.1 (3.4) | 2.1 (3.1) | 6.3 (3.6) |
| *Different view scenes* | 9.1 (5.5) | 16.4 (9.7) | 0.4 (0.8) | 3.4 (4.8) | 12.0 (5.8) | 2.1 (2.8) | 16.7 (5.2) |
| **New Items** | | | | | | | |
| *Faces* | 2.1 (3.1) | 2.4 (2.1) | 0.2 (0.7) | 1.7 (2.1) | 5.6 (4.7) | 3.5 (4.2) | 44.3 (9.1) |
| *Scenes* | 1.5 (1.7) | 2.6 (3.5) | 0.2 (0.5) | 0.8 (1.2) | 4.5 (4.0) | 2.1 (3.1) | 48.3 (6.9) |

***Each row sums to a total of 60 items (standard deviations presented in parentheses). R: remember; F: familiar; DK: don't know.***

### Recognition accuracy

The average recognition accuracy level for each condition is illustrated in Figure 4.2. There were significant main effects of "stimulus" and "view" ("stimulus": $F_{(1,18)} = 24.02$; $p < 0.001$; "view": $F_{(1,18)} = 180.73$; $p < 0.001$), but the interaction was not significant ($p > 0.1$). Similarly to the previous experiments, and as expected, performance was worse on the different-view than the same-view conditions. In contrast to control performance in the previous two experiments, however, the main effect of stimulus reflected better performance on the scene than the face conditions.

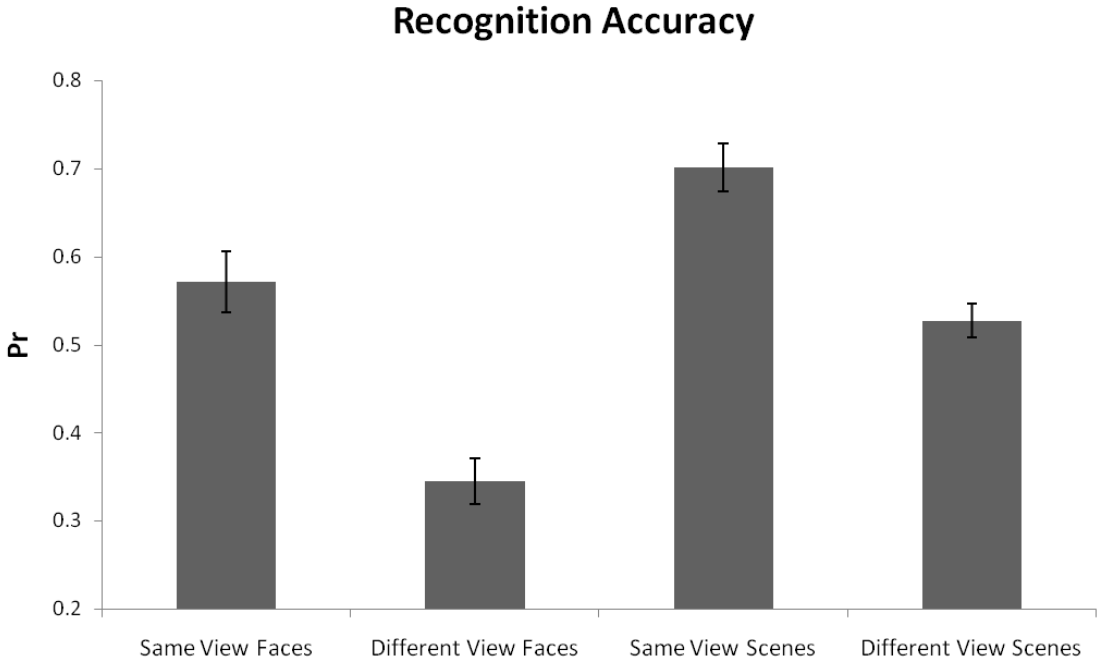


***Figure 4.2 Mean recognition memory performance (± S.E.) on each stimulus condition in Experiment 1 as measured by Pr (hits - false alarms).***

### Probability estimates of recollection and familiarity

Average probability estimates of recollection and familiarity corrected for false alarm rates for each condition are illustrated in Figure 4.3. There was a marginally significant interaction between "view" and "memory category" ($F_{(1,18)} = 4.14$; $p = 0.06$), which reflected a larger advantage for same-view items in terms of levels of recollection than familiarity. All other interactions were non-significant (all $p > 0.2$). Separate analyses performed on estimates of recollection and familiarity revealed a main effect of "view" in both cases (recollection: $F_{(1,18)} = 95.87$; $p < 0.001$; familiarity: $F_{(1,18)} = 40.11$; $p < 0.001$), reflecting higher levels of both recollection and familiarity for same- than different-view stimuli. Both analyses also

revealed a main effect of "stimulus" (recollection: $F_{(1,18)} = 29.45$; $p < 0.001$; familiarity: $F_{(1,18)} = 11.24$; $p < 0.005$), reflecting significantly higher levels of recollection and familiarity on the scene than the face conditions.

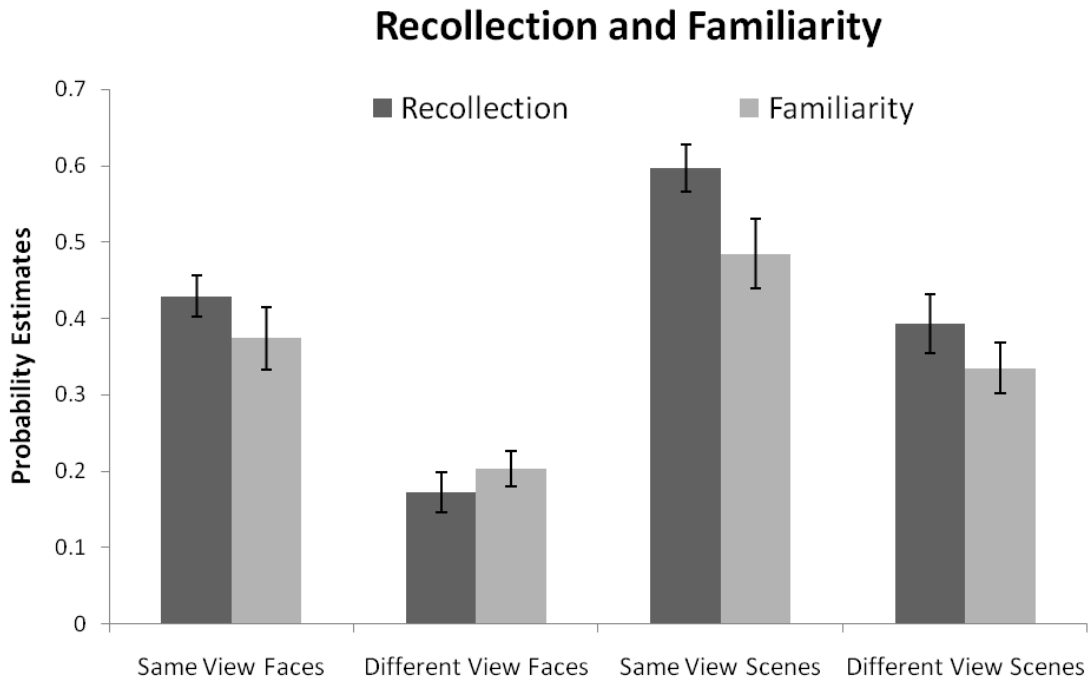


***Figure 4.3 Mean probability estimates (± S.E.) of recollection and familiarity on each condition in Experiment 1.***

The average proportion of hits for which participants responded R are presented in Figure 4.4. There was a significant interaction between the two factors, "stimulus" and "view" ($F_{(1,18)} = 4.87$; $p < 0.05$). This reflected a greater increase in the proportion of hits receiving R responses for scenes compared with faces when items were shown from a different-, as opposed to the same-view. Paired *t*-tests revealed, however, that scene hits were associated with a significantly higher proportion of R responses than face hits in both same- and different-view conditions (same-view: $t_{(18)} = 3{,}87$; $p < 0.005$; different-view: $t_{(18)} = 4.89$; $p < 0.001$).

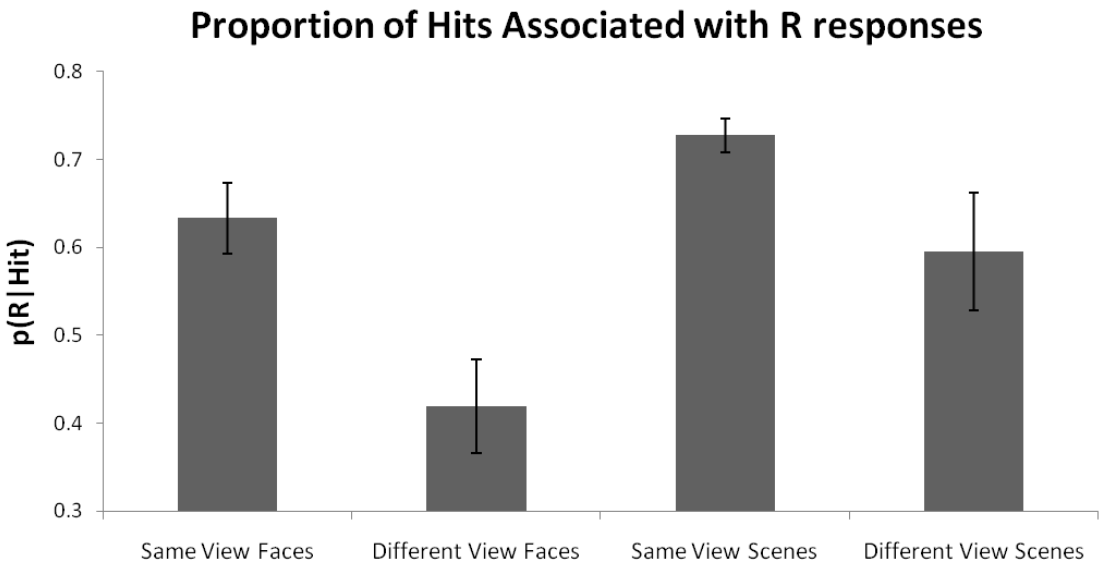


***Figure 4.4 Mean proportion of hits which received a remember (R) response for each condition in Experiment 1.***

### View discrimination

The mean performance level on the view judgement, ignoring whether subjects responded R or F, can be found in Figure 4.5. Performance was significantly better on the scene than the face conditions ($t_{(18)} = 2.72$; $p < 0.05$).

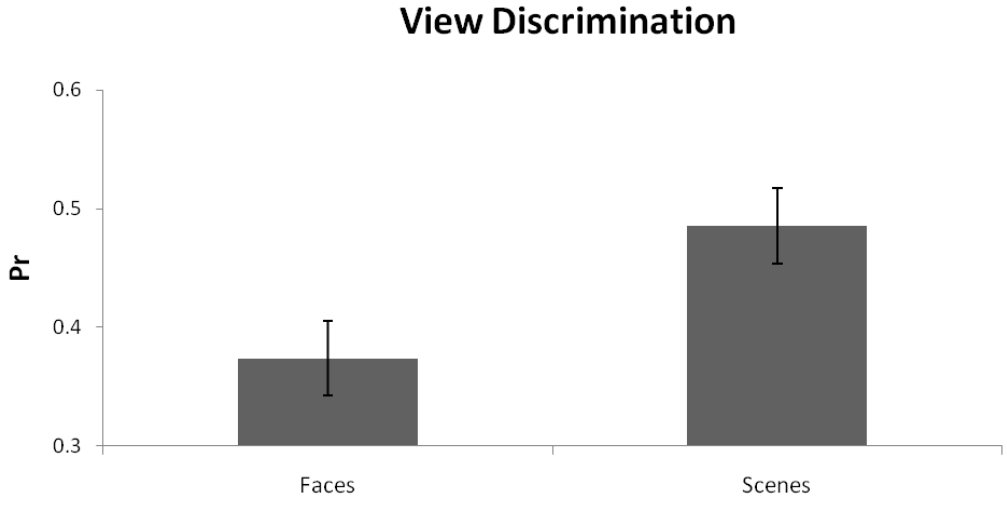


***Figure 4.5 Mean performance (± S.E.) on the view discrimination across the two stimulus categories in Experiment 1.***

Further analyses were performed in order to establish whether R responses led to better accuracy on the view judgement than F responses. The average accuracy levels on the view

judgement, split according to whether subjects responded R or F, for each condition, are illustrated in Figure 4.6. There was a significant 2-way interaction between both factors: "stimulus" and "memory category" ($F_{(1,18)} = 4.84$; $p < 0.05$), reflecting a larger advantage for view discrimination following R versus F responses on the scene than the face conditions. *T*-tests revealed, however, that R responses were associated with improved view judgement compared with F responses for both stimulus categories (faces: $t_{(18)} = 2.61$; $p < 0.05$; scenes: $t_{(18)} = 4.86$; $p < 0.001$). That said, view judgement performance was significantly above chance, both for items receiving F responses, as well as those receiving an R response, (F faces: $t_{(18)} = 3.48$; $p < 0.005$; R faces: $t_{(18)} = 8.01$; $p < 0.001$; F scenes: $t_{(18)} = 3.17$; $p < 0.01$; R scenes: $t_{(18)} = 10.90$; $p < 0.001$).

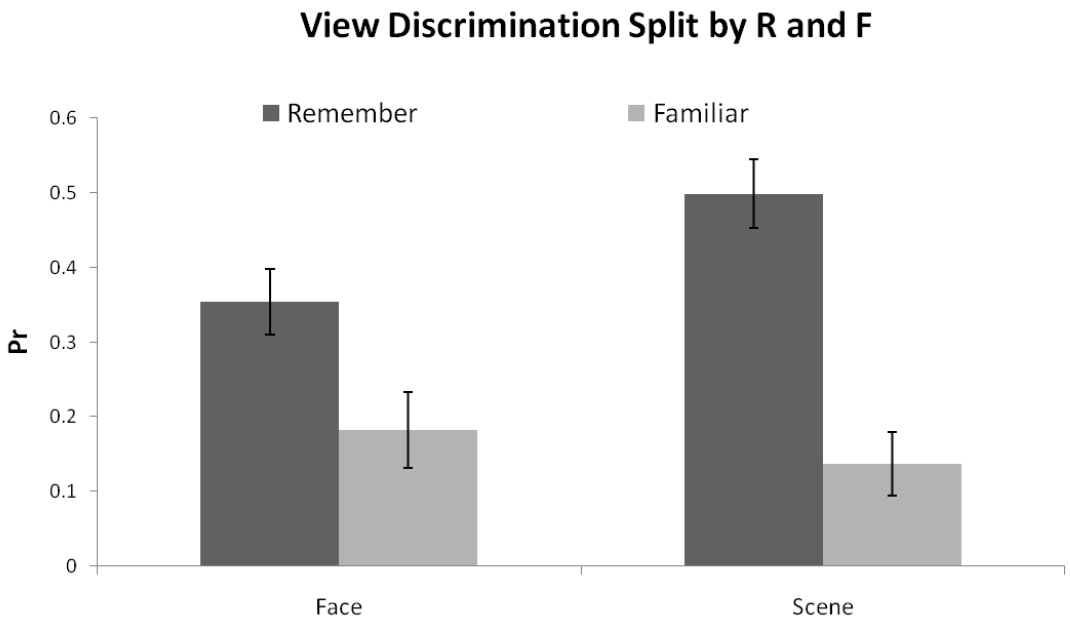


***Figure 4.6 Mean performance (± S.E.) on the view discrimination across the two stimulus categories in Experiment 1, split according to whether items received an R or F response.***

## *Discussion*

The results of the previous two chapters revealed stimulus-specific dissociations between the recognition memory impairments of patients with damage to different MTL structures. These results are consistent with theories proposing modality-specific specialisation in the MTL, with the hippocampus and perirhinal cortex supporting spatial and object processing respectively (Buckley et al., 2004 & Gaffan, 2004; Lee, Barense et al., 2005; Murray et al., 2007). It is possible, however, that these effects are related to dual-process models of MTL

function (Aggleton & Brown, 1999; Eichenbaum et al., 2007); more specifically, recognition memory for scenes might be more associated with recollection, which is thought to depend on the hippocampus, whereas recognition memory for faces may be more associated with familiarity signals in the perirhinal cortex. The findings of the current experiment provide mixed support for this possibility.

In one analysis, which assumed a relationship of independence between recollection and familiarity, levels of both processes were found to be higher for scenes than for faces, when corrected for false alarms, and there was no evidence of disproportionately high levels of recollection relative to familiarity for scenes compared with faces. A second analysis revealed, however, that correctly recognised scenes were more likely to be accompanied by recollection than correctly recognised faces, for both same- and different-views. This suggests that when recognition of old items occurs, it is more likely to be based on recollection when the stimuli involved are scenes rather than faces. The measures on which these two analyses were based differed in a number of ways, and there are therefore several possible reasons for the apparent discrepancy between the results of the two methods. The crucial point is that recognition memory for faces and scenes cannot be assumed to be equivalently supported by the two processes.

The current experiment, therefore, provides some evidence that the control participants reported in Chapters 2 and 3 may have relied on recollection to a greater extent on the scene than the face conditions. If one were to assume that recollection depends more than familiarity on the hippocampus, regardless of the stimulus category involved, then this might explain why selective damage to the hippocampus had a significantly greater impact on recognition memory for scenes than for faces in Chapter 2. A crucial question which follows from this possibility, however, is *why* recognition memory for scenes and faces should be more associated with recollection and familiarity respectively. One possibility is that there is something inherent in the visual form of the two stimulus categories which leads to different processing requirements. For example, faces tend to be processed holistically, as a "gestalt" (Schiltz & Rossion, 2006; Tanaka & Farah, 1993; Young, Hellawell, & Hay, 1987), which may increase reliance upon a signal detection-like familiarity process in perirhinal cortex (Yonelinas et al., 1999). Memory for complex scenes, on the other hand, may stress memory for associations between the various elements comprising the scene, which may not be adequately supported by familiarity and may therefore require hippocampally-dependent

recollection (Yonelinas, 1997, 2002). Strictly speaking, however, recollection normally refers to associations between a stimulus and the episodic context in which it was studied and the question then remains as to why scenes engender stronger item-context associations than do faces. Furthermore, the types of associative memory tests that have been shown to necessitate recollection generally involve pairwise recombinations of studied items such that familiarity for the two elements of each test item, be it target or foil, are equally familiar (e.g. Mayes et al., 2004; Yonelinas, 1997; Yonelinas et al., 1999). Since the scene stimuli used in the current experiment were not recombinations of studied elements, it is not immediately obvious why assessing the relative familiarity of target and foil items would not be sufficient to solve the task.

Moreover, there is no reason to assume that the behavioural association between scenes and levels of recollection suggested by the current experiment is indicative of a direct causal link, such as the one proposed above. The relationship between levels of recollection or familiarity and particular stimulus categories might arise, not because of an inherent difference in the processing requirements of particular stimuli, but simply as an artefact of parallel specialisations in particular brain regions. For example, the hippocampus is thought to be specialised for supporting spatial processing, and this is perhaps primarily because it receives the information required to do so, by virtue of its anatomical connections (e.g. Aggleton et al., 2000), and because it contains place cells which equip it for this function (Ekstrom et al., 2003; O'Keefe & Nadel, 1978). Similarly, the hippocampus is also thought to be particularly well equipped to support recollection, since sensory inputs from all modalities converge there (Lavenex & Amaral, 2000) and it has the appropriate computational capabilities (Norman & O'Reilly, 2003). These two potentially unlinked specialisations could result in an increased incidence of recollection for scenes, relative to stimuli processed elsewhere. In other words, perhaps scenes could theoretically be recognised just as well as faces on the basis of familiarity, but they just happen to be associated with higher levels of recollection by virtue of the fact that they are predominantly processed by the hippocampus.

The foregoing discussion assumes that the mapping between recollection and familiarity proposed by Aggleton and Brown (1999) holds for all stimulus categories. This is far from established, however, since the majority of studies which have investigated the anatomical bases of recollection and familiarity have used verbal memoranda, and very few have directly

compared different stimulus categories. As stated in the introduction, the possibility remains that in the case of visual stimuli, the brain regions required to support the processes underlying recognition memory vary according to the category of stimulus involved. This possibility will be explored in the fMRI experiments reported in Chapter 5, which may help to clarify the precise implications of the results from the current chapter for the effects reported in Chapters 2 and 3.

A surprising finding from the current experiment, is that recognition accuracy in the current experiment was significantly better for scenes than for faces, which is the opposite pattern to that found in controls in the previous two chapters. In fact, the advantage for scenes over faces was evident in terms of levels of recollection and familiarity and also view discrimination. The reversal in the pattern of recognition accuracy between the two experimental designs was probably the result of changing from a forced-choice to a yes/no test format, and/or the switch to using non-matched targets and foils. This change in performance must be kept in mind when comparing across the yes/no and forced-choice experiments in the current thesis. Unfortunately it is impossible to know whether the changes reflect an alteration in the relative contributions of recollection and familiarity for the two stimulus categories.

Although there are no data that speak directly to this issue (since comparisons across different stimulus categories have not been made), the question of whether switching between forced-choice and yes/no paradigms affects the contributions of recollection and familiarity to performance on tests of recognition memory has been addressed by a number of studies. It has been suggested that recognition memory tests which involve a yes/no format may depend more on recollection than forced-choice tests (Aggleton & Shaw, 1996; Bastin & Van der Linden, 2003; Parkin, Yeomans, & Bindschaedler, 1994). Others suggest, however, that this will only be the case when targets and foils are visually similar to one another (Holdstock et al., 2002; Westerberg et al., 2006). This follows from the Complementary Learning Systems model of recognition memory (Norman & O'Reilly, 2003).

According to this model, familiarity is supported by the neocortex, via a system of overlapping representations which enable generalisation among similar items. Familiarity levels are thought to be well described by signal detection theory (SDT), with target and foil stimuli being represented by overlapping Gaussian distributions. When targets and foils are

very similar, these distributions will be highly overlapping, meaning that the familiarity of foils matched to well-encoded targets may exceed that of targets which were encoded less well, i.e. the discriminability between targets and foils will be low. This means that when performance depends on the adoption of a single threshold level of familiarity, above which items are accepted as old, as is the case in a yes/no paradigm, errors will frequently occur. A high criterion will lead to a low hit rate, whereas a low criterion will lead to a high false alarm rate. In this case, hippocampally-based recollection which is supported via a network which is equipped to support pattern separation will provide much more reliable information. In a forced-choice format, however, the participant can take advantage of the fact that each target should have a reliably higher level of familiarity than its matched foils, thus performance may be relatively normal in the absence of recollection. In cases where targets and foils are unrelated, the familiarity distributions of targets and foils should be separate enough to support accurate recognition based on levels of familiarity, regardless of test format. Overall, familiarity can be relied upon in yes/no paradigms, provided the targets and foils are not visually related, and also in forced-choice paradigms, regardless of how similar targets and foils are.

Support for this view comes from findings in amnesic patients in whom impaired recollection combined with relatively intact familiarity has been established. For example, the bilateral hippocampal amnesic patient YR was equivalently impaired on a series of recognition memory tests for both visual and verbal stimuli which involved unrelated targets and foils, regardless of testing format (Mayes et al., 2002; see also Khoe, Kroll, Yonelinas, Dobbins, & Knight, 2000). In a recognition memory test involving silhouettes of objects in which there was a high degree of similarity between targets and foils, however, impairments were observed on a yes/no but not a forced-choice test in patient YR. This latter finding has been replicated in a group of MCI patients, who are assumed to have damage predominantly affecting the hippocampus and entorhinal cortex, using the same test materials (Westerberg et al., 2006).

Experiments in healthy participants using the remember/know procedure provide further support for this view. For example, Bastin and Van der Linden (2003) reported a disproportionately high contribution of familiarity to forced-choice compared with yes/no recognition memory for faces, when targets and foils were visually similar. In contrast, the contribution of recollection and familiarity to verbal recognition memory was not affected by

test format when targets and foils were unrelated (Khoe et al., 2000).

The above findings would suggest that, had the visually similar foils which were used in previous chapters been retained in the current experiment, then performance may have become very reliant on recollection due to the switch to a yes/no format. The switch to unrelated targets and foils may therefore have helped to cancel out some of the effects of the change in test format, in terms of the balance between recollection and familiarity. Since levels of recollection and familiarity were not measured in the previous chapters, it is difficult to establish what effect these changes in experimental design actually had in this case. It is reassuring, however, that the levels of recollection and familiarity were well below ceiling and above floor for all conditions in the current experiment, and there is no reason to think that this was not the case for the control participants in Chapters 2 and 3.

In the current experiment, as in those of the previous chapters, performance was significantly worse on the different- than on the same-view conditions. This was particularly true of levels of recollection which were affected to a significantly greater extent by a view change than levels of familiarity. The reason for the relatively small effect of view changes on levels of familiarity could be explained by the Complementary Learning Systems model of recognition memory (Norman & O'Reilly, 2003) described above. Since different views of the same item share many visual features with their original views, there will be a high degree of overlap between their representations, resulting in similar levels of familiarity for same and different views. The fact that the representations of different views of particular items are so similar may also account for the fact that performance on the view discrimination was poor for items which were familiar but not recollected, compared to those which were recollected. The ability to generalise across different views of items and the inability to distinguish between different views can be viewed as two sides of the same coin. This can be contrasted with recollection, which was more disrupted by altered views, but led to an increased ability, when items were accepted, to correctly judge whether a view change had occurred. This pattern of performance may reflect the fact that the representations which are thought to support recollection are also better able to support pattern separation. These contrasting effects highlight the complementary nature of the processes of recollection and familiarity.

In summary, the current experiment provided some evidence of an increased reliance upon recollection during recognition memory for scenes relative to faces. The implications of this

result will be explored further in Chapter 5, in the light of an MRI investigation into the neural correlates of recollection and familiarity for faces and scenes. It is unfortunate that the changes in experimental design between the current experiment and that used in Chapters 2 and 3 has resulted in a switch in advantage from face to scene recognition memory. This makes the assumption that the underlying processes across the two experimental designs are the same, less certain. Notably, this switch in performance would only be an issue if there were reasons to think that this change reflected a change in the relative contributions of recollection and familiarity to recognition of the two stimulus categories. A mini-review of the literature suggests that since unrelated foils were used in the current experiment, the switch from a forced-choice to a yes/no format is less likely to have significantly increased dependence on recollection in the current compared with the previous paradigm, than if related foils had been retained. Since it is not possible to rule out changes in the relative contribution of the two processes across the two experiments, however, these limitations should be kept in mind in the remainder of the thesis.

The following experiment investigated the performance of young participants on the same paradigm as that reported in Experiment 1 of the current chapter. The findings of this experiment will help to relate the findings reported in the thesis thus far, which all involve older participants, with those of the following chapter, which reports the results of two fMRI experiments investigating MTL activations associated with recognition memory for faces and scenes in young participants. In addition, the following experiment acted as a behavioural pre-trial for the imaging experiments reported in the following chapter.

# Experiment 2: Recollection and familiarity for faces and scenes in younger subjects

## *Materials and Methods*

### Participants

24 participants were recruited from the MRC Cognition and Brain Sciences volunteer panel. The data for four of the subjects were excluded for the same reason outlined in the previous experiment. In addition, the data for one further subject were excluded due to poor face recognition memory performance (> two standard deviations below average performance on both same- and different-view face conditions). This left 19 participants (9 female, mean age

20.3 years). All participants gave informed consent before undertaking the study. This investigation received ethical approval from the Cambridge and Southampton Health Authority Local Research Ethics Committees (UK).

### Behavioural Procedure

The behavioural procedure was identical to that of the previous experiment.

### Statistics

The statistical approach was identical to that of the previous experiment.

## *Results*

A complete breakdown of the average proportion of responses in each category across the 19 subjects who were included in the analyses below is presented in Table 4.2.

***Table 4.2 Mean number of each response combination for each category of item in Experiment 2.***

| **Yes/No** | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *No* |
|---|---|---|---|---|---|---|---|
| **R/F** | *R* | *R* | *R* | *F* | *F* | *F* | - |
| **View** | *Same* | *Different* | *DK* | *Same* | *Different* | *DK* | - |
| **Studied Items** | | | | | | | |
| *Same view faces* | 21.8 (7.3) | 5.6 (4.4) | 2.1 (2.0) | 5.3 (5.1) | 5.3 (3.6) | 6.2 (4.0) | 13.7 (6.1) |
| *Different view faces* | 3.4 (3.6) | 9.6 (6.0) | 1.1 (1.2) | 2.2 (1.8) | 7.8 (3.9) | 7.1 (5.1) | 28.8 (8.0) |
| *Same view scenes* | 33.0 (9.0) | 3.6 (3.5) | 1.6 (2.1) | 4.6 (4.8) | 3.9 (3.2) | 5.1 (4.6) | 8.2 (6.1) |
| *Different view scenes* | 6.4 (3.9) | 18.4 (8.7) | 1.2 (2.3) | 2.2 (2.0) | 9.1 (6.9) | 5.3 (4.2) | 17.5 (8.8) |
| **New Items** | | | | | | | |
| *Faces* | 0.7 (1.3) | 2.7 (4.7) | 0.4 (0.9) | 1.1 (1.5) | 3.2 (2.6) | 5.2 (3.7) | 46.8 (9.6) |
| *Scenes* | 0.4 (0.8) | 1.9 (2.2) | 0.1 (0.3) | 1.0 (1.1) | 3.6 (2.6) | 4.5 (4.3) | 48.5 (7.0) |

***Each row sums to a total of 60 items (standard deviations presented in parentheses). R: remember; F: familiar; DK: don't know.***

### Recognition accuracy

The average recognition accuracy level for each condition is illustrated in Figure 4.7. Unlike the results of Experiment 1, there was a significant interaction between "stimulus" and "view" ($F_{(1,18)} = 16.11$; $p < 0.001$). *T*-tests revealed, however, superior performance on the same- than the different-view conditions for both stimulus categories (face: $t_{(18)} = 10.23$; $p < 0.001$; scene: $t_{(18)} = 6.71$; $p < 0.001$). The "stimulus" x "view" interaction reflects a larger effect of "view" on recognition accuracy on the face than the scene conditions. As in the previous experiment, performance was better on the scene compared with the face conditions (same-view: $t_{(18)} = 4.01$; $p < 0.001$; different-view: $t_{(18)} = 5.72$; $p < 0.001$).

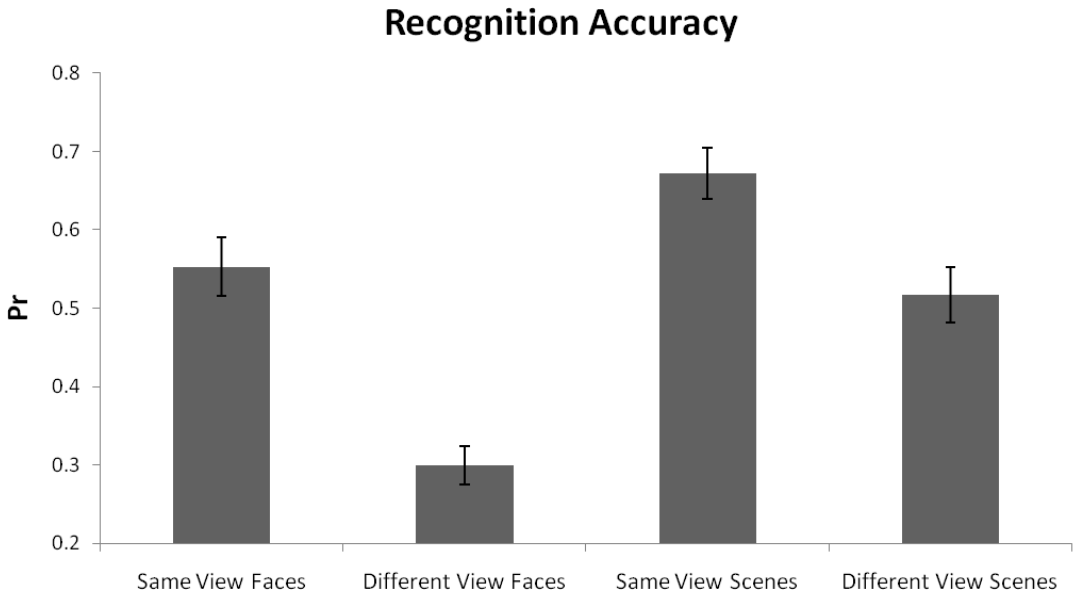


***Figure 4.7 Mean recognition memory performance (± S.E.) on each stimulus condition in Experiment 2 as measured by Pr (hits - false alarms).***

### Probability estimates of recollection and familiarity

Average probability estimates of recollection and familiarity for each condition are illustrated in Figure 4.8. Unlike the results of Experiment 1, there was a significant "stimulus" x "memory category" interaction ($F_{(1,18)} = 5.28$; $p < 0.05$), and the "view" x "memory category" interaction also reached significance ($F_{(1,18)} = 8.93$; $p < 0.01$). The interaction between "stimulus" and "memory category" reflects a greater increase in levels of recollection for scenes compared with faces, than the increase observed in familiarity. Similarly, the interaction between "view" and "memory category" reflects a greater increase in levels of recollection for same-view compared with different-view items, than the increase observed in familiarity for same- relative to different-view items. Separate analyses

performed on estimates of recollection and familiarity revealed a main effect of "stimulus" in both cases (recollection: "stimulus": $F_{(1,18)} = 36.44$; $p < 0.001$; familiarity: $F_{(1,18)} = 22.73$; $p < 0.001$), indicating significantly higher levels of recollection and familiarity on the scene than the face conditions. Both analyses also revealed a main effect of "view" (recollection: $F_{(1,18)} = 156.88$; $p < 0.001$; familiarity: $F_{(1,18)} = 38.73$; $p < 0.001$), reflecting higher levels of both recollection and familiarity for same- than different-view stimuli.

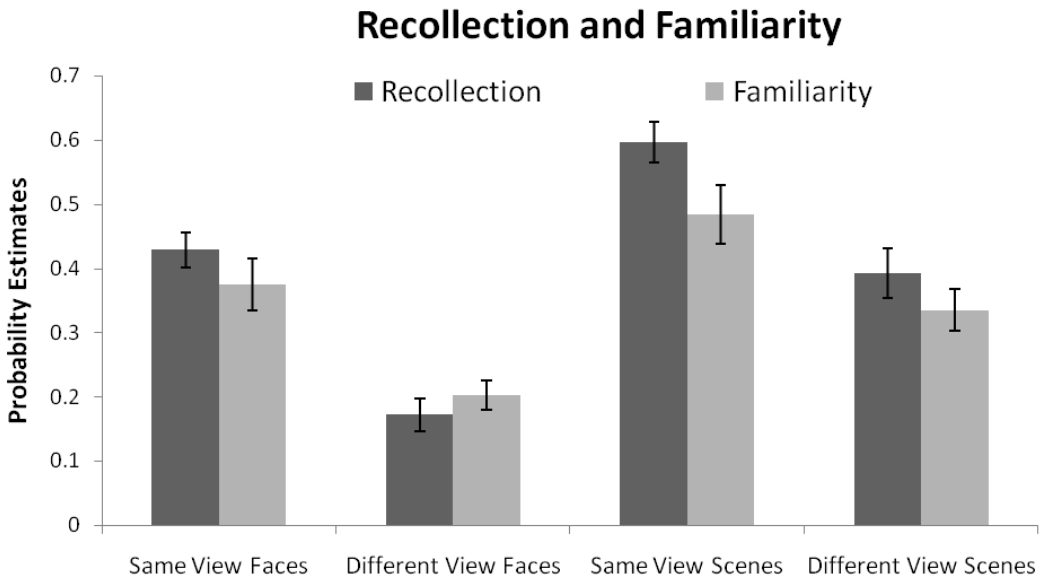


***Figure 4.8 Mean probability estimates (± S.E.) of recollection and familiarity on each condition in Experiment 2.***

The average proportion of hits for which participants responded R are presented in Figure 4.9. There were significant main effects of "stimulus" and "view" ("stimulus": $F_{(1,18)} = 37.42$; $p < 0.001$; "view": $F_{(1,18)} = 86.02$; $p < 0.001$), but unlike the previous experiment, the interaction was not significant ($p > 0.1$). The main effects reflected a greater proportion of R responses for hits in the scene than the face conditions, and also in the same- compared with the different-view conditions.

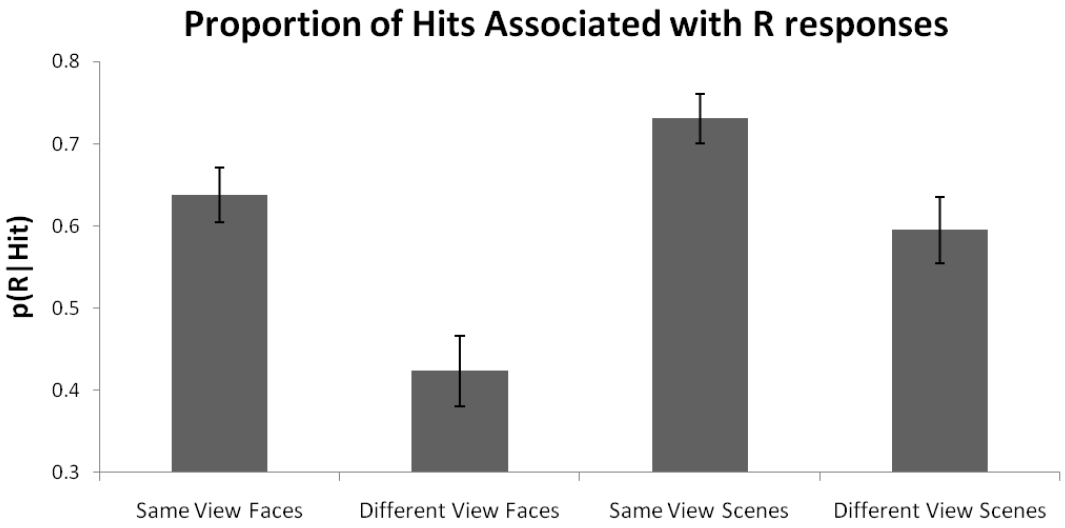


***Figure 4.9 Mean proportion of hits which received a remember (R) response for each condition in Experiment 2.***

### View discrimination

The mean performance level on the view judgement, ignoring whether subjects responded R or F, can be found in Figure 4.10. As in the previous experiment, performance was significantly better on the scene than the face conditions ($t_{(18)} = 3.77$; $p < 0.005$).

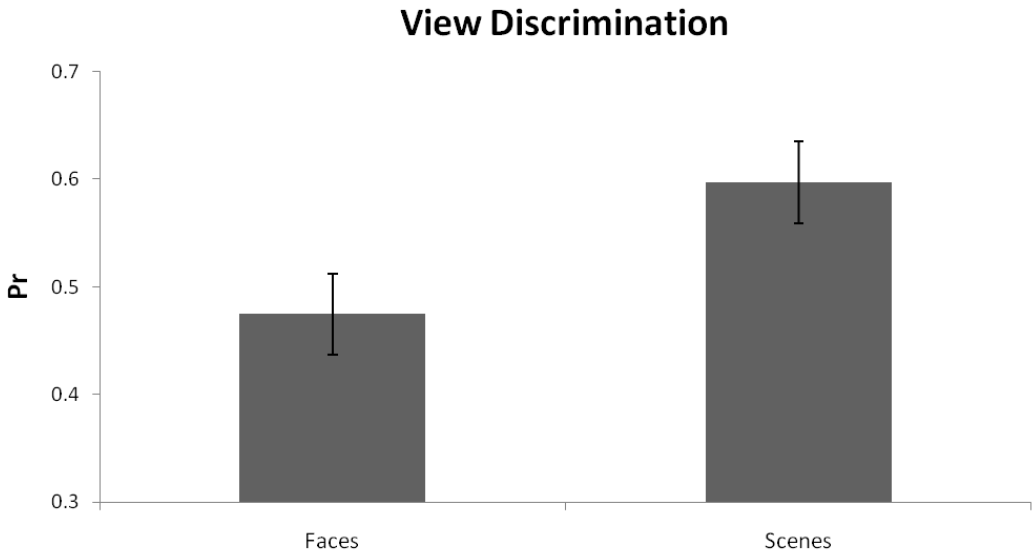


***Figure 4.10 Mean performance (± S.E.) on the view discrimination across the two stimulus categories in Experiment 2.***

As before, further analyses were performed in order to establish whether R responses led to better view discrimination than F responses. The average accuracy levels on the view judgement, split according to whether subjects responded R or F, for each condition, are

illustrated in Figure 4.11. Unlike the previous experiment, the interaction between "stimulus" and "memory category" was not significant ($p > 0.5$). There was, however, a significant main effect of "memory category" ($F_{(1,18)} = 34.49$; $p < 0.001$). This reflects improved view discrimination following R compared with F responses.

View discrimination performance was significantly above chance, both for items receiving F responses, as well as those receiving an R response, (F faces: $t_{(18)} = 3.83$; $p < 0.005$; R faces: $t_{(18)} = 12.08$; $p < 0.001$; F scenes: $t_{(18)} = 4.18$; $p < 0.001$; R scenes: $t_{(18)} = 21.44$; $p < 0.001$).

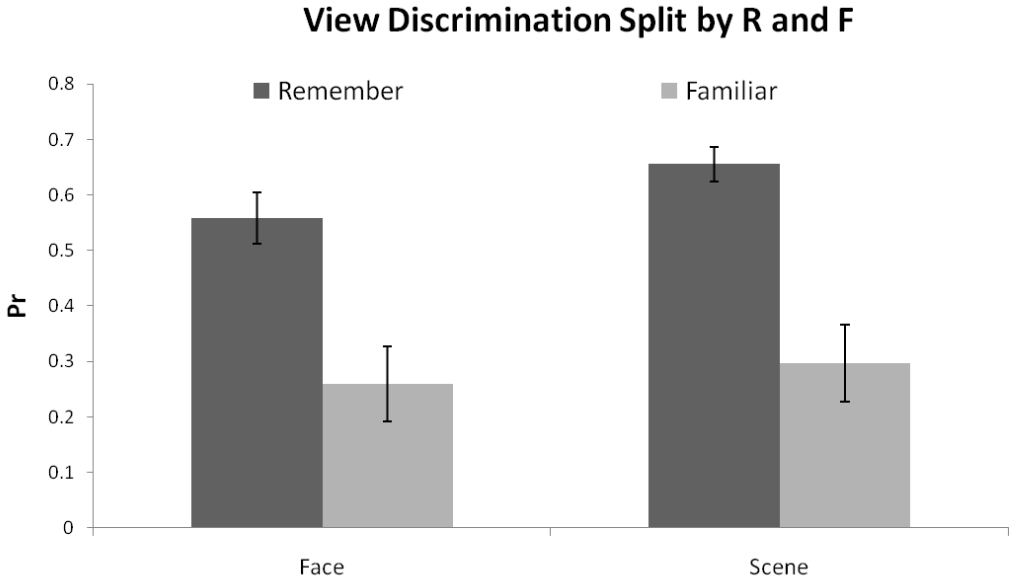


***Figure 4.11 Mean performance (± S.E.) on the view discrimination across the two stimulus categories in Experiment 1, split according to whether items received an R or F response.***

### Comparison of younger and older subjects

The data from Experiments 1 and 2 are presented side-by-side in Figure 4.12 to aid visual comparison between old and young participants. In order to assess the effect of aging on each element of the recognition memory task, each of the analyses described in the *statistics* section were performed on the combined results of Experiments 1 and 2, with the addition of the between-subjects factor "age".

The analyses of recognition accuracy, probability estimates of recollection and familiarity, and the proportion of hits receiving R responses revealed no main effect of, or interactions involving, the factor "age" (all $p > 0.2$). Performance by the two groups on these three

measures were therefore statistically indistinguishable. Analysis of data from the view discrimination, collapsed across R and F judgements, revealed significantly superior performance by the young participants ($F_{(1,36)}$ = 7.96; $p$ < 0.01), but no interaction with "stimulus" ($p$ > 0.8). The analysis of the view discrimination split for items receiving R and F responses also revealed a main effect of "age" ($F_{(1,36)}$ = 9.04; $p$ < 0.01), but once again, there were no significant interactions involving this factor (all $p$ > 0.2).

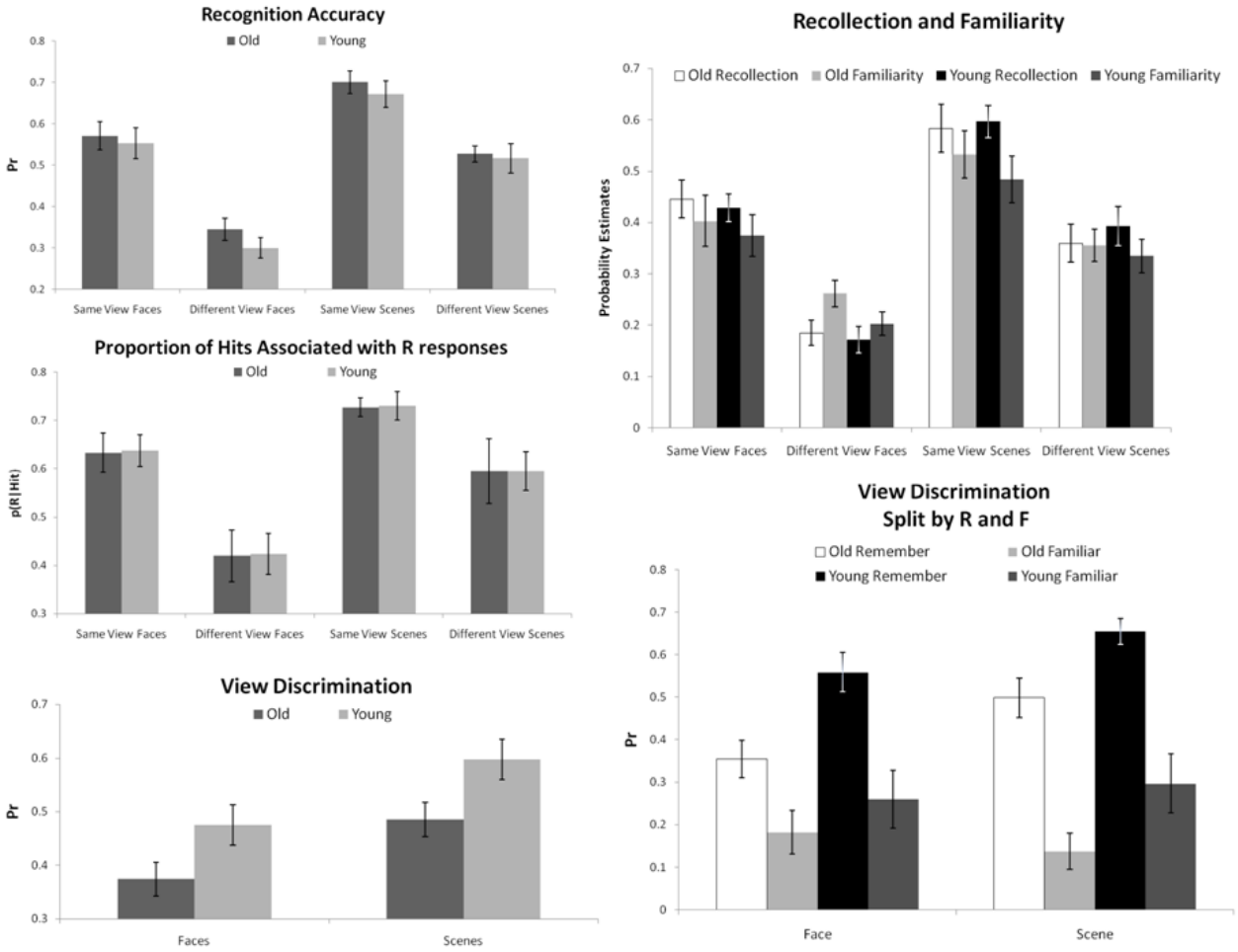


***Figure 4.12 Combined data from Experiments 1 and 2 for each of the five sets of analyses performed***

It is possible that older participants did not perform as well as young participants on the view discrimination due to a reluctance to use the *don't know* option as an alternative to guessing. In order to investigate this possibility, a further ANOVA was performed on the proportions of hits for each stimulus category to which participants responded *don't know*. Similarly to previous analyses, this ANOVA incorporated the factors "stimulus", "view", "memory category" and "age", each with two levels. Tables 4.1 and 4.2 include the raw data relevant

to this analysis. There was a significant "memory category" x "age" interaction ($F_{(1,36)}$ = 7.52; $p < 0.01$). Two further ANOVAs were therefore performed, with the data split according to whether participants responded R or F. In the analysis of items receiving an R response, there was a significant main effect of "stimulus" ($F_{(1,36)}$ = 11.85; $p < 0.01$), reflecting higher rates of *don't know* in the face than the scene conditions, but no other significant effects (all $p > 0.2$). In the analysis of items receiving an F response, however, there was a significant main effect of "age" ($F_{(1,36)}$ = 7.48; $p < 0.01$) reflecting significantly higher levels of *don't know* responses in the young participants than the older participants. The main effect of "stimulus" was also significant ($F_{(1,36)}$ = 10.13; $p < 0.01$), again indicating significantly higher numbers of *don't know* responses for faces than for scenes.

Since the younger participants were significantly more likely than older participants to respond *don't know* for items endorsed with F but not R responses, it is possible that the superior scores of the young participants on the view discrimination were driven by their performance on items receiving F responses, for which they may have been less likely to make incorrect guesses than older participants. Separate analyses of view discrimination for items receiving R responses revealed a main effect of age ($F_{(1,36)}$ = 14.69; $p < 0.001$), however, whereas the analysis of items receiving F responses did not ($p > 0.1$). It seems unlikely, therefore, that increased rates of *don't know* responses in younger participants were responsible for their improved view discrimination scores.

## *Discussion*

The performance observed in the present behavioural studies suggested that this task was suitable for adaptation for use in the subsequent imaging experiments. Unfortunately, it was not possible to equate performance on the face and scene conditions without making changes to one or more aspects of the task limited to one or other stimulus category. A manipulation such as increasing the exposure time to faces but not scenes, for example, may have helped to make the levels of performance more equivalent, but would have also confounded any effects of stimulus type with the effect that this change had in itself. Since the contrasts performed in the imaging experiments will be limited to items which received equivalent judgements, it was hoped that this difference in performance would not pose a problem.

The present experiment also provided a bridge between the imaging experiments, which

involved young participants, and the neuropsychological experiments described in Chapters 2 and 3, which involved older participants. The pattern of performance observed in Experiment 2 replicated many of the effects observed in Experiment 1. As in Experiment 1, overall recognition accuracy was superior on the same-view than the different-view conditions, and on the scenes compared to the faces. Performance on the view discrimination also replicated the advantage for scenes compared with faces, both for items receiving R responses as well as those receiving F responses. Unsurprisingly, there were also some differences in the patterns of performance between the two experiments. In Experiment 2, but not Experiment 1, there was a significant interaction in the analysis of recognition accuracy such that the advantage for same-view items was significantly greater on the face than the scene conditions. Conversely, in Experiment 1, but not Experiment 2, there was a significant interaction between memory category and stimulus on the view discrimination. These interactions are not of central importance, however, and direct statistical comparisons between the two experiments revealed that these differences in patterns of performance were not statistically significant.

The results of the current experiment replicated the finding from Experiment 1 that correct recognition of scenes was more likely to be associated with a remember response than correct recognition of faces. In addition, and in contrast to Experiment 1, the interaction between stimulus and memory category in the analysis of levels of recollection and familiarity was significant in the current experiment, suggesting that in young participants, levels of recollection, corrected for false alarms, relative to levels of familiarity, were disproportionately high for scenes relative to faces. It should be noted, however, that the two stimulus categories were not matched for overall difficulty, which may have influenced this finding. The levels of both processes were reliably higher for the scene than the face conditions and this result may therefore reflect a difference in scaling between recollection and familiarity, i.e. changes in the overall difficulty of a recognition memory task might always have a greater impact on recollection than familiarity. Since the relative difficulty of the face and scene tasks was reversed in the forced-choice paradigm used in Chapters 2 and 3, it is particularly difficult to know whether this difference would also apply to those experiments. Assuming that this result is genuine, however, and recognition memory for scenes and faces was disproportionately dependent on recollection and familiarity respectively in the controls reported in the previous chapters, this improves the ability of

dual-process theories of MTL function, to accommodate the findings reported in those chapters, as discussed previously.

Although, as outlined above, there were several differences between the results of the two experiments, direct comparisons between the two age groups revealed no significant differences in the pattern of performance on recognition accuracy or estimated levels of recollection and familiarity. This finding is helpful to the current thesis. Had significant differences been found between the two groups, then the validity of relating the findings of the imaging experiments in the following chapter, to the performance of the patient populations involved in Chapters 2 and 3 would have been questionable. Although one cannot assume that the neural processes underlying performance are necessarily equivalent in the healthy young and older populations, matched behavioural performance removes some of the potential problems associated with comparing performance across the experiments in this thesis which used young and older participants.

Although useful in terms of the thesis as a whole, the lack of any evidence for a difference between the two groups on levels of recollection and familiarity is somewhat surprising in the light of previous investigations into the effects of aging on recognition memory. The idea that recollection is impaired by aging is almost universally accepted, whereas familiarity is generally thought to remain intact in older participants. These ideas come in large part from studies which have used the process-dissociation procedure, and from the consistent finding that recall, associative and source memory are normally impaired in older participants whereas item recognition remains intact (Spencer & Raz, 1995; Yonelinas, 2002). Age-related impairments in recollection have frequently been observed in studies involving the remember/know paradigm (Bastin & Van der Linden, 2003; Friedman & Trott, 2000; Java, 1996; Norman & Schacter, 1997; Parkin & Walter, 1992). The study by Bastin et al. is of particular interest since it is one of the few which involved visual rather than verbal memoranda. The authors compared performance of young and older participants on both a yes/no and a forced-choice recognition memory test for unfamiliar faces in which each target was matched to a visually similar foil stimulus. For each trial in both experiments, participants were asked to make a single remember/know/guess judgement. Analysis of remember responses revealed impaired recollection in the older participants, as evidenced by reduced remember responses to old items (collapsed across test format) and increased

remember responses to new items on the yes-no task (with a trend towards this pattern in the forced-choice task), relative to the young participants. The older participants produced significantly higher rates of know responses to both old and new stimuli than the younger participants, indicating a greater reliance on familiarity in these subjects. The authors concluded that familiarity was significantly higher in older participants, although unlike the current experiment, this was based on the assumption of exclusivity between recollection and familiarity, so it is not clear whether the same conclusion would be made if the independence assumption was adopted.

Some recent studies have reported exceptions to the rule that recollection is universally impaired by aging and reveal that there is a high degree of variability in the older population (Cabeza, Anderson, Locantore, & McIntosh, 2002; Davidson & Glisky, 2002; Duarte et al., 2006). For example, Davidson and Glisky (2002) found that participants who scored poorly on one or both of two neuropsychological test batteries, thought to tap into MTL and frontal lobe function, demonstrated impaired recollection for verbal stimuli, as measured by the process-dissociation procedure. In contrast, levels of recollection in participants who performed well on both test batteries were equivalent to those of young participants. Familiarity was found to be normal in the older group with the exception of individuals who scored poorly on the MTL battery. More recently, Duarte et al. (2006) conducted an investigation of the effects of aging on the ERP correlates of recognition memory for simple pictures of objects. The authors split older participants into low- and high-performing groups based on overall recognition accuracy. High-performing groups exhibited intact recollection as measured by the remember/know procedure, and this was verified by the observation of an intact ERP correlate of recollection, the parietal old-new effect in these subjects. Levels of familiarity in this group were impaired, however, and no significant ERP correlates of familiarity were observed. Low-performing older participants showed impaired recollection and familiarity and an absence of any of the standard ERP correlates of either process which were observed in the younger participants. A possible explanation for the lack of any apparent aging effects on levels of recollection or familiarity in the current study, albeit speculative, is that the participants involved were particularly high-performing individuals relative to the general population. Since standard test scores were unavailable it was not possible to explore this possibility further.

Another possibility is that recognition memory performance in the older participants in the current study was unimpaired due to the nature of the stimulus materials. As mentioned previously, the vast majority of the investigations described above involved verbal memoranda. Schacter and colleagues (Schacter, Israel, & Racine, 1999), however, revealed an advantage in both older and younger participants in recognition memory for auditorily presented words which were encoded together with a picture, compared with items which were presented together with a written word. The source of the improvement in performance was an increased ability to avoid false recognition. Schacter and colleagues postulated that "...participants in the picture encoding condition may employ a general rule of thumb whereby they demand access to detailed pictorial information in order to support a positive recognition decision." This "rule of thumb" is dubbed the "distinctiveness heuristic". Although this effect was found to confer an advantage for both young and older participants, it was suggested that it may be of particular importance for older subjects who are thought to be especially prone to false recognition as a result of over-general encoding strategies. Indeed, a more recent study revealed that older participants were just as likely as younger participants to monitor their recollections in order to reject lures, provided that the associates they were required to recollect were pictures rather than words (Gallo, Cotel, Moore, & Schacter, 2007). The current experiment takes this effect a step further since rather than using pictures as associates to improve recognition memory for words, the stimuli themselves were pictures, and so older participants might have been able to use the distinctiveness of the stimuli to aid recognition just as well as younger participants. It is noteworthy that unlike the current study in which visually similar targets and foils were explicitly avoided, one of the few studies to report impaired recognition for pictures in older subjects (Bastin & Van der Linden, 2003) used visually similar foils which will have reduced the distinctiveness of the stimuli.

The only measure on which the older participants were significantly impaired compared to the young participants was their performance on the view discrimination, with no evidence that this was affected by stimulus category or whether they responded R or F. There are a number of possible explanations for why this should be the case. One is that older participants can only remember the gist of what was presented, which is in keeping with the idea discussed above, and put forward by Schacter et al. (1999), that older participants tend to rely more on overly-general encoding strategies. Another possibility is that younger

participants were more conservative in deciding to chose *same* or *different* rather than *don't know* to the view question. There was some evidence that this was the case for items which also received an F response, which young participants were more likely than older participants to follow with a *don't know* response. There was no significant difference in *don't know* response rates between the two age groups for items receiving R responses, however. There was no significant difference in the level of impairment on view discrimination depending on whether participants responded R or F, and separate analyses revealed a numerically larger impairment for items receiving R responses, and so it seems unlikely that this provides an adequate explanation of the impairment in older participants on this aspect of the task. The lack of a behavioural match between the two age groups on this aspect of the task, although interesting, is of little concern, since the ability to recognise trials for which a view change has occurred is not of central theoretical interest in the current thesis.

## Summary

The current chapter had two main aims. One was to establish, behaviourally, whether the stimulus-specific dissociations observed in Chapters 2 and 3 of the current thesis, and elsewhere in the literature, could possibly be the consequence of a disproportionate reliance of recognition memory for faces and scenes on familiarity and recollection respectively. Of the four sets of analyses designed to address this issue across the two experiments, three were consistent with this possibility. The second aim was to compare the patterns of performance in this first group of participants with the performance of a younger group who were age-matched to the participants involved in the imaging experiments reported in Chapter 5. No significant differences were observed in the patterns of performance between the two groups on the measures which are of central interest in the current thesis, i.e. recognition accuracy and levels of familiarity and recollection. This increases the likelihood that the patterns of activations observed in Chapter 5 will provide a reasonable reflection of the kinds of processing which may have supported performance in the controls in Chapters 2 and 3.

The findings reported in the thesis so far indicate that recognition memory for faces and scenes rely on distinct structures within the MTL, and that this may be associated with a disproportionate contribution of recollection and familiarity to performance on the two categories. Since recollection and familiarity were not assessed in the patients reported in

Chapters 2 and 3, however, it is unclear whether the deficits observed in these patients were a consequence of impaired recollection, familiarity or both. As a result, the way that specialisation in the MTL according to stimulus category relates to specialisation according to recollection versus familiarity is unclear. Chapter 5 will therefore describe two experiments designed to investigate the interaction between these two factors in terms of MTL contributions to recognition memory.

# Appendix: Instructions for participants

## *General Instructions*

The experiment will be split into four identical sections. In the first part of each section, I will show you a series of 60 faces and scenes on the touchscreen. I want you to decide whether you find each picture pleasant or unpleasant and respond by pressing the corresponding button on the screen. There is no right or wrong answer; your responses should merely reflect your personal preferences. Each picture will appear for 4 seconds; please try to respond within this time but if you do miss one, don't worry, just carry on with the next one.

Once you have seen all 60 pictures, I will be assessing your memory for them. 90 pictures will appear on the screen one at a time and there will be a mixture of faces and scenes which you have seen before and faces and scenes that you have not. The ratio of old pictures to new pictures will be 2:1. Of the faces and scenes that you have seen before, half will be shown from the same view that you saw them originally, and half will be presented from a different view. Old scenes which are shown from a different view will contain the same central features, but viewed from a different angle, so although some features may appear or disappear on the periphery, the main features should be recognisable from before. New pictures will be of completely new locations/faces although sometimes they may be similar to some of the other pictures that you've seen.

For each picture, you will be asked a series of questions. First, you will be asked whether you think you have seen the face or scene before. You should respond "Yes" if you think you have seen the face or scene before from any angle or "No" if it is completely new. If you respond "No" there will be no further questions and the next picture will appear. If you respond "Yes" you will be asked whether you *remember* the face or scene from before or whether it seems *familiar* in the absence of any specific recollection of seeing it previously. More details about this decision will follow. Finally, you will be asked whether you think the face or scene was shown from the same or a different view when presented originally. If you think you

know whether the view is the same or not, even if you're not completely confident, please press the appropriate button. If you don't know, please don't guess but press the "don't know" response. You will have a total of 5 seconds to answer all of these questions; only when these 5 seconds have elapsed will the next picture appear. This may not seem like much time but in fact, it should be plenty. If you're too slow on the occasional trial then that's ok. Once you have reached the end of this part of the experiment, you will move onto the next set of pictures and so on until you have completed all four sections.

Although you will be aware that your memory for the pictures I'm about to present is going to be assessed, please focus on the pleasant/unpleasant task rather that using any kind of memorising strategy. It is essential that you stick to this rule or the experiment will not work. You are not expected to be able to get everything right!

### *Remember/Familiar Instructions*

Please read the following instructions to find out how to make the "remember" and "familiar" judgements.

- Remember judgements: If your recognition of the face or scene is accompanied by a conscious recollection of its prior presentation, then choose "Remember". "Remember" indicates the ability to become consciously aware again of some aspect or aspects of what happened or what was experienced at the time the picture was presented (e.g. details in the picture, or of something that happened in the room, or of what you were thinking and doing at the time). In other words, the "remembered" face or scene should bring back to mind a particular association, image, or something more personal from the time of study, or something about its appearance or position (i.e., what came before or after that picture).

- Familiar judgements: "Familiar" responses should be made when you recognise that the face or scene was presented earlier but you cannot consciously recollect anything about its actual occurrence or what happened at the time of its occurrence. In other words, press "Familiar" when you are certain of recognising

the face or scene but it fails to evoke any specific conscious recollection from when you saw it earlier.

To further clarify the difference between these two responses, here are some real-life examples. Often when you see somebody you know outside the context from which you know them, for example, if you bump into your dentist in the supermarket, you have the feeling that the person is familiar but can't think where you know them from. This is a good example of what the familiar response is indicating. However, when asked the last movie you saw, you would typically respond in the "remember" sense, that is, becoming consciously aware again of some aspects of the experience. If you have any questions regarding these judgements, or any other aspect of the experiment, please ask the experimenter now.

Thanks for participating!

# Chapter 5

# Medial temporal lobe activations in recognition memory: Effects of stimulus category and process

## Introduction

The stimulus-specific mnemonic deficits observed in Chapters 2 and 3 in patients with damage to different MTL regions are suggestive of clear differences in the contribution of MTL structures to recognition memory for faces and scenes. Current theories regarding MTL function point to a number of, not necessarily mutually exclusive, explanations for this dissociation. The most direct explanation is that different MTL regions are specialised to support mnemonic processing of different stimulus categories, with the hippocampus supporting memory for scenes, and surrounding regions (e.g. perirhinal cortex), supporting memory for faces, regardless of the particular mnemonic processes (e.g. recollection or familiarity) that are involved. This would be consistent with reports of impaired recollection and familiarity for scenes but not faces following hippocampal damage (Bird et al., 2007; Carlesimo et al., 2001; Cipolotti et al., 2006). A related possibility is that, as suggested by some recent neuropsychological and neuroimaging investigations of non-mnemonic tasks (Lee, Buckley et al., 2006; Lee, Buckley et al., 2005; Lee et al., 2008), the hippocampus and perirhinal cortex support perceptual processing of scenes and faces respectively. Damage to these regions may therefore have resulted in disruption to the formation of perceptual representations, leading to secondary impairments in recognition memory in the patients reported in Chapters 2 and 3.

An alternative explanation comes from some dual-process models of MTL function, according to which, recollection depends on a network of regions which include the hippocampus (and possibly the parahippocampal cortex), whereas familiarity depends on a network which includes the perirhinal cortex (Aggleton & Brown, 1999; Eichenbaum et al., 2007). A possible explanation for the patterns of deficits described in Chapters 2 and 3, that would be consistent with these models, is that damage to the hippocampus resulted in impairments in recognition memory for scenes, because performance on the scene conditions depended more on recollection, whereas damage extending into non-hippocampal MTL structures resulted in impairments in recognition memory for faces, because performance on

the face conditions depended more on familiarity.

This possibility was explored behaviourally in Chapter 4 which investigated the relationship between stimulus category and the relative contributions of recollection and familiarity to recognition accuracy using an adaptation of the remember/know (R/K) procedure. Correct recognition of previously viewed scenes in both young and older healthy participants was more likely to be accompanied by an R response than was correct recognition of previously viewed faces. There was also a significant interaction between estimated levels of recollection versus familiarity and stimulus category in younger participants, such that levels of recollection, relative to familiarity, were disproportionately high for scenes relative to faces. Together, these results suggest that participants may, indeed, ordinarily rely on recollection to a greater extent on tests of recognition memory for scenes than for faces. Recognition memory for faces, on the other hand, might be adequately supported by familiarity.

Thus, the results of Chapter 4 established the dual-process model as a viable potential explanation for the data reported in Chapters 2 and 3. This does not, however, rule out the modality-specific explanations described above. For the dual-process explanation to be accepted as more likely than the remaining two explanations, there would also need to be some evidence that recollection for faces and scenes depends on the hippocampus, whereas familiarity for faces and scenes depends on adjacent MTL regions. If, on the other hand, the hippocampus was found to support recollection and familiarity of scenes whereas surrounding regions were found to support recollection and familiarity of faces, dual-process models of MTL function would face a significant challenge. The experiments described in the current chapter were designed to investigate these hypotheses using functional magnetic resonance imaging (fMRI). There follows a brief review of existing evidence for dual-process and modality-specific views of MTL function derived from this technique.

## *fMRI investigations of recollection and familiarity*

Several investigations of *verbal* recognition memory using functional neuroimaging have provided support for the view that recollection and familiarity are dependent on the hippocampus and perirhinal cortex respectively (see Diana et al., 2007 for a review). Particularly compelling evidence comes from two within-study double-dissociations

(Davachi et al., 2003; Ranganath et al., 2004). In both cases, activity in the hippocampus and parahippocampal cortex at study was found to predict subsequent performance on a source memory task (a measure of recollection), but did not predict subsequent familiarity, as assessed by item memory (Davachi et al., 2003) or recognition confidence (Ranganath et al., 2004). In contrast, activity in the rhinal cortex predicted subsequent familiarity but not recollection.

Although similar effects have been observed in several studies, there are some notable exceptions. For example, Yonelinas et al. (2005) scanned the test phase of a word recognition memory test in which participants were asked to rate items as recollected (R), or on a scale from 4-1 with 4 indicating confident recognition in the absence of recollection, and 1 indicating high confidence that an item had not been presented previously. Greater activity in response to items receiving R relative to those receiving 4 responses was observed in the bilateral hippocampus and the left parahippocampal cortex, which is in keeping with the proposed role for these structures in recollective processing. Activity in the left portion of the hippocampal region which showed a recollection effect was also correlated with decreasing levels of familiarity (i.e. 1 > 2 > 3 > 4), however, with a trend for the same effect in the right hemisphere also. Activity in no other MTL region was found to correlate with familiarity. Other studies have observed similar patterns of activity across several MTL regions. For example Dobbins, Rice, Wagner, & Schacter (2003) observed greater activity in the hippocampus, posterior parahippocampal gyrus and rhinal cortex during correct versus incorrect source retrieval. In contrast, Gold, Smith, Bayley, Shrager, Brewer, Stark, et al. (2006) found that whereas activity in the hippocampus, perirhinal and parahippocampal cortices predicted subsequent item, but not source memory, activity in the entorhinal cortex predicted subsequent source but not item memory. These results conflict with the idea that the hippocampus and perirhinal cortex can be differentiated according to their involvement in recollection versus familiarity (see also Henson, 2005).

Of more relevance here, however, are studies which have investigated the neural correlates of recollection and familiarity for visual rather than verbal memoranda. Three such studies have investigated recognition memory for visual scenes, one examining encoding-related activity (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998), and two examining activity during retrieval (Montaldi et al., 2006; Weis et al., 2004). The remember/know (R/K) method was

adopted by Brewer and colleagues (Brewer et al., 1998) in an investigation of scene recognition memory. There was no attempt, however, to individually isolate subsequent recollection- or familiarity-related activity, and the lack of clear hypotheses regarding the various potential patterns of activity that can arise from the method made the relation of the observed effects to the processes of recollection and familiarity difficult. The authors looked for regions in which activity at study showed a significant rank order correlation with subsequent responses, i.e. R > K > miss. The analysis revealed that activity in the bilateral posterior parahippocampal gyrus predicted subsequent memory, with post-hoc analyses revealing a significant pair-wise difference between activity leading both to R versus K responses and between subsequent K responses and misses. The significant difference between activity associated with subsequent R and K responses is consistent with a role for this region in supporting subsequent recollection. The additional difference between subsequent K responses and misses, however, indicates a role in supporting subsequent familiarity. It is possible, therefore, that this region supports both processes. Alternatively, the region might only play a role in supporting subsequent familiarity and not recollection, since items receiving R responses will often also be associated with high levels of familiarity (Donaldson, 1996; Dunn, 2004; Yonelinas et al., 2005). These two possibilities are difficult to distinguish with certainty. Therefore, although valuable insights were gained from this study, it did not address the issue of whether dissociations can be found between regions supporting recollection versus familiarity. Insights into the roles of different MTL structures were further limited since the area of the brain covered was restricted to four roughly coronal slices through the centre of the brain which did not cover more anterior regions of the MTL.

The study by Brewer et al. (1998) therefore raises an important issue that is pertinent to the experiments reported in the current chapter, which also adopted a modification of the R/K procedure. The patterns of activity across R, K and misses or correct rejections can be difficult to interpret in relation to recollection and familiarity. A thorough discussion of several potential patterns of activity across these response categories will therefore be made in the fMRI Analysis section below, together with some suggestions for how each pattern can be related to the two processes.

Weis and colleagues (2004) identified recollection effects by finding regions in which activity was greater for hits associated with correct source judgements (H+SC) than for hits

associated with incorrect source judgements (H+SI). Effects of familiarity were identified by finding regions in which activity in response to misses was greater than activity in response to H+SI. Recollection-related activity was observed in a bilateral region which included the anterior hippocampus, parahippocampal gyrus and the amygdala. Familiarity-related activity was observed in a region identified as the right anterior MTL, centred on the parahippocampal gyrus. Examination of the activation patterns from the paper reveal that although focussed in opposite hemispheres, there appears to be some overlap between the regions showing effects of recollection and familiarity, particularly in the anterior hippocampus. Indeed, the region showing an effect of familiarity also appeared to show a trend towards an effect of recollection, i.e. H+SC > H+SI. These findings do not, therefore, provide strong support for a dissociation of function in the MTL, particularly given the proximity of the observed effects which, given the low spatial resolution of MRI images and the spatial smoothing performed on the data, are difficult to distinguish with any certainty.

More convincing evidence for a dissociation in the MTL comes from the study by Montaldi et al. (2006). Activity in the bilateral perirhinal cortex was found to be linearly modulated by familiarity strength, such that it was greatest for scenes receiving the lowest familiarity ratings (F1 or miss), and lowest for items receiving high familiarity ratings (F3). Activity in response to recollected items in this region was similar to that observed for F3 items. In contrast, activity in an area of the bilateral posterior hippocampus was significantly greater in response to recollected relative to F3 items, but was not modulated by differing levels of familiarity. These findings therefore support the proposal that the hippocampus and perirhinal cortex selectively support recollection and familiarity respectively (Aggleton & Brown, 1999; Eichenbaum et al., 2007).

One study used a one-step R/K/new procedure to investigate retrieval effects during face recognition memory (Gonsalves, Kahn, Curran, Norman, & Wagner, 2005). The aim was to identify neural correlates of item memory strength within the MTL, although the authors also related the results to the dual-process debate. Behavioural investigations revealed that perceived memory strength was greatest for R responses and reduced across K responses, misses and correct rejections (CRs). ROI analyses revealed that activity in the perirhinal and parahippocampal cortices correlated with decreasing memory strength, i.e. CR > M > K > R. This was interpreted as evidence for a role for these regions in signalling item familiarity

(although see Vilberg & Rugg, 2007, for a failure to replicate this effect in the MTL at a liberal threshold and discussion of the validity of the analyses employed). Further analyses failed to reveal any significant effects of recollection within the MTL, as operationalised using the contrast R > K. The study therefore failed to find a dissociation between the contribution of different MTL structures to recollection versus familiarity for faces, although it was consistent with the suggestion that the perirhinal cortex supports familiarity.

## *fMRI investigations of spatial and object processing*

Imaging investigations of spatial memory or navigation frequently activate the hippocampus (e.g. Burgess et al., 2001; Lee et al., 2008; Maguire et al., 1998; Parslow et al., 2004), whereas activity in the perirhinal cortex is often associated with memory and discrimination of objects (Devlin & Price, 2007; Lee, Bandelow et al., 2006; Lee et al., 2008; Tyler et al., 2004). In addition, a region in the parahippocampal cortex, known as the "parahippocampal place area" (PPA, Epstein & Kanwisher, 1998; see also Aguirre et al., 1998) has been consistently associated with processing of spatial scenes, with evidence for a specific role in perception and/or mnemonic encoding (Epstein, Harris, Stanley, & Kanwisher, 1999; Epstein, Parker, & Feiler, 2007). These findings point towards a potential dissociation in the MTL according to stimulus category.

More convincing evidence for such a dissociation comes from within-study double dissociations (Kohler et al., 2005; Lee et al., 2008; Pihlajamaki et al., 2004). In the study by Pihlajamäki et al. (2004), participants passively viewed grids containing an array of objects. Increased activity was observed in the perirhinal cortex, anterior hippocampus and anterior parahippocampal cortex on trials where one of the objects was replaced with a novel object in the same location, relative to no change or a location change. In contrast, increased activity was observed in the posterior hippocampus and parahippocampal cortex on trials where one object changed location relative to object change or no change trials. Similarly, Lee et al. (2008) observed increased activity in the anterior hippocampus and perirhinal cortex during face relative to scene and size oddity tasks, whereas increased activity was observed in posterior hippocampus and parahippocampal cortex during scene relative to size and face oddity tasks. Finally, Köhler et al. (2005) found that a region in the right perirhinal cortex selectively responded to novel objects relative to familiar objects, whereas a region in the right middle hippocampus selectively responded to novel spatial arrangements and novel

combinations of familiar objects relative to familiar object *pairs*. Regions in the anterior hippocampus and posterior parahippocampal cortex responded to all three categories of novel items.

Each of the three experiments described above provided some evidence that the perirhinal cortex is involved in processing objects, whereas the middle or posterior hippocampus is involved in spatial/relational processing. The patterns of responses in anterior hippocampus and parahippocampal cortex were less consistent across the three studies, but there was a general trend for more anterior regions to process objects and for more posterior regions to support spatial processing. Evidence in conflict with these findings comes from a recent study which found activity in the perirhinal cortex and posterior parahippocampal cortex during the study phase of both spatial and object conditions of a memory task (Buffalo, Bellgowan, & Martin, 2006). In contrast, anterior parahippocampal cortex activity was only observed during the spatial condition. These discrepancies can potentially be explained by the fact that the reported effects were obtained by contrasting activity during the encoding tasks with baseline. Since both tasks involved memory for objects, it is perhaps not surprising that the perirhinal cortex was activated relative to baseline, even in the condition where it was the location and not the identity of the objects which was later tested. Direct comparisons between the spatial and identity conditions would have provided a more appropriate test of the underlying hypotheses.

## *Aims and predictions*

The preceding mini-review of the literature revealed some evidence, predominantly from the verbal, but also from the visual domain, for the dual-process model of MTL function, with the hippocampus (and in some cases the parahippocampal cortex) being selectively associated with recollection, and the perirhinal cortex being associated with familiarity/novelty. On the other hand, investigations of visual memory and discrimination have often revealed roles for the posterior hippocampus in spatial memory, and perhaps perception, and for the perirhinal cortex in object memory/perception, with a less consistent pattern observed in the parahippocampal cortex. The discussion also highlighted several findings which are less consistent with these two apparent functional divisions, however. Furthermore, it is unclear how they interact: for example, conflicting predictions concerning the regions which would support familiarity for scenes, or recollection of objects would

follow from each view, as will be discussed below.

The fMRI experiments reported in the present chapter represent the first attempt to tackle this issue by investigating these two apparent functional divisions within a single experiment. The experimental paradigm was almost identical to that described in the previous chapter; the only significant difference being that face and scene trials were intermixed to enable direct comparisons between them, unconfounded by changes in, for example, the participants' levels of attention or environmental factors over the course of the experiment. Although, as with the paradigm in Chapter 4, the design incorporated same- and different-views and view judgement, the analyses reported below focus on the factors of central interest to the current thesis, i.e. stimulus category (faces or scenes) and recollection vs. familiarity. Scanning was performed during both the study and test phases which enabled investigation both of the neural correlates of recollection and familiarity, as well as activity which was predictive of subsequent recollection and familiarity, through use of the subsequent memory paradigm.

The findings reported above together with the evidence from previous chapters of the current thesis lead to potentially conflicting predictions. One possibility, following on from the stimulus-specific effects observed in Chapters 2 and 3 and some of the findings in the imaging literature, is that MTL subregions will dissociate according to their responses to faces versus scenes. Evidence for stimulus-specific *mnemonic* processing would come from significant interactions between stimulus category and memory performance. For example, at test, one might predict the hippocampus to show equivalent activity during face trials, regardless of memory performance, whereas for scenes, the level of activity might depend on whether an item is familiar, remembered or correctly rejected. This would indicate that the hippocampus selectively supports memory for scenes, but not faces during retrieval. On the other hand, significant main effects of stimulus category, in the absence of a significant interaction with memory performance, might be interpreted as evidence for stimulus-specific *perceptual* processing.

In contrast, following the imaging studies reported above which were consistent with dual-process models of MTL function, one might predict that the hippocampus, and perhaps the parahippocampal cortex will show effects of recollection but not familiarity, whereas the perirhinal cortex will show effects of familiarity, regardless of stimulus category in both cases. This would be in keeping with the imaging study described previously (Montaldi et

al., 2006), as well as with the observation, using functional imaging, of novelty- and familiarity-related effects in the MTL which were common to a wide range of visual stimulus categories, including faces and scenes (Strange, Hurlemann, Duggins, Heinze, & Dolan, 2005).

Experiment 1 employed a standard, whole-brain approach using a gradient-echo GE sequence. Although this technique provided good coverage of the hippocampus and parahippocampal cortex, more anterior regions were, similarly to previous studies in the literature, subject to signal drop-out due to susceptibility artefacts. Experiment 2 therefore employed a specialised dual-echo sequence to focus on the MTL. The sequence consisted of alternating GE and spin-echo (SE) acquisitions. Although known to produce lower levels of blood oxygenation level dependent (BOLD) contrast, SE sequences have been shown to suffer fewer susceptibility artefacts relative to GE sequences (Bandettini, Wong, Jesmanowicz, Hinks, & Hyde, 1994; Norris, 2006), and it was therefore hoped that improved signal coverage of the anterior MTL would be obtained in the SE data. The field of view was also adjusted in the second experiment, with the slices being tilted along the line of the temporal lobe in the hope that this would improve signal coverage in both the GE and SE datasets.

Statistical analyses comprised a voxel-based search within three anatomically defined regions of interest (ROIs): the perirhinal cortex, hippocampus and parahippocampal gyrus, using "Small-Volume Correction" (SVC) in SPM to correct for multiple comparisons within these ROIs. The justification behind the use of a voxel-based rather than a more standard ROI-based approach followed from the prediction that functional differences may be observed within particular anatomical regions. For example, previous findings have highlighted a potential functional division within the hippocampus, with more anterior regions supporting object processing and more central/posterior regions supporting spatial processing (Kohler et al., 2005; Lee et al., 2008; Pihlajamaki et al., 2004). In addition, the anterior hippocampus has been associated with increased responding to novel stimuli, whereas the posterior hippocampus has been associated with increased responding to familiar stimuli (Strange, Fletcher, Henson, Friston, & Dolan, 1999). Since there is no objective way to define the location of the anterior/posterior divide, and indeed it may vary, and since similar, more complex dissociations may be present throughout the MTL, a voxel-based approach was thought to be the most appropriate method to employ.

# Experiment 1: Activations observed during recognition memory using a standard full-brain gradient-echo sequence

## *Materials and Methods*

### Participants

18 participants were recruited from the MRC Cognition and Brain Sciences volunteer panel. The data for four of the subjects were excluded from the analyses due to a strong bias to respond either remember or familiar (<1 familiar response for every 10 remember responses or vice versa). The data for one subject were removed due to excessive movement during functional scanning. A further data set was removed due to the presence of radio-frequency artefacts in several scanning blocks (the artefacts were thought to be caused by an air-conditioning unit malfunction which is not believed to have affected any other sessions). This left 12 participants (7 female, mean age 20.0 years). All participants gave informed consent before undertaking the study. This investigation received ethical approval from the Cambridgeshire Local Research Ethics Committees (UK).

### Behavioural Procedure

The behavioural procedure was based on that described in Chapter 4. There were four study blocks each containing 30 face trials and 30 scene trials. Each study block was followed by a test block containing 15 same-view trials, 15 different-view trials and 15 new trials for each stimulus category. As before, no items were repeated across study blocks. There was a short gap (approx. 1 min.) between each study block and the following test block and participants were given the opportunity to rest for as long as required before the commencement of each study block.

The stimuli were identical to those used in Chapter 4. Images were displayed against a black background, projected onto a screen approximately 80cm behind the participant, which they viewed via a mirror placed above the eyes. All responses were made using pre-specified buttons on a four button response box using the right hand. The questions to which the participants were required to respond appeared on the screen during each trial, along with the response options, which appeared in the same spatial order as the corresponding buttons on the response box. Following each response, the response options were greyed-out to indicate to the participant that the button press had been registered. This was particularly helpful in

the test phase which was relatively high-paced.

On each study trial, a stimulus appeared for 4s, during which time participants were required to rate the picture as pleasant or unpleasant. There was a gap of 500ms between trials during which time a fixation cross was presented (see Figure 5.1A).

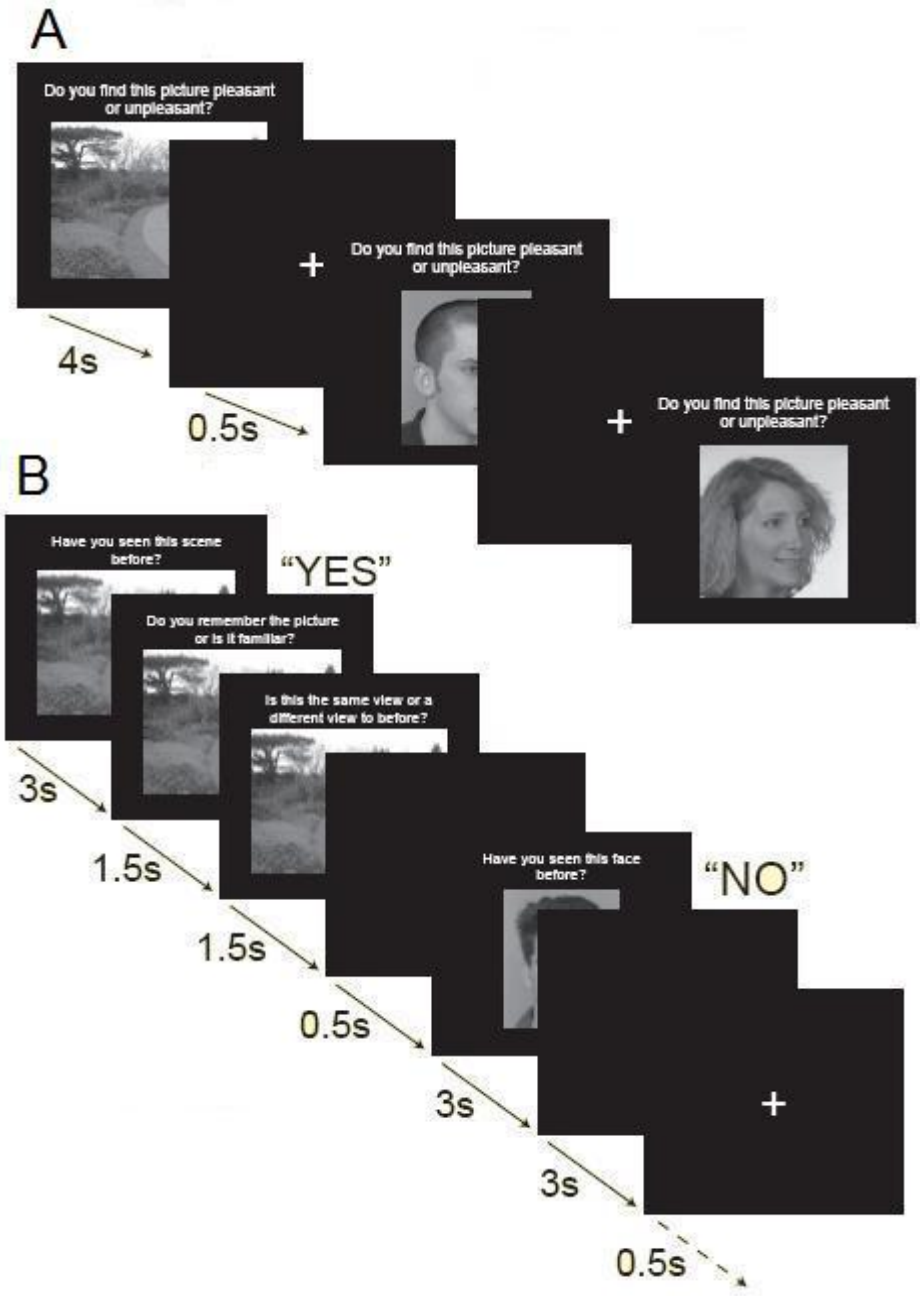


***Figure 5.1 Schematic illustration of the behavioural procedure during study (A) and test (B).***

Each test trial proceeded in a similar manner to that described in Chapter 4. On presentation of each item, participants were allowed 3s to decide whether they had seen the item before (responding "yes" to items they recognised regardless of whether they thought the view had

changed). If they responded "yes" they had 1.5s in which to respond R or F and then a further 1.5s to decide whether the view had changed (same/different/don't know). These time periods were signalled by a change in the question and response options which appeared on the screen. Trials were only included in subsequent analyses if a single response was made during each of these three time periods. If a "no" response was made to the first question, the screen was cleared for the following 3s. A fixation-cross then appeared for 0.5s to signal the beginning of the next trial. Each trial therefore lasted for a total of 6.5s (see Figure 5.1B). The order of trials within each study and test block was pseudo-randomised and the assignment of stimuli to conditions and blocks was counterbalanced across subjects.

As in previous experiments, a short practice session which included both a study and a test block was administered prior to the initial study block for each stimulus category, to ensure subjects understood the instructions, and to ensure that they were able to keep up with the rate of questions presented during the test phase.

Note that the fMRI analyses reported in this thesis collapse across the view manipulation, which was not essential to the theoretical claims made here, and for which preliminary analyses did not add any particularly novel findings beyond those reported here.

**fMRI Data Acquisition**

BOLD T2*-weighted transverse gradient-echo echoplanar (EPI) images (64x64 matrix, in-plane resolution 3 x 3mm, TR = 2000ms, TE = 30ms, flip-angle = 78º) were acquired using a 3T TIM Trio system (Siemens, Erlangen, Germany). Each EPI volume comprised 32 3mm-thick, 0.75mm-gap near-transverse slices, tilted up by approximately 30º at the front to minimise eye-ghosting and posterior lateral inferior temporal susceptibility artefacts. The slices were acquired in a sequential descending direction. The numbers of volumes acquired in each study and test block were 155 and 313 respectively, the first 10 volumes being discarded to allow for equilibration effects. An MPRAGE T1-weighted structural image was also acquired for each participant with 1 x 1 x 1mm voxels using GRAPPA parallel imaging (flip-angle = 9º; TE = 2.99s; acceleration factor = 2).

**fMRI Analysis**

Data were preprocessed and analysed using statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK), batched using "automatic

analysis" (MRC CBU, www.mrc-cbu.cam.ac.uk/~rhodri/aa). Preprocessing of the image volumes involved (i) spatial realignment to correct for movement; (ii) coregistration of the EPI images to the structural image; (iii), spatial normalisation which was performed over two stages, both using SPM5's combined normalisation & segmentation facility (Ashburner & Friston, 2005). The raw T1-weighted MPRAGE structural images for each individual contained substantial inhomogeneity in intensity across the brain, so the first stage corrected for this. For the second stage, linear and nonlinear normalisation parameters were estimated by warping each participant's structural image to a T1-weighted template image from the Montreal Neurological Institute (MNI). These parameters were then applied to the EPI images; and finally, (iv) spatial smoothing of the re-sampled images (voxel size 3x3x3 mm) using an 8mm FWHM Gaussian kernel (final smoothness approximately 11x11x11mm).

Statistical analysis was performed in a two-stage approximation to a Mixed-Effects model (Holmes & Friston, 1998). In the first stage, neural activity was modelled by a delta function at stimulus onset. The ensuing BOLD response was modelled by convolving these functions with a canonical HRF (Friston et al., 1998). The resulting timecourses were downsampled at the midpoint of each scan to form regressors in a General Linear Model. Separate regressors were modelled for each event type. For the test phase, there were twelve event types for each stimulus category (faces or scenes). These corresponded to CRs, false alarms (FAs), same-view misses, different-view misses and eight categories of hits, corresponding to each possible combination of three factors: view (same or different); memory category (R or F) and view judgement (correct or incorrect). Trials in the study phase were classified into equivalent conditions according to responses given in the subsequent test phase, with the obvious exclusion of CRs and FAs, leaving ten conditions per stimulus category. An additional regressor was added to both models (study and test) to model trials on which one or more responses to the three questions at test were too slow. For the test phase, a further additional regressor was added to model the presence or absence of additional questions within each trial (which depended on whether participants responded yes or no to the initial question). To account for some residual artefacts after realignment, the model also included a further six regressors representing the estimated movement parameters. Voxel-wise parameter estimates for these regressors were obtained by maximum-likelihood estimation, using a temporal high-pass filter (cut-off 128 s) to remove low-frequency drifts, and modelling temporal autocorrelation across scans with an AR(1) process (Friston et al., 2002).

A series of contrasts were then performed for each subject to derive parameter estimates of six conditions of interest for each phase, three for each stimulus category (faces or scenes). For the study phase, these corresponded to the subsequent response given to stimuli: subsequent R (sR), subsequent F (sF) or subsequent miss (sM) for faces and scenes. For the test phase, these corresponded to R and F responses and CRs. The contribution of each event type to these contrasts was weighted according to the number of trials which occurred in each case, i.e. equal weight was given to each individual trial, regardless of view (same or different) or view judgement (correct or incorrect).

Images of the resulting parameter estimates were entered into two 2x3 ANOVAs, one for each phase, with the factors "stimulus" (face or scene) and "memory category" (study phase: sR, sK and sM; test phase: R, K or CR), and with participants treated as a random effect. The ANOVAs used a pooled error (Henson & Penny, 2003) to ensure sufficient degrees of freedom that the corrections for multiple comparisons across voxels afforded by Random Field Theory were not overly conservative (Nichols & Holmes, 2002). A voxel-based analysis was performed within three ROIs: perirhinal cortex (this was defined using a probabilistic map of the perirhinal cortex from Devlin and Price (2007) which was restricted to the area which corresponded to perirhinal cortex in at least 50% of participants in the Devlin and Price study); hippocampus (defined as the dentate gyrus, the uncus, and the hippocampus proper), and parahippocampal gyrus (both defined using the Automated Anatomical Labelling brain atlas, Tzourio-Mazoyer et al., 2002). Significant effects observed within the region of overlap between the parahippocampal and perirhinal ROIs were classified as perirhinal cortex. Note that the resolution of the images acquired and the processes of normalisation and smoothing make precise anatomical distinctions difficult. Significant activations close to the edges of the ROIs may, in some cases, therefore, derive from adjacent structures. For example, at its anterior, superior extent, the hippocampal ROI included some voxels which are likely to correspond to the amygdala in some or all participants. Effects for which localisation is unclear will be highlighted in the Discussion. Small volume corrections (SVCs) were applied to all contrasts for each ROI and the results were thresholded at a value of $p < 0.05$ using a family wise error (FWE) correction for multiple comparisons. Stereotactic coordinates of the maxima within the thresholded SPMs correspond to the MNI template. These coordinates bear a close, but not exact, match to the atlas of Talairach & Tournoux (1988).

Unfortunately, as will be illustrated below, it was not possible to investigate activity in the perirhinal cortex in the current experiment, due to signal drop-out in anterior temporal regions across several participants.

## *Behavioural Results*

Behavioural performance on the conditions of interest for the imaging analyses from Experiment 1 are presented in Table 5.1. Since the imaging analyses did not address view or view judgement, the scores are collapsed across these two factors. A more complete breakdown is, however, provided in Table 5.5 in the Appendix for this chapter.

***Table 5.1 Mean number of events for each condition of interest in Experiment 1[3].***

| | **Old Items (max = ~120 )** | | | **New Items (max = ~60 )** | | |
|---|---|---|---|---|---|---|
| **Yes/No** | *Yes* | *Yes* | *No* | *Yes* | *Yes* | *No* |
| | *(Hit)* | *(Hit)* | *(Miss)* | *(FA)* | *(FA)* | *(CR)* |
| **R/F** | *R* | *F* | - | *R* | *F* | - |
| **Faces** | 36.8 | 45.6 | 33.0 | 2.1 | 15.2 | 41.3 |
| | (17.3) | (9.8) | (14.0) | (3.1) | (6.6) | (8.7) |
| **Scenes** | 59.8 | 31.9 | 23.9 | 1.4 | 10.6 | 46.3 |
| | (12.8) | (8.9) | (11.5) | (2.1) | (6.5) | (9.2) |

***Scores collapsed across view and view judgement and derived solely from participants included in the imaging analyses. Standard deviations given in parentheses. FA: False alarm; CR: Correct rejection; R: Remember; F: Familiar.***

Overall recognition accuracy collapsed across view, as measured using *Pr* (hits-false alarms), was at a reasonable level for faces (0.71 - 0.29 = 0.42) and scenes (0.79 - 0.21 = 0.58). Similarly to the experiments in Chapter 4, recognition accuracy for scenes was significantly better than recognition accuracy for faces ($t_{(11)}$ = 4.23, $p$ < 0.01). Similarly, $p$(R|Hit) was

[3] The total number of old and new items are slightly less than planned due to occasional scanner crashes which cut the length of some blocks for a small number of participants, and also due to some trials being excluded since one or more responses were not made on time.

significantly greater for scenes (0.65) than faces (0.43) which is also in keeping with the experiments in Chapter 4 ($t_{(11)}$ = 5.24, $p$ < 0.001). The value of *Pr* corresponding to F responses (i.e. $p$(F|old) – $p$(F|new)) was significantly greater than zero for both stimulus types (faces: *Pr* (F) = 0.14, $t_{(11)}$ = 3.39, $p$ < 0.01; scenes: *Pr* (F) = 0.09, $t_{(11)}$ = 2.75, $p$ < 0.05), indicating that F responses were based on more than guessing. (Note that the actual level of familiarity would be higher if scored under the independence assumption).

Reaction time (RT) data for the conditions of interest in the test phase are presented in Table 5.2. Note that the RTs correspond to the time between stimulus onset and the response to the first question only.

***Table 5.2 Mean of median reaction times for each condition of interest in Experiment 1.***

| | **Old Items** | | | **New Items** | | |
|---|---|---|---|---|---|---|
| **Yes/No** | *Yes* | *Yes* | *No* | *Yes* | *Yes* | *No* |
| | *(Hit)* | *(Hit)* | *(Miss)* | *(FA)* | *(FA)* | *(CR)* |
| **R/F** | *R* | *F* | - | *R* | *F* | - |
| **Faces** | 1095 | 1327 | 1517 | 1232 | 1479 | 1335 |
| | (105) | (112) | (333) | (325) | (178) | (269) |
| **Scenes** | 1164 | 1563 | 1737 | 1675 | 1838 | 1535 |
| | (57) | (161) | (344) | (705) | (390) | (328) |

***Reaction times for the initial response to each test item collapsed across view and view judgement and derived solely from participants included in the imaging analyses. Standard deviations given in parentheses. R: Remember; F: Familiar.***

Since there was only a small number of false alarms and since this response category did not feature in the imaging analyses, only RT data for R hits, F hits, Ms and CRs were analysed. These values were entered into a repeated-measures ANOVA with two within-subjects factors, "stimulus" (faces or scenes) and "response" (R, F, M or CR). The results of this analysis were corrected for non-sphericity, where applicable, using the Greenhouse-Geisser correction. There was a trend towards an interaction between the two factors ($F_{(1.8,\ 19.6)}$ = 2.81, $p$ < 0.1) suggesting that the pattern of the reaction time data across each response

category differed between the two stimulus categories. There were also significant main effects of both factors ("stimulus": $F_{(1, 11)} = 41.04$, $p < 0.001$; "response": $F_{(1.3, 13.9)} = 15.74$, $p < 0.001$). The main effect of stimulus reflects slower RTs to scenes than faces across all response categories. Paired *t*-tests were performed separately for each stimulus category to investigate differences between response types. In the analysis of face trials, R hits were significantly quicker than the remaining three responses (all $t_{(11)} > 2.8$, $p < 0.05$). Misses were significantly slower than CRs ($t_{(11)} = 6.48$, $p < 0.001$) and marginally slower than F hits ($t_{(11)} = 1.93$, $p < 0.1$). There was no significant difference between F hits and CRs ($p > 0.9$). The pattern for scene trials was almost identical, except for a larger difference between R hits and the three remaining responses: (all $t_{(11)} > 4.0$, $p < 0.01$), which explains the trend towards an interaction described above. Scene misses were significantly slower than CRs ($t_{(11)} = 4.17$, $p < 0.01$) and marginally slower than F hits ($t_{(11)} = 1.81$, $p < 0.1$). There was no significant difference between F hits and CRs ($p > 0.7$).

## *fMRI Results: Study Phase*

Subsequent memory effects were identified using the contrast sR > sM. This contrast provides an inclusive way of testing for effects of subsequent memory, since effects of both subsequent recollection and familiarity were predicted to present with a significant difference between these two factors. This is based on the assumption that the majority of recollected items will be associated with high levels of familiarity. Follow-up contrasts involving sF-related activity were performed in order to categorise significant results as effects of subsequent recollection or familiarity. It was reasoned that a significant effect of sF > sM would only be predicted in regions which support familiarity. Regions which exclusively supported subsequent recollection were therefore predicted to show the following pattern: sR > sF = sM. If the pattern was sR = sF > sM, this was assumed to reflect an effect of familiarity. When the level of activity for sFs was intermediate between activity predicting subsequent Rs or Ms (with either no significant effects of sR > sF or sF > sM, or both effects being significant, i.e. sR > sF > sM), the processes performed by the region were difficult to establish with certainty. The inverse of this pattern at test has been attributed to familiarity (Gonsalves et al., 2005), but some contribution from processes leading to subsequent recollection could not be ruled out.

Main effects of stimulus were identified by contrasting activity in response to faces versus

scenes, collapsed across memory category. Interactions between stimulus and subsequent memory were also investigated using the contrasts faces > scenes x sR > sM and scenes > faces x sR > sM. Significant interactions were followed up in a similar manner to that described for the main effects of memory by testing for interactions involving sF, e.g. a significant scene > face x sR > sM interaction was followed up with scene > face x sR > sF and scene > face x sF > sM.

**Main effects of stimulus at study**

Comparisons between activity in response to faces versus scenes are illustrated in Figure 5.2.

*Faces > Scenes*

The only area of the MTL which showed a greater response to faces than scenes was an anterior region of the hippocampal ROI on the left (-18, -9, -12, $Z$ = 3.76, 21 voxels). This effect was marginally significant in a corresponding region of the right-hemisphere (18, -9, -12, $Z$ = 3.37, 16 voxels, $p_{(SVC\text{-}FWE)} < 0.1$). Similar observations have been made previously: for example, activity in an almost identical region (-18, -9, -15) was recently observed during face processing, relative to scene processing in a non-mnemonic oddity task (Lee et al., 2008). As described below, activity in this region was also associated with subsequent memory performance.

*Scenes > Faces*

The reverse contrast revealed a more posterior, bilateral area of the hippocampus (right peak: 30, -36, -9, $Z$ > 5.8, 115 voxels; left peak: -33, -36, -9, $Z$ = 4.89, 39 voxels), with local maxima ranging from y = -39 to y = -33. This is in keeping with studies which have observed increased activity in the posterior hippocampus during spatial tasks, such as navigation, or passive viewing of spatial alterations to arrays of objects (Burgess et al., 2001; Lee et al., 2008; Maguire et al., 1998; Parslow et al., 2004; Pihlajamaki et al., 2004). Increased activity in response to scenes relative to faces was also observed in a posterior portion of the parahippocampal gyrus (right peak: 30, -45, -9, $Z$ > 7.3, 108 voxels; left peak: -27, -42, -9, $Z$ > 7.3, 103 voxels) which is in keeping with previous descriptions of the PPA (Epstein & Kanwisher, 1998). A portion of this region was also associated with subsequent memory for scenes, as described below.

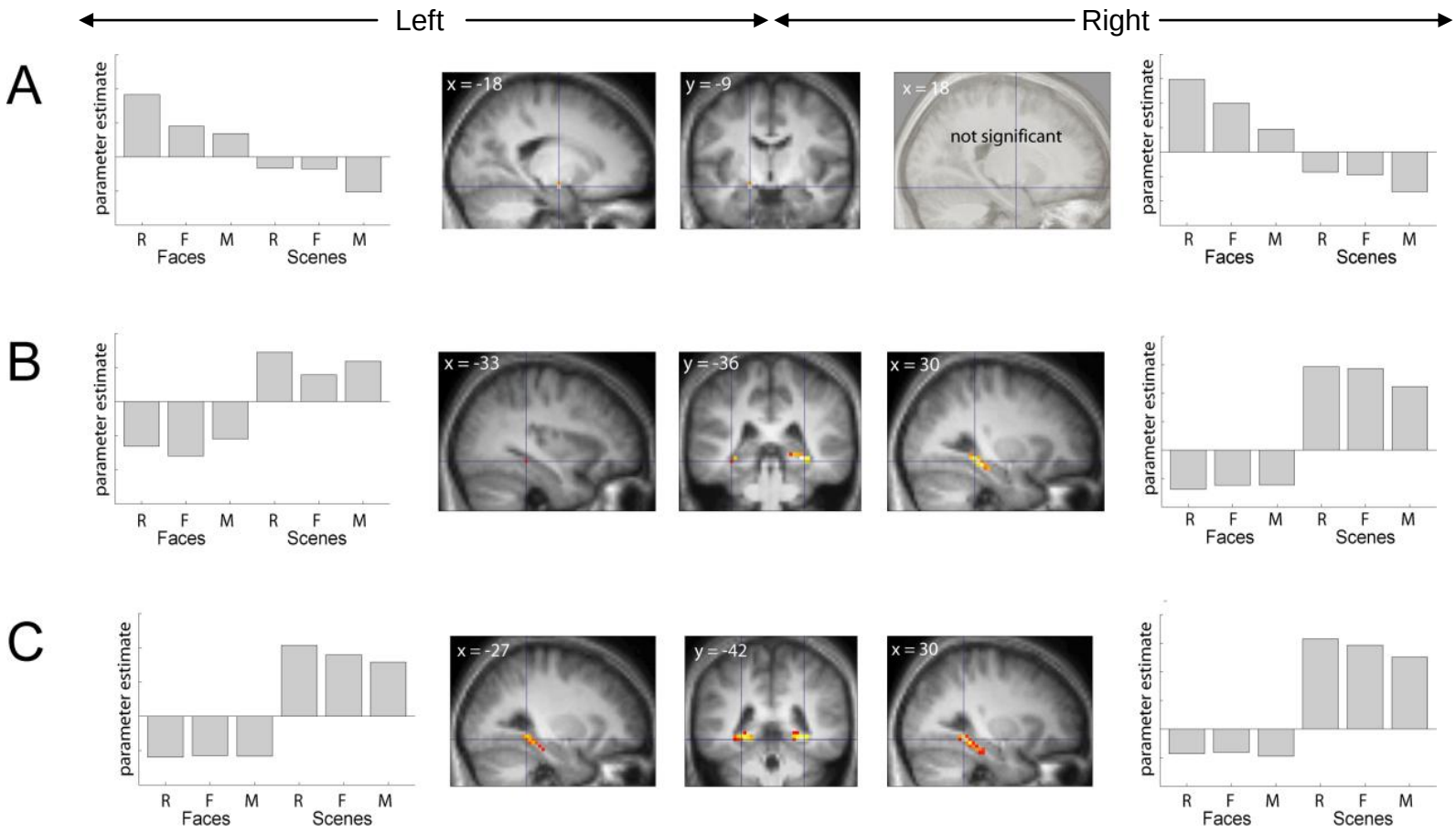


***Figure 5.2 Significant main effects of stimulus observed during the study phase of Experiment 1 within the MTL ROIs ($p_{(SVC\text{-}FWE)} < 0.05$). The central column illustrates the observed effects on coronal sections of the normalised mean structural image. The effects are also illustrated on sagittal slices to the left and right (representing the left and right hemisphere respectively). Effects which were only significant in one hemisphere are illustrated as such. Only significant activations within a particular ROI are shown in each panel; significant effects outside the ROI have been masked out. The left- and right-most columns represent the corresponding parameter estimates for the six conditions of interest, which reflect the responses subsequently given to items during the test phase (R = remember, F = familiar, M = miss). For illustration, in cases where effects were only significant in one hemisphere, parameter estimates are provided for the corresponding voxel in the contralateral hemisphere. Greater activity in response to faces than scenes was observed in an anterior region of the aal hippocampal ROI on the left (A). The reverse effect was observed bilaterally in large sections of the posterior hippocampal (B) and parahippocampal (C) ROIs.***

**Main effects of subsequent memory (sR > sM)**

Contrasts between items which subsequently received R responses and subsequent misses revealed a significant effect in a single region of the MTL, located in an anterior portion of the hippocampal ROI on the left (Figure 5.3). The global maximum of the effect was located in the same voxel as the effect of faces versus scenes described above (-18, -9, -12, $Z$ = 3.66, 54 voxels). Follow-up contrasts between sF and sR and between sF and sM revealed no reliable effects (both $Z < 2.3$, $p_{(SVC\text{-}FWE)} > 0.3$), making it difficult to establish whether activity in this region supports subsequent recollection or familiarity. Contrary to what may have been predicted, there was no interaction with stimulus category: the mnemonic effects were no greater for the face than the scene stimuli.

**Subsequent memory x stimulus interaction (sR > sM x scenes > faces)**

As illustrated in Figure 5.4, the only MTL region to show a reliable interaction between stimulus and subsequent memory was located in a lateral, anterior portion of the PPA (30, -30, -18, $Z$ = 3.52, 59 voxels). There was a greater positive correlation between activity in this region and subsequent memory performance (measured as sR > sM) for scenes than for faces. Numerically, activity predicting sF responses to scenes was intermediate between that predicting sRs and sMs, whereas for faces, activity was similar across the three categories of subsequent responses. Despite this, post-hoc tests failed to find any significant stimulus x mnemonic interactions involving sF (both $Z < 2.5$, $p_{(SVC\text{-}FWE)} > 0.4$).

The reverse interaction was not significant in any of the three ROIs.

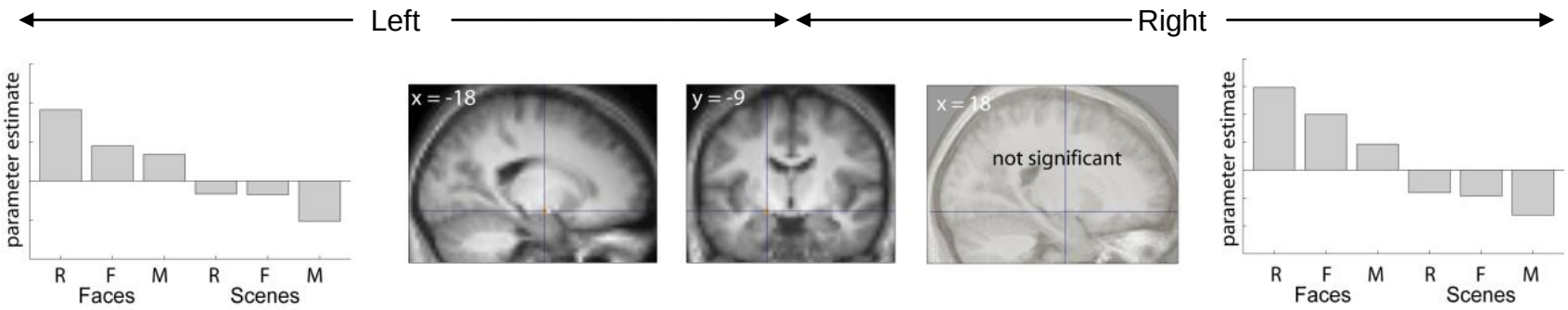


***Figure 5.3 Significant main effect of subsequent memory (sR > sM) observed in Experiment 1 within the aal hippocampal ROI, on the left ($p_{(SVC\text{-}FWE)} < 0.05$).***

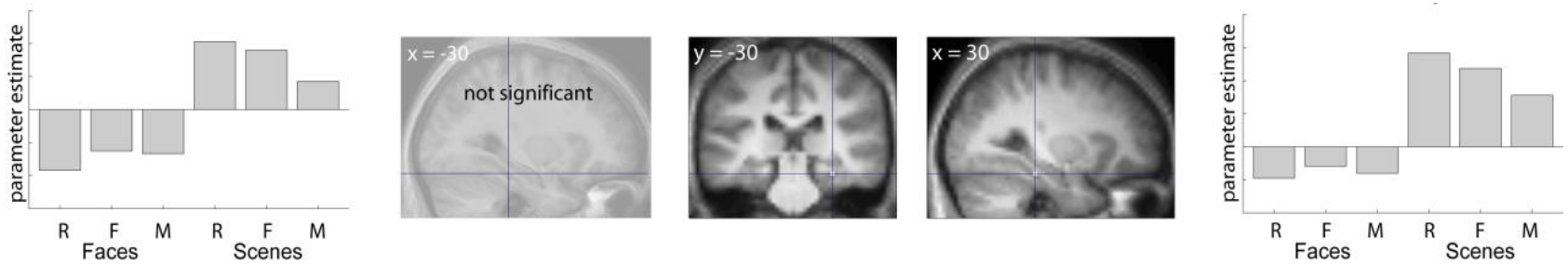


***Figure 5.4 Significant stimulus x subsequent memory interaction (scenes > faces x sR > sM) observed in Experiment 1 on the right of the aal parahippocampal ROI (p < 0.05 SVC-FWE).***

## *fMRI Results: Test Phase*

Effects of recollection were identified using the contrast R > F. Effects of familiarity were identified using both the contrasts F > CR and CR > F (thus the term familiarity is used bi-directionally, to include both familiarity and novelty). Note the caveat that since RTs for Rs were significantly quicker than those for Fs, any significant effects of R > F could reflect increased processing time rather than differences in the kinds of processing underlying each response. The same cannot be said of contrasts between CR and F, however, since there was no significant difference in RTs for these two categories. Similarly to the analyses of the study phase, interpretation of significant effects as being associated with recollection or familiarity was qualified in the context of the complete pattern of activity across all conditions. For example, a region showing a significant effect of R > F could not be assumed to exclusively support recollection if the effect of CR > F or F > CR was also significant. In this case, the region may support both processes or it may exclusively support familiarity. Similarly, a region showing an effect of CR > F could not be assumed to exclusively support familiarity if the effect R > F was also significant. Possible interpretations of these more complex patterns of activity will be evaluated further in the Discussion.

### Main effects of stimulus at test

Comparisons between activity in response to faces versus scenes revealed similar effects during the test phase to those found at study (Figure 5.5).

*Faces > Scenes*

A region showing greater activity for faces than scenes was observed in a similar region of the hippocampal ROI, on the left, to that found at the study (-18, -6, -15, $Z = 3.41$, 31 voxels). The effect of recollection in this region was marginally significant ($p < 0.1$ SVC-FWE).

*Scenes > Faces*

Bilateral increases in activity in response to scenes relative to faces were observed in the hippocampal and parahippocampal ROIs, again in similar locations to those found at study (right hippocampal peak: 30, -36, -9, $Z > 6.4$, 149 voxels; left hippocampal peak: -24, -39, -3, $Z = 6.23$, 60 voxels;: right parahippocampal peak: 33, -45, -6, $Z > 7.0$, 115 voxels; left parahippocampal peak: -27, -45, -6, $Z > 7.0$, 108 voxels). Local maxima in the hippocampus ranged from y = -39 to -21. A portion of this hippocampal region was also associated with recollection (see below).

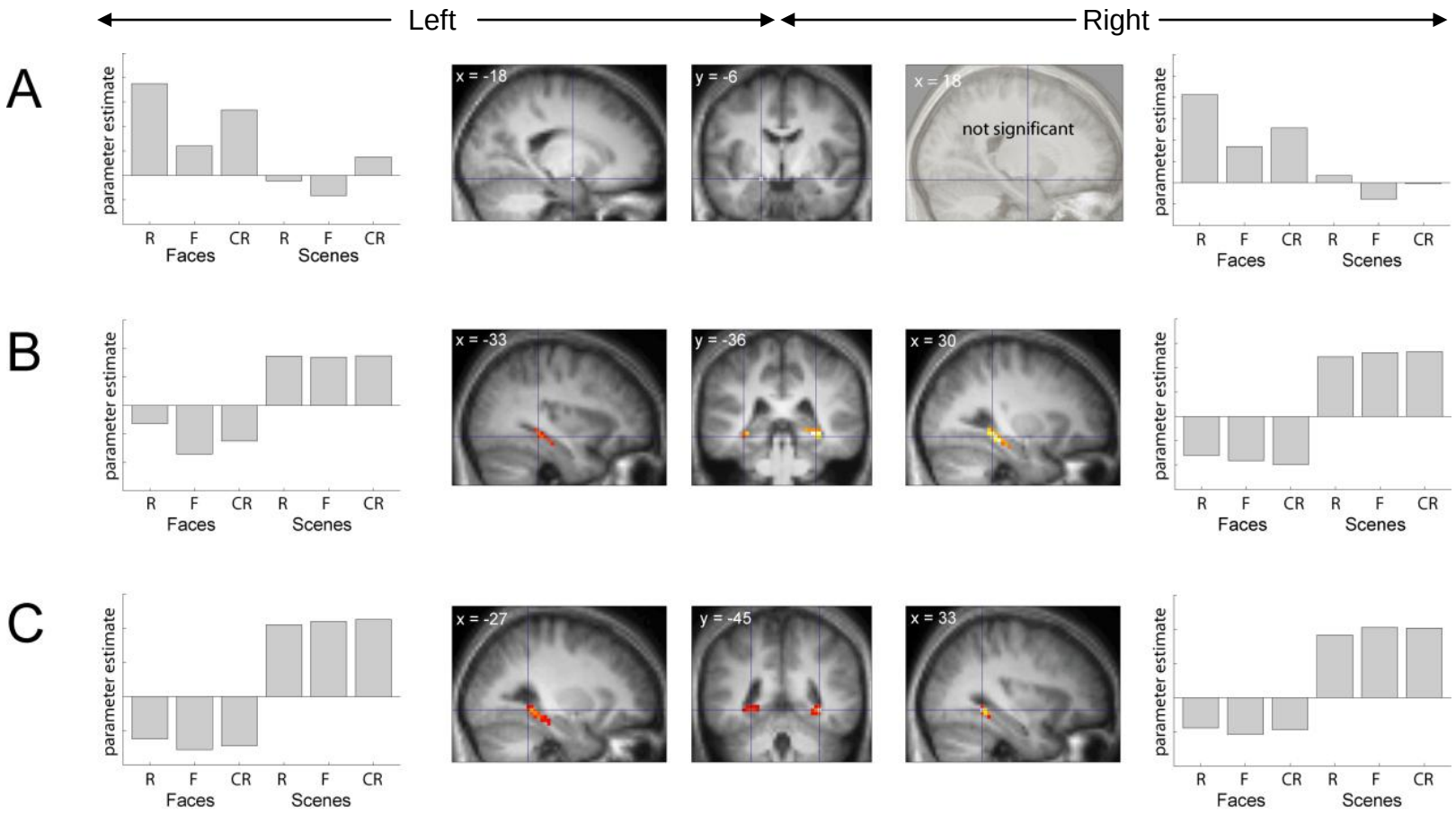


***Figure 5.5 Significant main effects of stimulus observed during the test phase of Experiment 1 within the MTL ROIs ($p_{(SVC\text{-}FWE)} < 0.05$), along with corresponding parameter estimates for the six conditions of interest (R = remember, F = familiar, CR = correct rejection). Greater activity in response to faces than scenes was observed in a similar, anterior region of the left aal hippocampal ROI to that found at study (A). The reverse effect was observed bilaterally in large sections of the posterior hippocampal (B) and parahippocampal (C) ROIs, again with similar foci to those found at study.***

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**Main effects of R > F at test**

Significant effects of recollection were observed bilaterally within the hippocampal ROI (right peak: 27, -21, -12, $Z$ = 3.75, 96 voxels; left peak: -18, -6, -12, $Z$ = 3.71, 133 voxels). Three distinct patterns of activity were identified, varying in terms of relative responses to the two stimulus categories (Figure 5.6).

The posterior-most sub-maximum in the left hemisphere (-30, -27, -12, $Z$ = 3.43) was also associated with significantly greater activity for scenes relative to faces ($Z$ = 3.86). The anterior, bilateral maximum (left: -18, -6, -12; right: 18, -6, -12, $Z$ = 3.53) showed a marginally significant effect of faces versus scenes ($Z$ > 3.2, $p_{(SVC\text{-}FWE)}$ < 0.1, both hemispheres), with the left-portion being directly adjacent to the region, described above, in which this effect was reliable. The intermediate, global maximum in the right hemisphere (27, -21, -12) did not show a reliable effect of stimulus ($Z$ < 1.8, $p_{(SVC\text{-}FWE)}$ > 0.8). Interestingly, there was a numerical increase in activity across all sub-maxima for CRs relative to Fs, although this effect was not significant in any of the sub-maxima (all $Z$ < 2.8, $p_{(SVC\text{-}FWE)}$ > 0.2).

**Main effects of CR > F at test**

The contrast CR > F revealed a significant effect in the hippocampal ROI on the left (-27, -6, -18, $Z$ = 3.74, 100 voxels). Although R responses were associated with numerically more activity in this region than F responses (see Figure 5.7), the effect of R > F was not significant ($Z$ < 2.9, $p_{(SVC\text{-}FWE)}$ > 0.19).

**Non-significant effects**

There were no significant interactions and no significant main effects of F > CR in any of the ROIs.

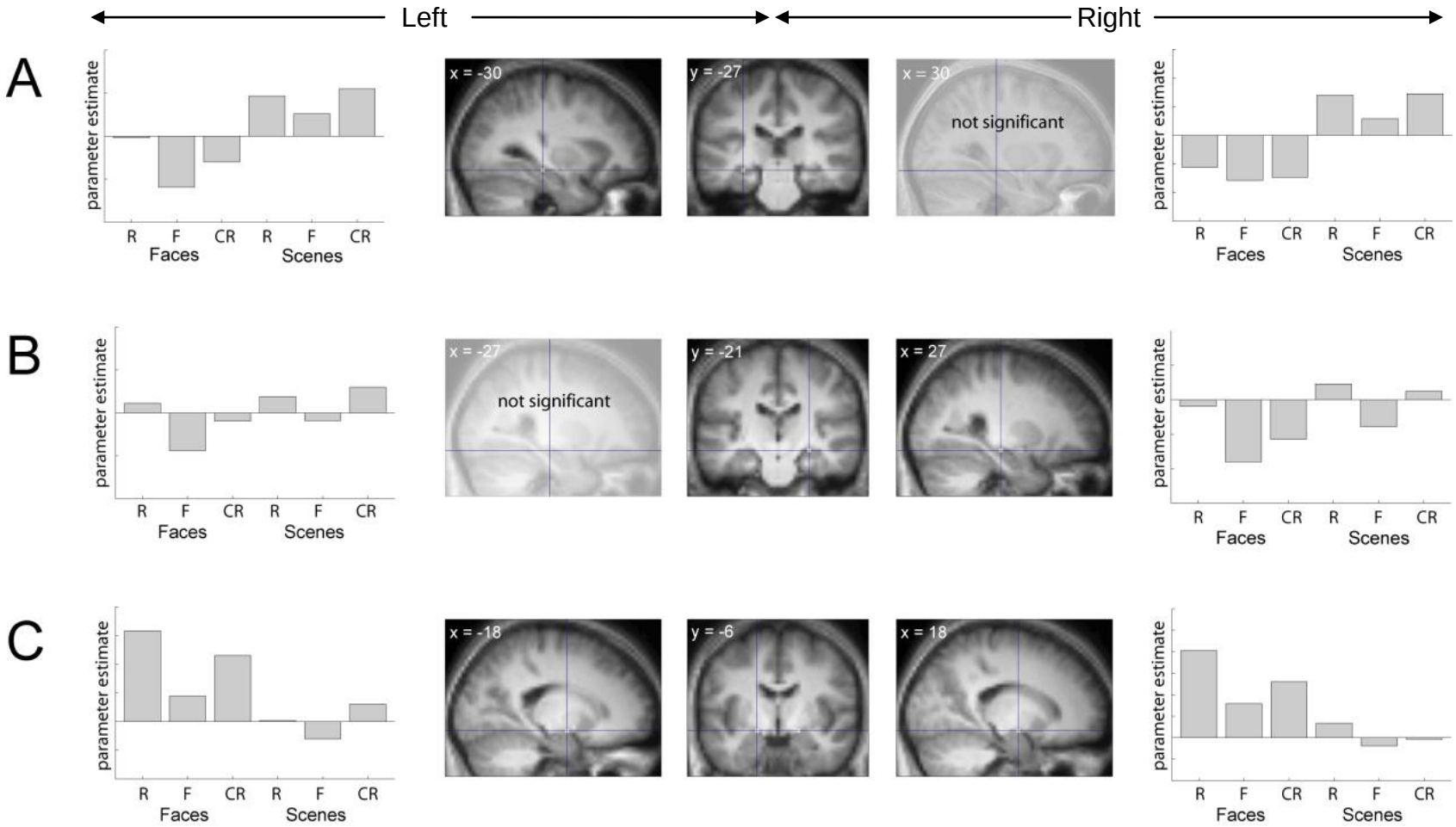


***Figure 5.6 Significant main effects of R > F observed during the test phase of Experiment 1, which were all located within the aal hippocampal ROI ($p_{(SVC\text{-}FWE)} < 0.05$). The three sub-maxima illustrated above also showed a significant effect of scenes > faces (A); a marginally significant effect of faces > scenes (C) or no significant effect of stimulus (B).***

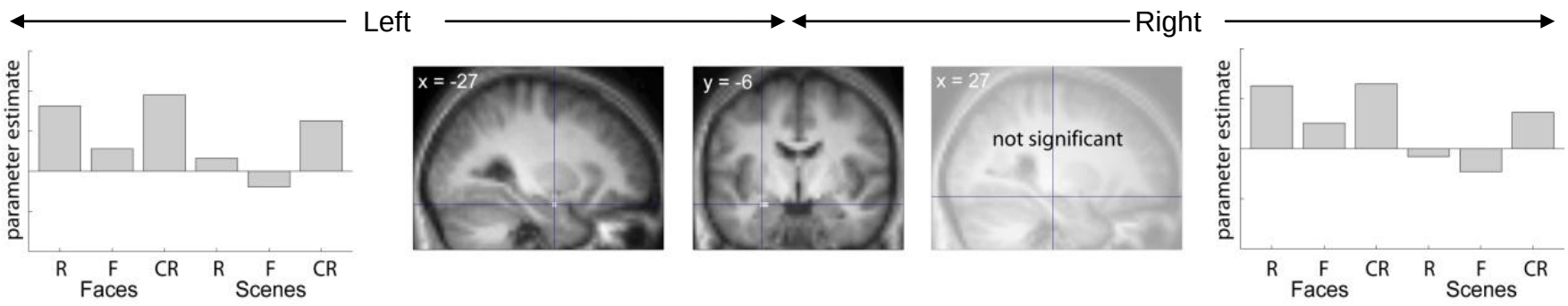


***Figure 5.7 Significant main effect of CR > F observed in Experiment 1 within the aal hippocampal ROI, on the left ($p_{(SVC\text{-}FWE)} < 0.05$).***

## *Experiment 1 Summary*

There was consistent evidence, across the study and test phases, for a dissociation of function in the MTL according to stimulus category. Across both phases, increased activity in response to faces relative to scenes was observed in an anterior portion of the hippocampal ROI. In contrast, a posterior hippocampal region and a posterior parahippocampal region, presumed to correspond to the PPA, were more active for scenes than faces.

There were no regions in which activity could confidently be attributed exclusively to either recollection or familiarity during either the study or the test phases. Hence there was no evidence for a functional dissociation in the MTL according to recollection versus familiarity. Activity in two regions predicted subsequent memory performance. There was a main effect of sR > sM in the anterior region of the hippocampal ROI which also showed a main effect of faces > scenes. There was an interaction in a portion of the PPA such that activity predicted subsequent R responses versus misses for scenes but not faces. In neither case was there any evidence of a significant difference in activity between items subsequently given F responses relative to subsequent R responses or misses. These effects, therefore, most likely reflect processes supporting subsequent familiarity, but there may also be some contribution from these regions, during study, to subsequent recollection.

At test, contrasts designed to capture effects of recollection and familiarity revealed several areas of the hippocampal ROI which showed differential responses across Rs, Fs and CRs. A large cluster spreading across the posterior to anterior extent of the hippocampal ROI showed a main effect of R > F and not CR > F, which, in theory, is consistent with an effect of recollection. A more confined region of the anterior hippocampal ROI showed a significant effect or CR > F but not R > F, consistent with an effect of familiarity. Numerically, however, the pattern of activity across each of these regions was R > F < CR, with little difference between regions showing an apparent effect of recollection and those showing an apparent effect of familiarity. Moreover, since these effects were all present within the hippocampal ROI, they do not support a division of labour between MTL regions according to contributions to recollection versus familiarity.

Finally, although there were no significant interactions between memory and stimulus at test, the regions within the hippocampus showing an effect of R > F varied in their responses to

faces and scenes, with more anterior regions also showing a main effect of faces > scenes; more posterior regions also showing an effect of scenes > faces, but central regions showing no effect of stimulus.

As mentioned above, it was not possible to investigate activity in the perirhinal cortex in the current experiment, due to signal drop-out. A change in the scanning procedure used in the following experiment partially rectified this problem, which enabled a more complete investigation of the MTL. The implications of the findings from the current experiment will therefore be explored further in the light of the results obtained in this second experiment.

# Experiment 2: Further investigation of MTL activity using a dual-echo sequence

## *Materials and Methods*

### Participants

13 participants were recruited from the MRC Cognition and Brain Sciences volunteer panel. The data for one of the subjects were excluded from the analyses due to poor behavioural performance ($Pr < 0.1$ for different-view faces). The data for three subjects were removed due to gradual movement during functional scanning which caused the anterior temporal lobe to shift out of the field of view. This left 9 participants (7 female, mean age 20.0 years). All participants gave informed consent before undertaking the study. This investigation received ethical approval from the Cambridgeshire Local Research Ethics Committees (UK).

### Behavioural Procedure

The behavioural procedure was identical to that described for the previous experiment with the exception of some adjustments to the timing of each trial, which were required due to the slight increase in TR which resulted from using the dual-echo sequence. On each study trial, the stimulus was presented for 4s as before, but this was then followed by a blank screen for 300ms and then a fixation cross for 500ms, increasing the total trial length from 4.5s to 4.8s. On each test trial, the time allowed to answer the initial, yes/no, question was increased from 3s to 3.55s. The timings for the remainder of each trial were unchanged. This increase in time allowed before the first question was beneficial since it reduced the occurrence of late responses.

**fMRI Data Acquisition**

The same scanner was used as for the previous experiment. A single-shot dual echo EPI sequence was used for simultaneous acquisition of GE- and SE-EPI images (64x64 matrix, in-plane resolution 3.5 x 3.5 mm, TR = 2170ms) as illustrated in Figure 5.8 (Mondadori et al., 2006). Each slice was acquired as follows: following a non-selective $90^o$ fat suppression pulse and a slices-selective $90^o$ excitation pulse, a GE-EPI image was acquired. The temporal evolution of the transverse magnetisation was then reversed by applying a slices-selective $180^o$ refocusing pulse and an SE-EPI image was acquired, with the spin echo occurring in the centre of k-space. The corresponding echo times were $T_{GE}/T_{SE}$ = 30/100 ms. The phase-encoding direction was from anterior to posterior. Each EPI volume comprised 16 3mm-thick, 1mm-gap near-transverse slices, tilted down by approximately $30^o$ to follow the axis of the temporal lobe. The bottom slice was positioned directly beneath the temporal pole to ensure maximum coverage of the MTL. To match Experiment 1, the numbers of volumes acquired in each study and test block were 155 and 313 respectively, the first 10 volumes being discarded to allow for equilibration effects. An MPRAGE structural image was acquired for each participant as described for Experiment 1. A single full-brain GE EPI volume was also acquired for each participant using the same parameters as those used in Experiment 1 to aid co-registration of the EPI images to the structural image.

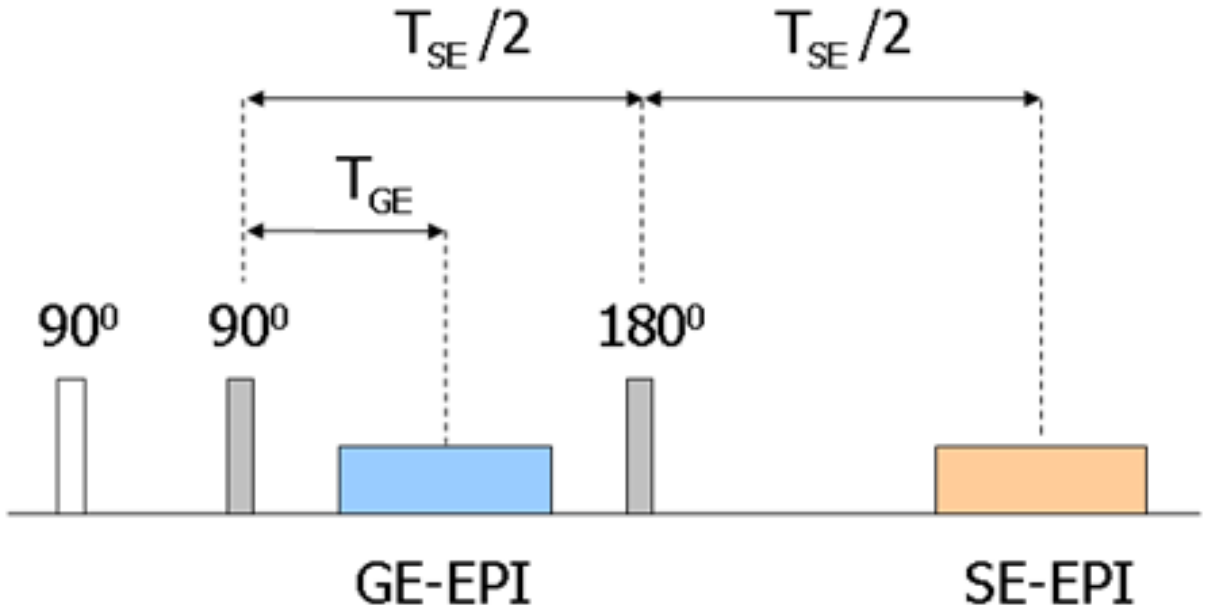


***Figure 5.8 Illustration of the time course for the acquisition of a single pair of GE and SE slices.***

**fMRI Analysis**

The fMRI data were preprocessed and analysed using SPM5 as before. Spatial realignment, followed by undistortion of the EPI images, to correct for magnetic field distortions (Cusack, Brett, & Osswald, 2003), were performed on the GE and SE datasets independently of each other. Since the EPI images only contained 16 slices and therefore only covered approximately half the brain, co-registration of these images to the structural image was performed in three stages. First, the full-brain GE EPI image was co-registered to the structural image. The mean functional GE EPI image was then co-registered to the full-brain EPI image. The coregistration parameters for these two steps were then applied to the remaining GE and SE EPI images. This ensured that the GE and SE data were in the same space. The data were then normalised and smoothed as described for Experiment 1.

Statistical analyses were performed in exactly the same way as for Experiment 1.

The GE and SE mask images produced by SPM, which indicate the areas of the brain contained within the EPI images for all subjects, were compared. This enabled regions which suffered from signal drop-out to be identified. This confirmed increased coverage of anterior MTL regions in the SE relative to the GE dataset. It also confirmed greater coverage of anterior MTL in the GE data from Experiment 2 relative to Experiment 1. These differences are illustrated in Figure 5.9.

Unfortunately, the signal-to-noise ratio of the SE data was reduced relative to the GE data. This meant that only the most robust effects (e.g. the main effect of stimulus in the PPA) reached statistical significance in the SE data. There were no effects which reached significance in the SE data which were not also observed in the GE data. The results described below are therefore restricted to the GE data.

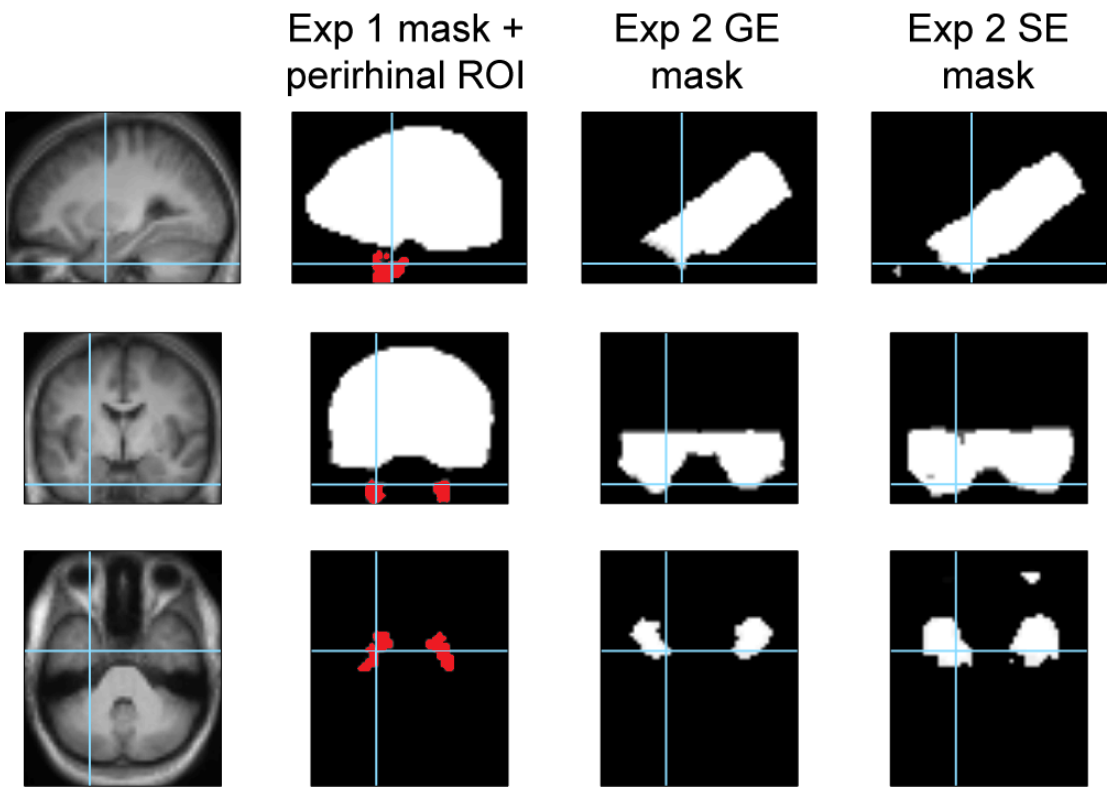


***Figure 5.9 Co-registered images of the total voxel masks from Experiments 1&2, alongside the normalised mean structural image from Experiment 1. For illustration, the perirhinal ROI has been superimposed on the mask from Experiment 1 in red, revealing that there is no overlap between the two images. The crosshairs indicate a region of the perirhinal ROI included in the GE mask from Experiment 2, but increased coverage surrounding this region can clearly be seen in the SE mask.***

## *Behavioural Results*

Behavioural performance on the conditions of interest for the imaging analyses from Experiment 2 are presented in Table 5.3. As for the previous experiment, a complete breakdown of performance is provided in Table 5.6 of the Appendix.

Overall recognition accuracy collapsed across view, as measured using *Pr* (hits-false alarms), was at a reasonable level for faces (0.75 - 0.22 = 0.53) and scenes (0.76 - 0.14 = 0.61). Unlike Experiment 1 and the experiments reported in Chapter 4, the numerical advantage of scenes over faces in recognition accuracy did not reach significance ($p > 0.1$), which may reflect the lower power with only nine subjects. Similarly, while $p$(R|Hit) was numerically greater for scenes (0.62) than faces (0.52), this was only marginally significant ($t_{(8)} = 2.11$, $p < 0.1$). The value of *Pr* corresponding to F responses (i.e. $p$(F|old) – $p$(F|new)) was significantly greater than zero for both stimulus types (faces: *Pr* (F) = 0.18, $t_{(8)} = 3.28$, $p < 0.05$; scenes: *Pr* (F) = 0.14, $t_{(8)} = 3.66$, $p < 0.01$), indicating that F responses were based on

more than guessing. (Note that, as for Experiment 1, the actual level of familiarity would be higher if scored under the independence assumption).

***Table 5.3 Mean number of events for each condition of interest in Experiment 2[4].***

| | **Old Items (max = ~120)** | | | **New Items (max = ~60 )** | | |
|---|---|---|---|---|---|---|
| **Yes/No** | *Yes* | *Yes* | *No* | *Yes* | *Yes* | *No* |
| | *(Hit)* | *(Hit)* | *(Miss)* | *(FA)* | *(FA)* | *(CR)* |
| **R/F** | *R* | *F* | - | *R* | *F* | - |
| **Faces** | 46.0 | 39.6 | 28.7 | 3.4 | 9.9 | 44.7 |
| | (24.3) | (15.8) | (14.5) | (5.2) | (7.6) | (11.6) |
| **Scenes** | 54.2 | 32.1 | 28.0 | 1.7 | 6.4 | 49.1 |
| | (21.6) | (14.7) | (16.2) | (2.5) | (4.9) | (6.8) |

***Scores collapsed across view and view judgement and derived solely from participants included in the imaging analyses. Standard deviations given in parentheses. FA: false alarm; CR: correct rejection; R: Remember; F: Familiar.***

Mean RTs for the initial responses in the conditions of interest from the test phase are presented in Table 5.4.

Similarly to Experiment 1, RT data for R hits, F hits, misses and correct rejections to faces and scenes were entered into a repeated measures analysis of variance (ANOVA), with non-sphericity corrected for using the Greenhouse-Geisser correction where applicable. There was a significant main effect of both factors ("stimulus": $F_{(1, 8)} = 15.86$, $p < 0.01$; "response": $F_{(1.3, 10.4)} = 17.98$, $p < 0.001$), but the interaction was not significant. As with Experiment 1, the main effect of stimulus reflects slower RTs to scenes than faces across all response categories. Paired *t*-tests collapsed across stimulus category were performed to investigate differences between response types. R hits were significantly quicker than the remaining

[4] The total number of old and new items are slightly less than planned due to occasional scanner crashes which cut the length of some blocks for a small number of participants, and also due to some trials being excluded since one or more responses were not made on time.

three responses (all $t_{(8)} > 3.6$, $p < 0.01$). Misses were slower than CRs ($t_{(8)} = 5.38$, $p < 0.001$). There was no significant difference between F hits and CRs or misses ($p > 0.1$).

***Table 5.4 Mean of median reaction times for each condition of interest in Experiment 2.***

| | **Old Items** | | | **New Items** | | |
|---|---|---|---|---|---|---|
| **Yes/No** | *Yes* | *Yes* | *No* | *Yes* | *Yes* | *No* |
| | *(Hit)* | *(Hit)* | *(Miss)* | *(FA)* | *(FA)* | *(CR)* |
| **R/F** | *R* | *F* | - | *R* | *F* | - |
| **Faces** | 1123 | 1540 | 1687 | 1449 | 1907 | 1547 |
| | (166) | (206) | (280) | (530) | (390) | (320) |
| **Scenes** | 1304 | 1823 | 1980 | 1480 | 1884 | 1697 |
| | (166) | (123) | (434) | (260) | (349) | (378) |

***Reaction times for the initial response to each test item were collapsed across view and view judgement and derived solely from participants included in the imaging analyses. Standard deviations given in parentheses. R: Remember; F: Familiar.***

## *fMRI Results: Study Phase*

The contrasts performed to identify significant effects were identical to those described for Experiment 1. Where possible, local maxima with close proximity to the effects illustrated in Experiment 1 have been illustrated, with additional maxima being presented in some cases to give a more complete picture of activity within each region.

### Main effects of stimulus at study

Results of analyses contrasting responses to faces and scenes provided an almost exact replication of the equivalent analyses from Experiment 1, with improved signal coverage revealing the fuller extent of some of these effects (Figure 5.10).

*Faces > Scenes*

Greater activity in response to faces than scenes was observed in the same area of the left anterior hippocampal ROI which showed this effect in Experiment 1, although the effect was only marginally significant in this case (-18, -6, -15, $Z = 3.36$, 9 voxels, $p_{(SVC\text{-}FWE)} < 0.1$).

Since the effect was focussed in precisely the same voxel as for Experiment 1, it seems likely to be a genuine effect, despite its low statistical significance.

*Scenes > Faces*

Increased activity in response to scenes versus faces was observed in the hippocampus, with identical foci to those found in the study phase of Experiment 1 (right peak: 30, -36, -9, $Z$ = 6.68, 125 voxels; left peak: -33, -36, -9, $Z$ = 5.77, 42 voxels), as well as in the PPA bilaterally (right peak: 24, -36, -15, $Z$ > 7.5, 144 voxels; left peak: -24, -42, -9, $Z$ > 7.5, 160 voxels). The effect in both regions extended further anteriorly than in the previous experiment, most likely due to increased signal coverage. For example, as illustrated in Figure 5.10, a local maximum was observed in the hippocampus at 21, -15, -24 ($Z$ = 3.99). This location lies outside the region with measurable signal in Experiment 1.

**Main effects of subsequent memory (sR > sM)**

Unlike Experiment 1, which revealed a subsequent memory effect in an anterior portion of the hippocampal ROI, contrasting trials which led to subsequent R responses versus misses revealed significant effects in the right parahippocampal (30, -27, -24, $Z$ = 4.27, 52 voxels) and left perirhinal (-30, -3, -36, $Z$ = 3.62, 18 voxels). ROIs (Figure 5.11).

Numerically, the pattern of activity in both regions increased with increasing levels of subsequent memory performance, ie. R > F > M, for both faces and scenes. Post-hoc tests, however, revealed no reliable differences between sR and sF or between sF and sM in either region (all $Z$ < 2.7, $p_{(SVC\text{-}FWE)}$ > 0.1), making it difficult to establish whether the effects were related to subsequent recollection or familiarity.

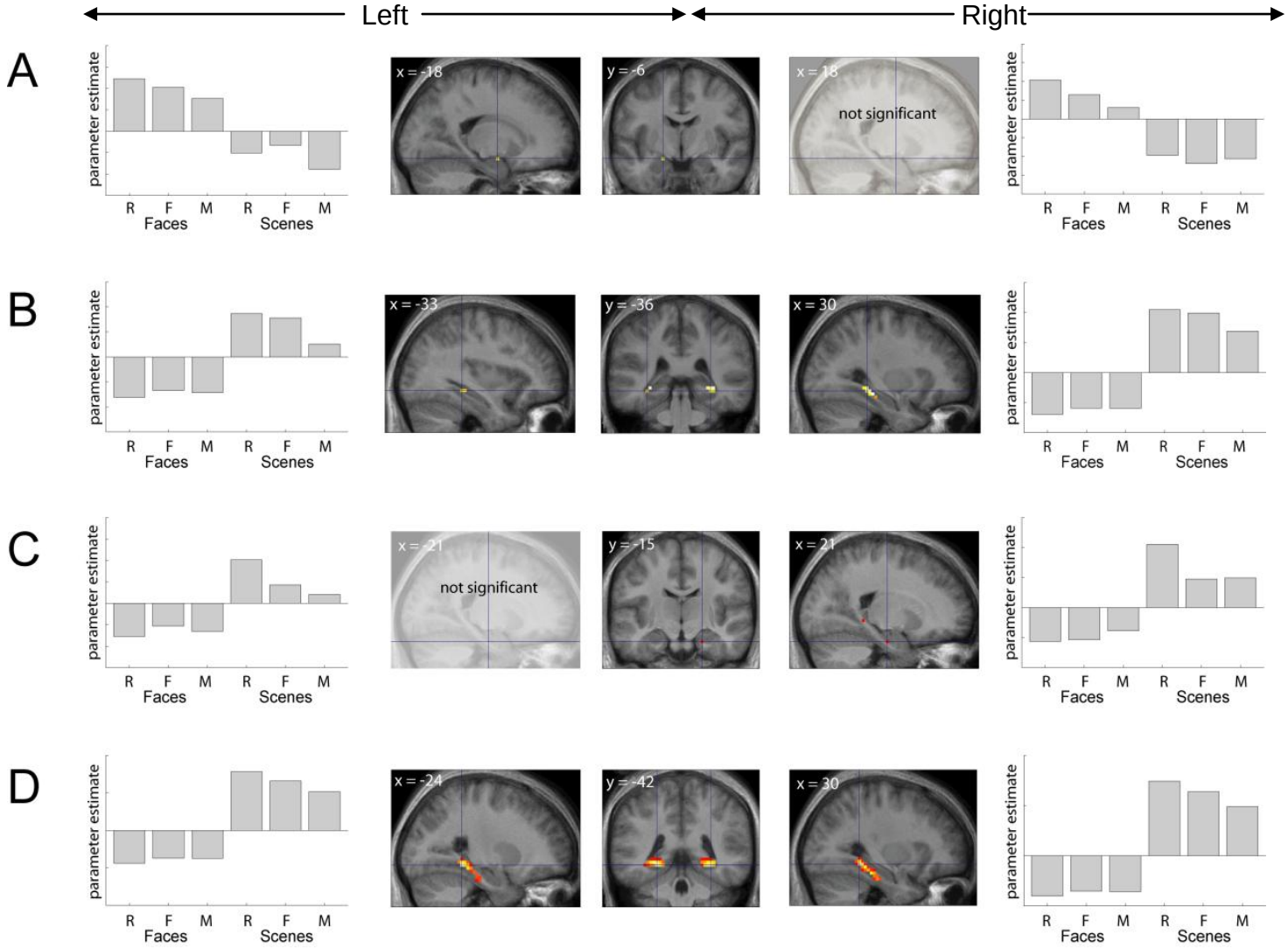


***Figure 5.10 Significant main effects of stimulus observed during the study phase of Experiment 2 within the MTL ROIs. The effect of faces versus scenes in the hippocampal ROI (A) was only revealed when the statistical threshold was reduced to $p_{(SVC\text{-}FWE)} < 0.1$ and thus is illustrated at this threshold. Also in keeping with Experiment 1, increased activity in response to scenes relative to faces was observed bilaterally in large posterior sections of the hippocampal (B) and parahippocampal (D) ROIs, both effects being significant at a threshold of ($p_{(SVC\text{-}FWE)} < 0.05$). Panel C illustrates that the hippocampal region showing increased responses to scenes relative to faces extended further anteriorly, into a region from which adequate signal was not acquired in Experiment 1.***

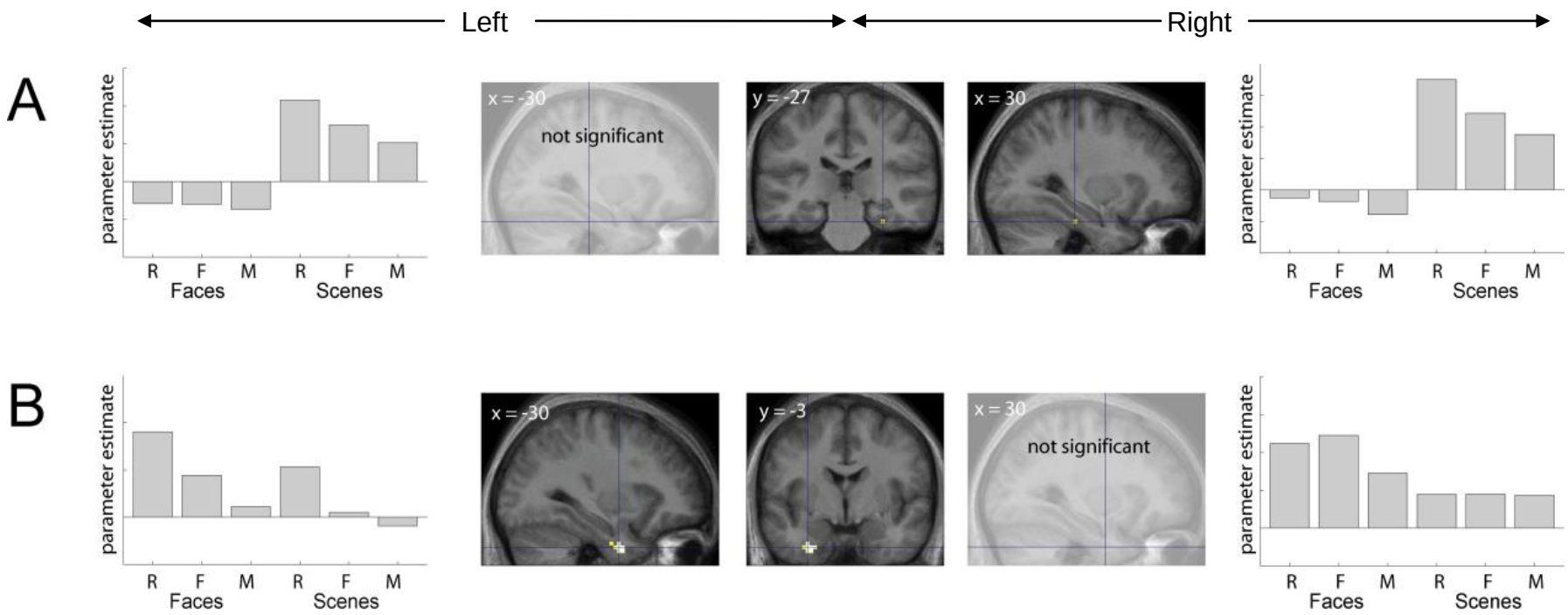


***Figure 5.11 Significant main effects of subsequent memory (sR > sM) observed in Experiment 2 within (A) the parahippocampal ROI, and (B) the perirhinal ROI ($p_{(SVC\text{-}FWE)} < 0.05$). If present, these effects could not have been observed in Experiment 1 due to lack of signal at both locations.***

**Subsequent memory x stimulus interaction (sR > sM x scenes > faces)**

The interaction between stimulus and subsequent memory performance was significant in the left hippocampus (21, -9, -27, $Z$ = 3.58, 68 voxels) and, consistent with Experiment 1, in the parahippocampal cortex, in this case bilaterally (right peak: 21, -33, -15, $Z$ = 4.47, 129 voxels; left peak: -21, -33, -18, $Z$ = 4.33, 122 voxels), indicating that the positive association between improved subsequent memory performance and activity in both regions at study was larger for scenes than for faces (Figure 5.12).

This hippocampal effect was adjacent to the anterior tip of the region showing a main effect of scenes versus faces described above, although it did not itself show a reliable main effect of stimulus ($Z$ < 3; $p_{(FWE\text{-}SVC)}$ > 0.1). In contrast, the parahippocampal effect was located within the PPA described above. Numerically, activity in both regions in response to scene stimuli was greatest for items which were subsequently recollected, and lowest for items which were subsequently forgotten, with items later receiving F responses producing an intermediate level of activity, i.e. sR > sF > sM. Interestingly, for faces, this pattern was reversed: sM > sR > sF. Despite these apparent trends, there were no significant interactions between stimulus and subsequent memory involving sF in either region (all $Z$ < 2.6; $p_{(FWE\text{-}SVC)}$ > 0.4). The hippocampal effect, if present, could not have been detected in Experiment 1 due to poor signal coverage.

The reverse interaction was not significant in any of the ROIs.

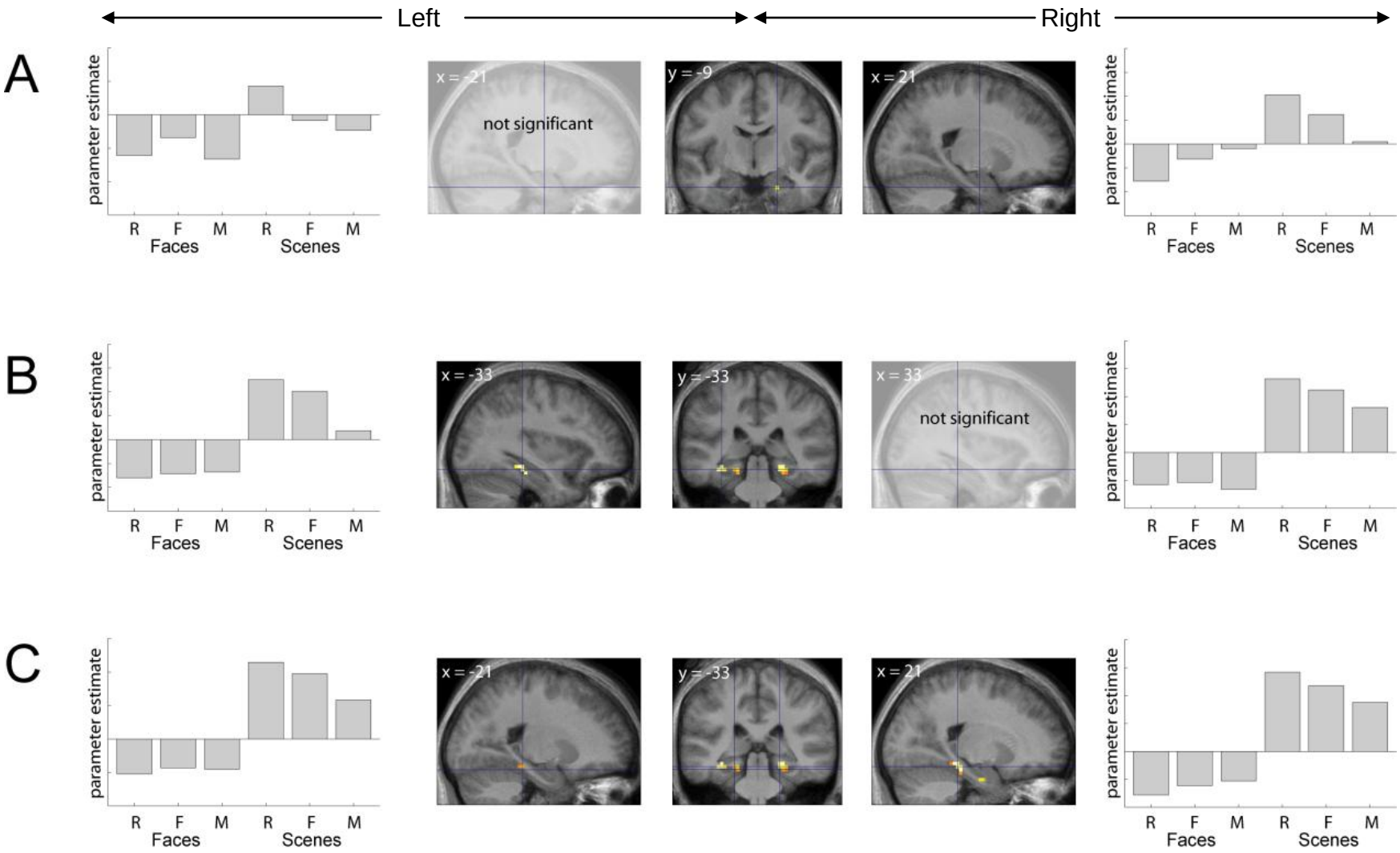


***Figure 5.12 Significant stimulus x subsequent memory interactions (scenes > faces x sR > sM) observed in Experiment 2 within (A) an anterior region of the hippocampal ROI, and (B) & (C) the parahippocampal ROI ($p_{(SVC\text{-}FWE)} < 0.05$). The sub-maximum represented in A falls within an area of signal drop-out in Experiment 1. The sub-maximum represented in B replicates the effect observed in Experiment 1 (see Figure 5.4), and those in C reveal the bilaterality of the effect in a more medial location in the current experiment.***

## *fMRI Results: Test Phase*

As with the study phase of the current experiment, the contrasts performed at test were identical to those described for Experiment 1. Note that the caveat highlighted in Experiment 1, regarding the interpretation of effects of R > F given the significant difference in RTs between these two responses, also applies here.

### Main effects of stimulus at test

Results from the test phase of Experiment 2 provided further evidence of larger responses to faces at the anterior extent of the hippocampal ROI, and to scenes in more posterior hippocampal and parahippocampal regions. Notably, an additional region showing greater responses to faces relative to scenes was observed in the left perirhinal cortex (Figure 5.13).

*Faces > Scenes*

The main effect of faces versus scenes observed at the anterior extent of the hippocampal ROI, on the left, in both phases of Experiment 1 was replicated, in this case the effect being significant bilaterally (left peak: -18, -6, -15 $Z = 4.84$, 10 voxels; right peak: 18, -6, -15, $Z = 4.79$, 13 voxels). This region also exhibited a main effect of recollection versus familiarity (left: $Z = 4.10$; right: $Z = 4.11$).

A region of the left perirhinal cortex showed greater activity in response to faces versus scenes (-27, -3, -39, $Z > 3.57$, 13 voxels). This effect was also marginally significant in two clusters in the right perirhinal cortex (30, 6, -30, $Z = 3.09$, 5 voxels; 30, -3, -36, $Z = 2.91$, 8 voxels; both $p_{(SVC\text{-}FWE)} < 0.1$). The peak voxel of the effect on the left also showed a main effect of recollection ($Z = 4.02$).

*Scenes > Faces*

Global maxima of a bilateral main effect of scenes versus faces were observed in the same loci in the hippocampus as those reported previously (right peak: 30, -36, -9, $Z > 7.79$, 180 voxels; left peak: -33, -36, -9, $Z = 7.12$, 86 voxels). Consistent with the study phase of the current experiment, this effect extended further anteriorly than in Experiment 1, with bilateral local maxima being observed at y = -15, as illustrated in Figure 5.13. Once again, a large bilateral swathe of increased activity in response to scenes relative to faces was found in the parahippocampal cortex (left peak: -27, -45, -6, $Z > 7.31$, 174 voxels; right peak: 24, -36, -15, $Z > 7.31$, 145 voxels).

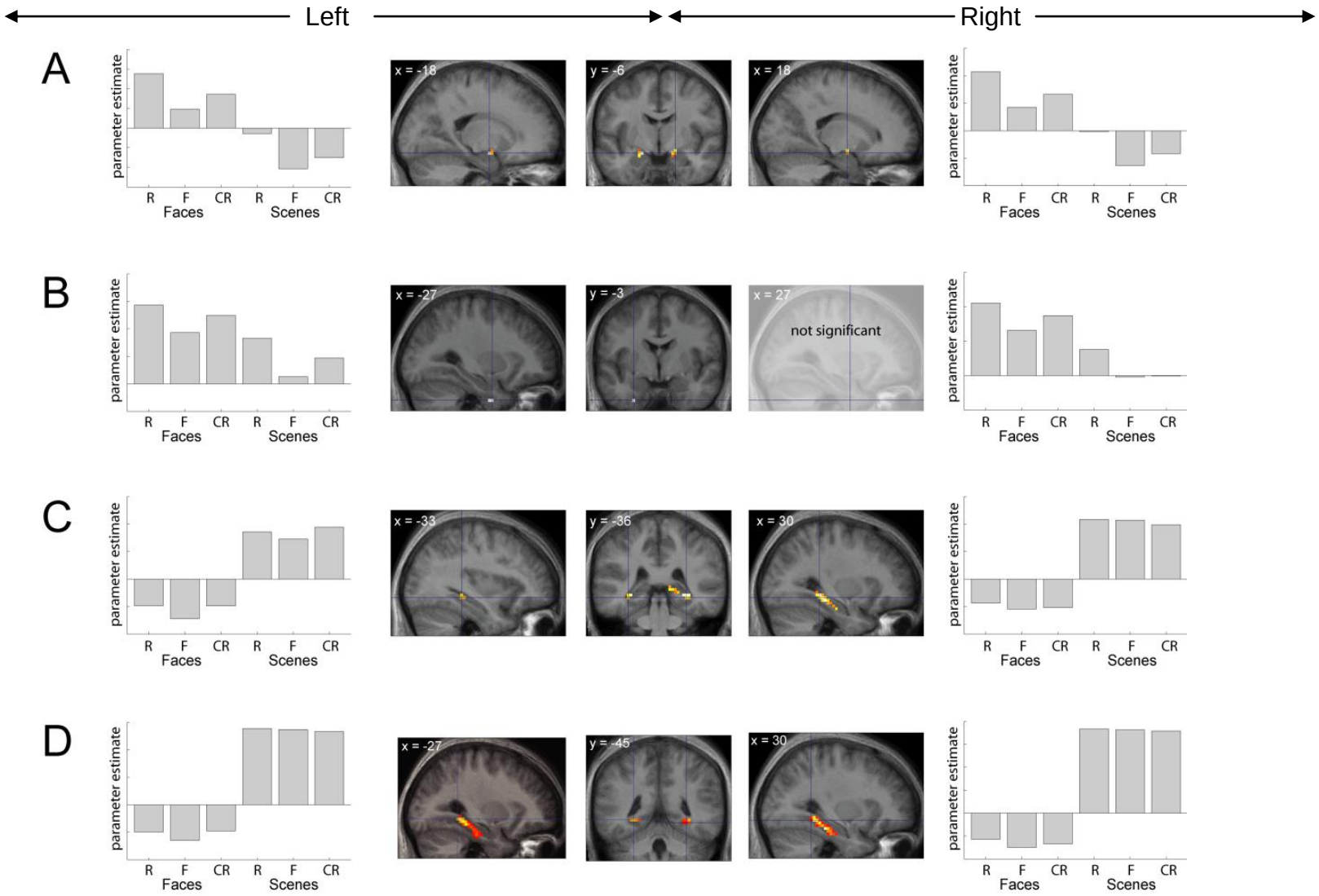


***Figure 5.13 Significant main effects of stimulus observed during the test phase of Experiment 2. In keeping with the study phase, and Experiment 1, greater activity in response to faces than scenes was observed in an anterior region of the hippocampal ROI, this time the effect being significant bilaterally (A). The same effect was also observed in the perirhinal ROI on the left (B). The reverse effect was observed in the hippocampal (C) and parahippocampal (D) ROIs, again with similar foci to those found at study, spreading further anteriorly than in Experiment 1.***

**Main effects of R > F at test**

*Hippocampal ROI*

Similarly to Experiment 1, there was a large bilateral cluster of increased activity associated with R relative to F responses in the hippocampus (left peak: -21, -18, -18, $Z$ = 5.57, 160 voxels; right peak: 21, -27, -12, $Z$ = 5.05, 208 voxels). The pattern of activity across the cluster was very similar to that found in Experiment 1 (see Figure 5.14 A-D), with greater activity in the posterior- (A, D) and anterior-most portions (C) in response to scenes and faces respectively. Activity in voxels located closest to the sub-maxima from Experiment 1 (B-D) replicated the numerical pattern observed previously: R > F < CR, making it difficult to conclude that they exclusively support recollection, although as before, the effect of CR > F was not significant in any of these regions (all $Z$ < 3.4, $p_{(SVC\text{-}FWE)}$ > 0.1). A posterior maximum (A), not present in Experiment 1, showed a pattern of activity more consistent with that expected for a region exclusively involved in recollection (R > F ≈ CR).

*Parahippocampal ROI*

A significant main effect of R > F, not observed in Experiment 1, was observed in the posterior left parahippocampal gyrus (-36, -36, -15, $Z$ = 3.67, 23 voxels), as illustrated in Figure 5.14 (panel E). This region also showed a main effect of scenes > faces. As with the majority of regions showing an R > F effect, the numerical pattern of activity was R > F < CR, although the effect of CR > F was not significant ($Z$ < 3.1, $p_{(SVC\text{-}FWE)}$ > 0.2).

*Perirhinal ROI*

Three clusters in the perirhinal ROI showed a significant main effect of R > F, two on the left (-24, -3, -36, $Z$ = 4.50, 19 voxels & -24, 0, -30, $Z$ = 3.71, 3 voxels), and one on the right (27, 6, -33, $Z$ = 3.77, 7 voxels). One peak from each hemisphere is illustrated in Figure 5.14 (panel F). Although the main effect of faces versus scenes was not significant in any of the three voxels corresponding to these three maxima (all $Z$ < 2.2, $p_{(SVC\text{-}FWE)}$ > 0.1), there was some overlap between the main effects of recollection and stimulus as highlighted above. Once again, the numerical pattern of activity in each cluster was R > F < CR, but with no significant effects of CR > F (all $Z$ < 2.5, $p_{(SVC\text{-}FWE)}$ > 0.4).

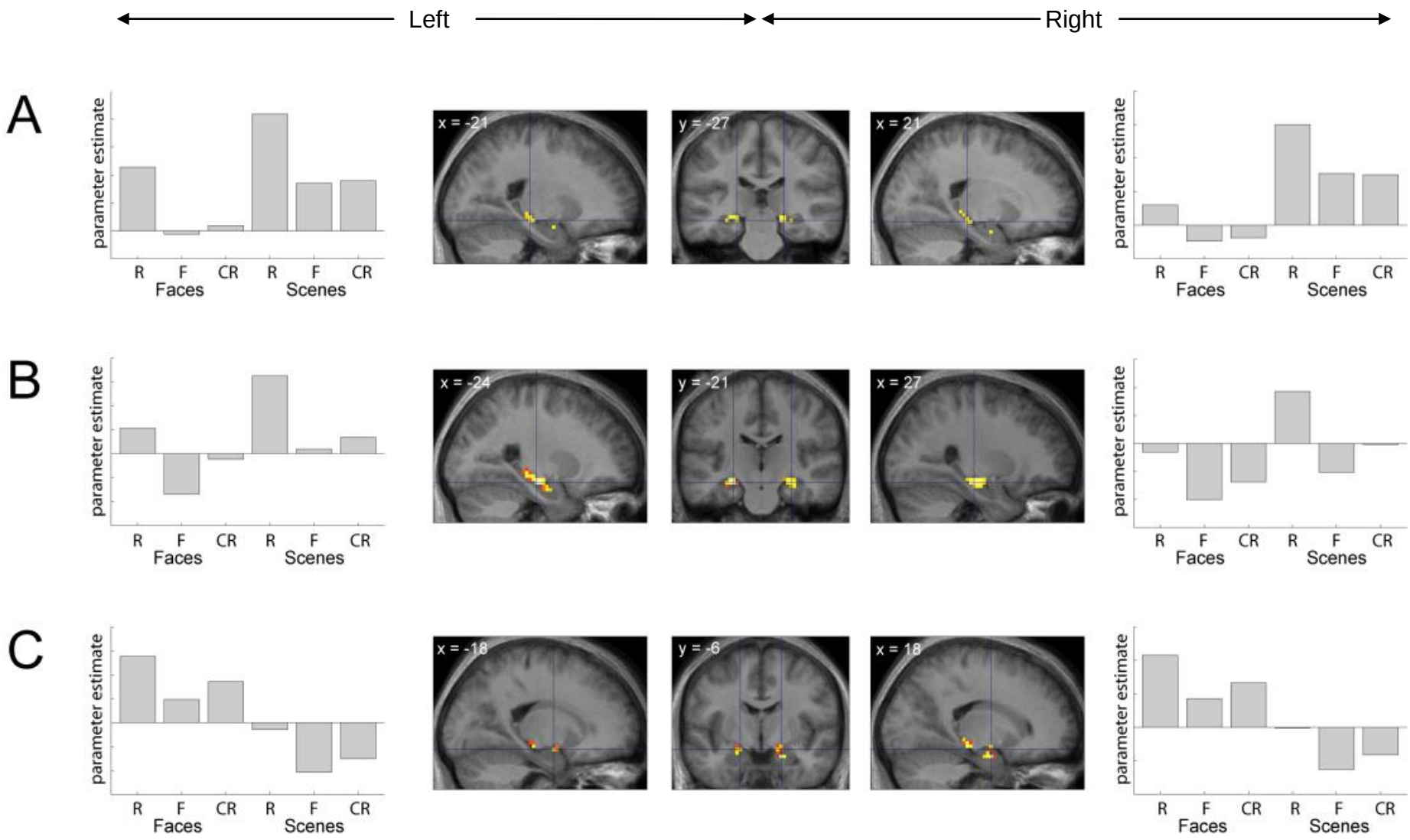


***Figure 5.14 (Continued overleaf)***

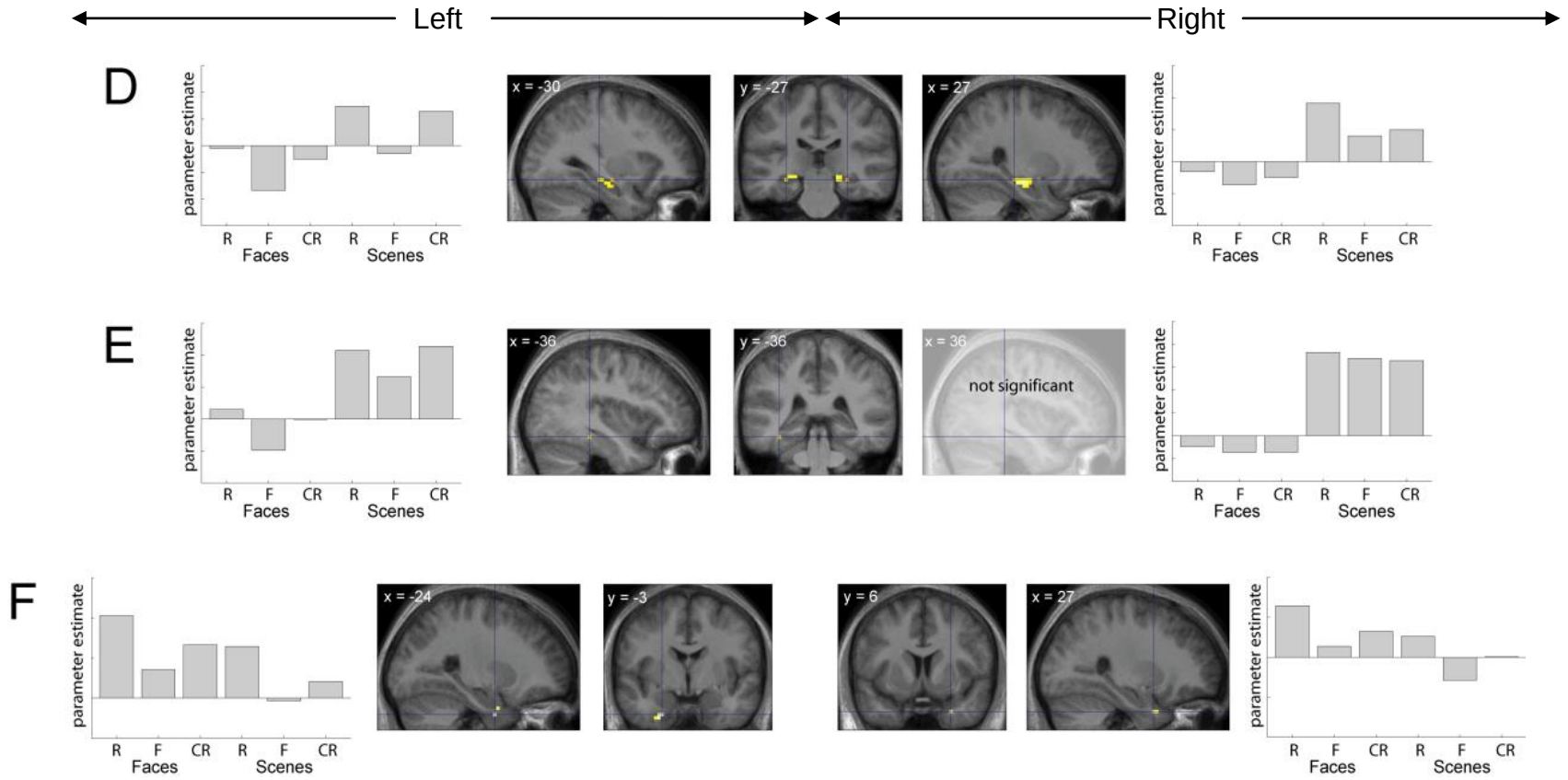


***Figure 5.14 (continued) Significant main effects of R > F observed during the test phase of Experiment 2 in the hippocampal (A-D), parahippocampal (E) and perirhinal (F) ROIs. The local maxima illustrated in panels A-C are matched in terms of y co-ordinates to the sub-maxima illustrated in panels A-C of Figure 5.6 which illustrate main effects of R > F in Experiment 1. For comparison between the two experiments, panel D illustrates the pattern of activity in voxels more closely matched in terms of x and z co-ordinates to panel A of Figure 5.6, although these voxels do not correspond to local maxima in the current experiment. Similarly to Experiment 1, the posterior-most sub-maxima from the right, but not the left hemisphere illustrated above (A&D) also showed significantly greater activity in response to scenes than faces. The parahippocampal maximum (E) was also significantly more active for scenes than faces. The anterior-most sub-maxima (C) of the hippocampal ROI showed a significant effect of faces-scenes in both hemispheres. The intermediate hippocampal region (B) did not show a significant effect of stimulus. Insufficient signal was available to illustrate directly corresponding voxels across the two hemispheres in the perirhinal cortex (F). Neither of the maxima illustrated showed a significant effect of stimulus.***

**Main effects of CR > F at test**

The contrast CR > F revealed a significant bilateral effect in the hippocampal ROI (left peak: -27, -15, -21, $Z$ = 4.24, 182 voxels; right peak: 30, -12, -12, $Z$ = 4.75, 103 voxels). The region on the left overlapped with the region showing the same effect in Experiment 1, and a sub-maximum from the current experiment which is located close to the global maximum of the previous effect is illustrated in Figure 5.15. The effect R > F was significant at the global maximum of both hemispheres (left: $Z$ = 4.48, right: $Z$ = 3.81; both $p_{(SVC\text{-}FWE)} < 0.05$). Within the voxels illustrated in Figure 5.15, the effect of R > F was significant on the right ($Z$ = 4.06, $p_{(SVC\text{-}FWE)} < 0.05$) but not the left ($Z$ = 2.80, $p_{(SVC\text{-}FWE)} > 0.1$). The general trend for this region, therefore was significant effects of both CR > F and R > F.

**Non-significant effects**

There were no significant interactions between the two experimental factors and no significant main effects of F > CR in any of the ROIs.

## *Experiment 2 Summary*

Unfortunately, it was not possible to take advantage of the improved coverage provided by the SE data, due to a low signal-to-noise ratio. Increased coverage was also obtained in the GE data in the current experiment, however, relative to Experiment 1, which enabled analysis of activity in more inferior anterior hippocampal regions and, crucially, the perirhinal cortex.

There was an almost exact replication of all of the main effects of stimulus observed in the study and test phases of Experiment 1, i.e. increased activity for faces relative to scenes in an anterior portion of the hippocampal ROI, and increased activity for scenes relative to faces in the posterior hippocampus and PPA, although the latter effects extended further anteriorly in the current experiment, presumably due to increased signal coverage. In addition, coverage of the perirhinal cortex enabled detection of a main effect of faces > scenes in the left hemisphere during the test phase.

Similarly to Experiment 1, there were no regions in which activity at study could confidently be attributed exclusively to either recollection or familiarity, although the subsequent memory effects which were observed seemed most likely to be attributable to effects of familiarity. Experiment 2 did not replicate the main effect of sR > sM observed in Experiment 1 in the anterior end of hippocampal ROI. Instead, main effects were observed in

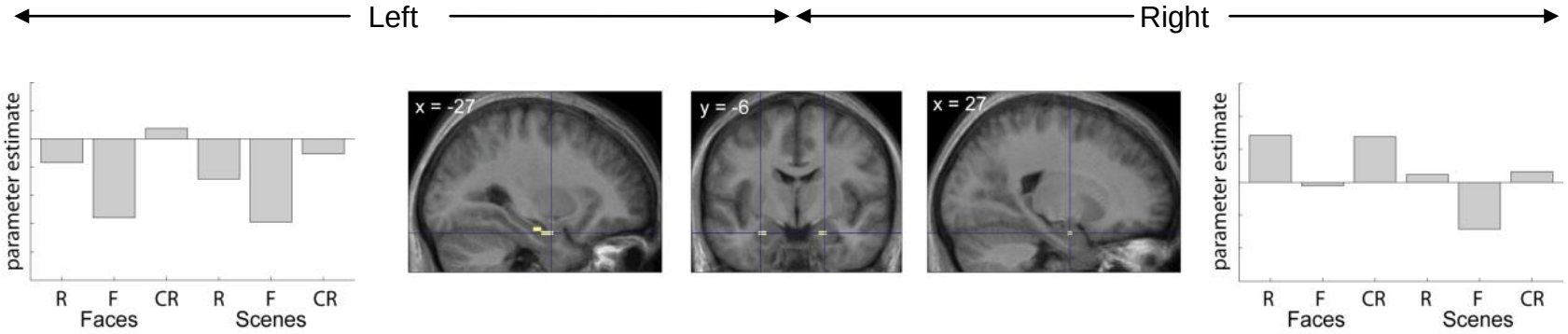


***Figure 5.15 Significant bilateral main effect of CR > F observed in Experiment 2 within the aal hippocampal ROI ($p_{(SVC\text{-}FWE)} < 0.05$).***

the right PPA and left perirhinal cortex. Similarly to Experiment 1, a more posterior region of the PPA showed an interaction such that activity was positively correlated with subsequent memory (sR > sM) for scenes but not faces. This interaction was also significant in the anterior hippocampus, (in an area of signal dropout in Experiment 1).

The results for the test phase replicated and extended the findings of Experiment 1. Effects of R > F and CR > F were observed in almost identical regions of the hippocampal ROI to those found for Experiment 1, in most cases the numerical pattern of activity being R > F < CR, although in most cases the effect of CR > F was not significant. In addition, significant main effects of R > F were also observed in left parahippocampal and bilateral perirhinal cortex. Similarly to the majority of the hippocampal effects, there was a numerical trend towards an effect of CR > F in these regions but none of these effects were reliable. In contrast to each of these regions, the activity in one posterior bilateral hippocampal sub-maximum, which showed a significant main effect of R > F, was approximately equal for Fs and CRs, making this the only region identified in the study which appears, fairly convincingly, to exclusively support recollection. Similarly to Experiment 1, there were no significant interactions between stimulus and memory at test. Rather there were trends, within regions showing a main effect of R > F, for more posterior sub-maxima to show a main effect of scenes > faces, and for more anterior sub-maxima to show a main effect of faces > scenes, like in Experiment 1.

## *Antero-posterior gradient in the processing of faces versus scenes*

A consistent feature of the significant main effects of stimulus observed across both experiments was that the peaks of the effects of faces > scenes were located more anteriorly than the peaks of the effects of scenes > faces. An interesting question is whether these effects are separated by anatomical boundaries, or whether this pattern reflects a general trend or gradient within the MTL, such that more anterior regions preferentially process faces, whereas more posterior regions preferentially process scenes, regardless of particular anatomical boundaries. To investigate this issue, the two main effects of stimulus are illustrated in Figure 5.16 at a relatively liberal threshold throughout the anterior-posterior extent of the MTL. Notably, unlike previous illustrations, the activation patterns shown in the figure are not limited to the ROIs used in the study. Rather than showing a general shift from processing of scenes in posterior regions, to processing of faces in anterior regions, it appears that each effect is contained within particular anatomical regions. The majority of

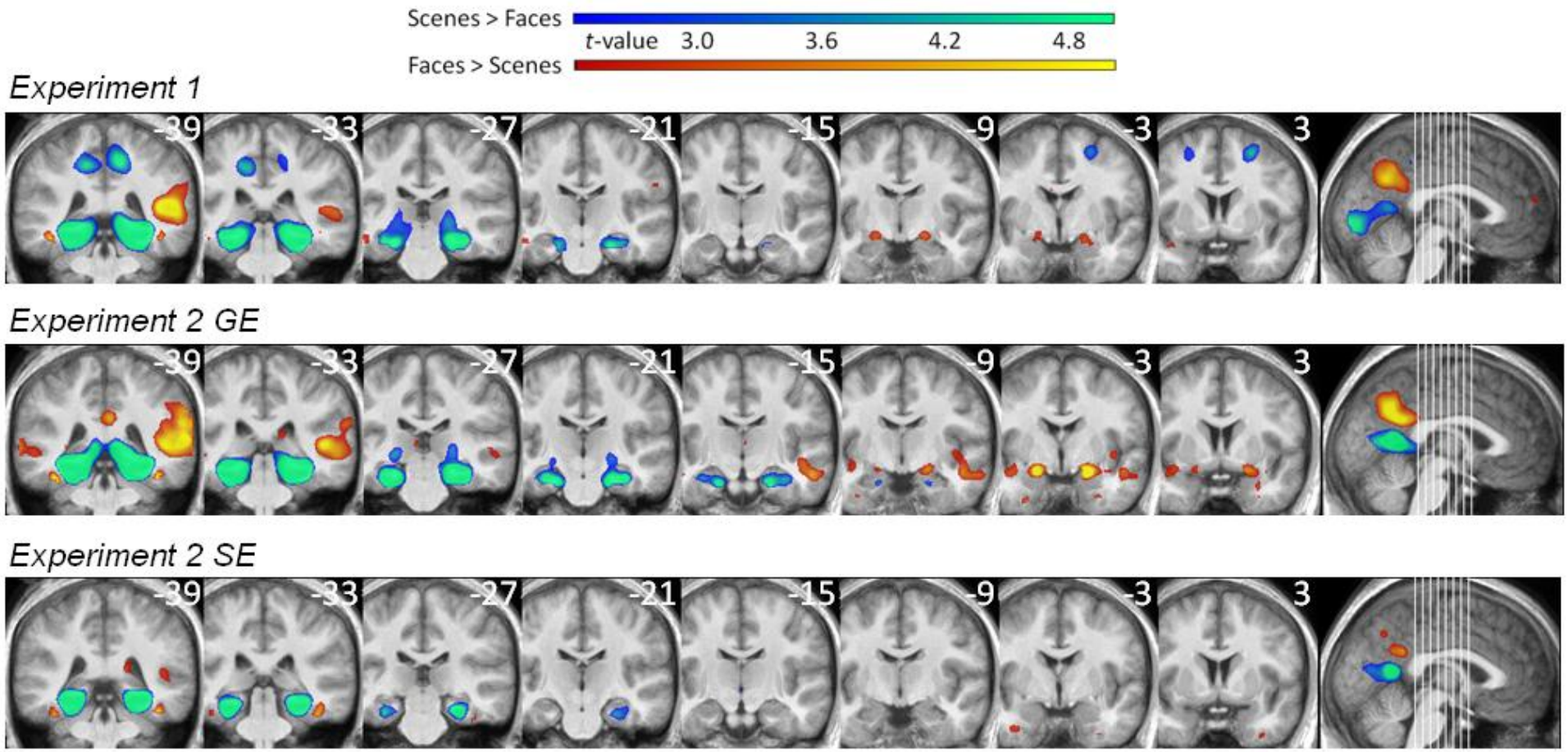


***Figure 5.16 Series of equally spaced coronal sections illustrating the extent of the main effects of stimulus within the MTL during the test phase across the three datasets, overlaid on the normalised mean structural image, at a threshold of $p < 0.01$ uncorrected.***

the hippocampus and parahippocampal cortex showed an effect of scenes > faces, even at their most anterior extent. The effects of faces > scenes, in contrast, appeared to be contained within the amygdala and perirhinal cortex. Of particular interest is the GE data from Experiment 2 at the level of y = -9. Effects of faces > scenes are visible in superior and more inferior MTL regions, most likely corresponding to the amygdala and perirhinal cortex, whereas a region in between, corresponding to the hippocampus, shows an effect of scenes > faces. These anatomical assertions are made cautiously, given the aforementioned limitations of the technique, with reference to the atlas of Duvernoy (1999).

Since the data for Experiment 1 and for both echo-types from Experiment 2 are shown, Figure 5.16 also provides further illustration of the improved MTL coverage obtained in Experiment 2, as well as the reduced power obtained in the SE relative to the GE dataset.

### *Comparison between activation patterns in Experiment 2 and regions of atrophy in the patients reported in Chapter 2*

In order to investigate whether the stimulus-specific deficits observed in Chapter 2 could be explained by the stimulus-specific effects observed in the current chapter, the regions of lesion overlap for each patient group (HC and MTL), described in Chapter 2, were superimposed on the activation patterns of the main effects and interaction involving the factor "stimulus" from the current chapter using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/). For each effect, the GE data from Experiment 2 were examined since these effects were generally more extensive than those of Experiment 1, in which coverage was more limited. Data from the test phase, rather than the study phase of Experiment 2 were used to illustrate main effects of stimulus, since these effects were similarly more extensive, presumably due to the increase in power resulting from the increase in trials contributing to the contrasts in the test phase. Note that, similarly to Figure 5.16, the activity patterns illustrated in the figure were not restricted to the ROIs used in this Chapter. The following limitations of this method should be noted: (i) the co-registration between the lesion and functional images is only approximate, particularly since the two sets of images were pre-processed using different versions of SPM (SPM99 and SPM5) and because normalisation of patient brains is notoriously difficult; (ii) the extent of the MTL for which comparisons could be made was limited to those regions in which sufficient signal was obtained in Experiment 2; (iii) the lesion overlay method does not take

into account areas of damage which are not common to both patients, or areas of underfunctioning which appear structurally normal.

**Can main effects or interactions involving stimulus explain the scene-specific deficits in HC patients?**

As illustrated in Figure 5.17, despite being focussed in the hippocampus and parahippocampal cortex, there was no overlap between regions showing an interaction between stimulus and subsequent memory (cyan) and the regions damaged in both HC patients (red). This suggests that the scene-specific mnemonic effects observed during study in the current chapter are unlikely to explain the scene-specific deficits observed in the HC patients in Chapter 2. Figure 5.17 illustrates that there was some considerable overlap, however, between the region of lesion overlap and the main effect of scenes > faces (green) from the test phase of Experiment 2. The area of overlap appears to include medial portions of the hippocampus as well as anterior parahippocampal cortex. Hence, damage to these regions is likely to have played a central role in the deficits in recognition memory for scenes reported in Chapter 2.

**Can main effects of stimulus explain the additional deficits on face recognition memory in MTL patients?**

As illustrated in Figure 5.18, there was no overlap between the region thought to correspond to the amygdala that showed a main effect of faces > scenes (blue), and the regions of common damage in the MTL patients (red). There was some overlap, however, between the main effect of faces > scenes and the area of lesion overlap in the region of the perirhinal cortex. As can be seen in panels B, C and D of Figure 5.18, adjacent regions of the perirhinal cortex that were damaged in both MTL patients suffered from signal drop-out in Experiment 2. It is possible, therefore, that the effect of faces > scenes extended further into this region. Damage to this area therefore seems the most likely cause for the impairments in recognition memory for faces observed in Chapter 2.

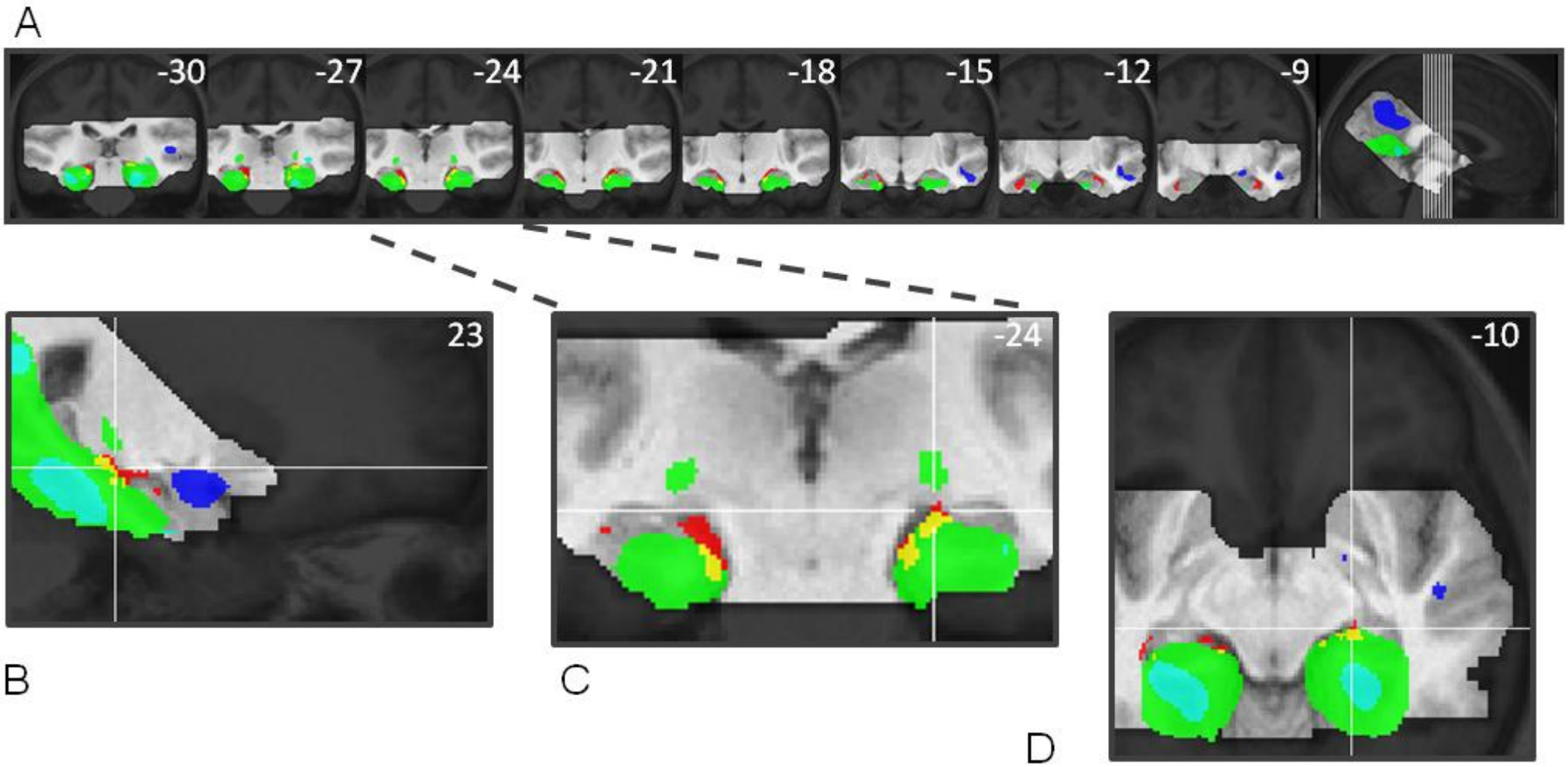


*Figure 5.17 Overlapping regions of atrophy for the HC patients from Chapter 2 (red), together with main effects of faces > scenes (blue) and scenes > faces (green), and the interaction sR > sM x scenes > faces (cyan) from the test phase of Experiment 2 (GE; p < 0.001 uncorrected), overlaid on the normalised mean structural image from Experiment 2. Brighter regions indicate the total voxel mask from Experiment 2. Panel A illustrates a series of equally-spaced coronal sections. Panel C illustrates a zoomed in version of a slice from panel A showing overlap (yellow) between the lesion and the main effect of scenes > faces. Corresponding sagittal (B) and horizontal (D) slices are also shown.*

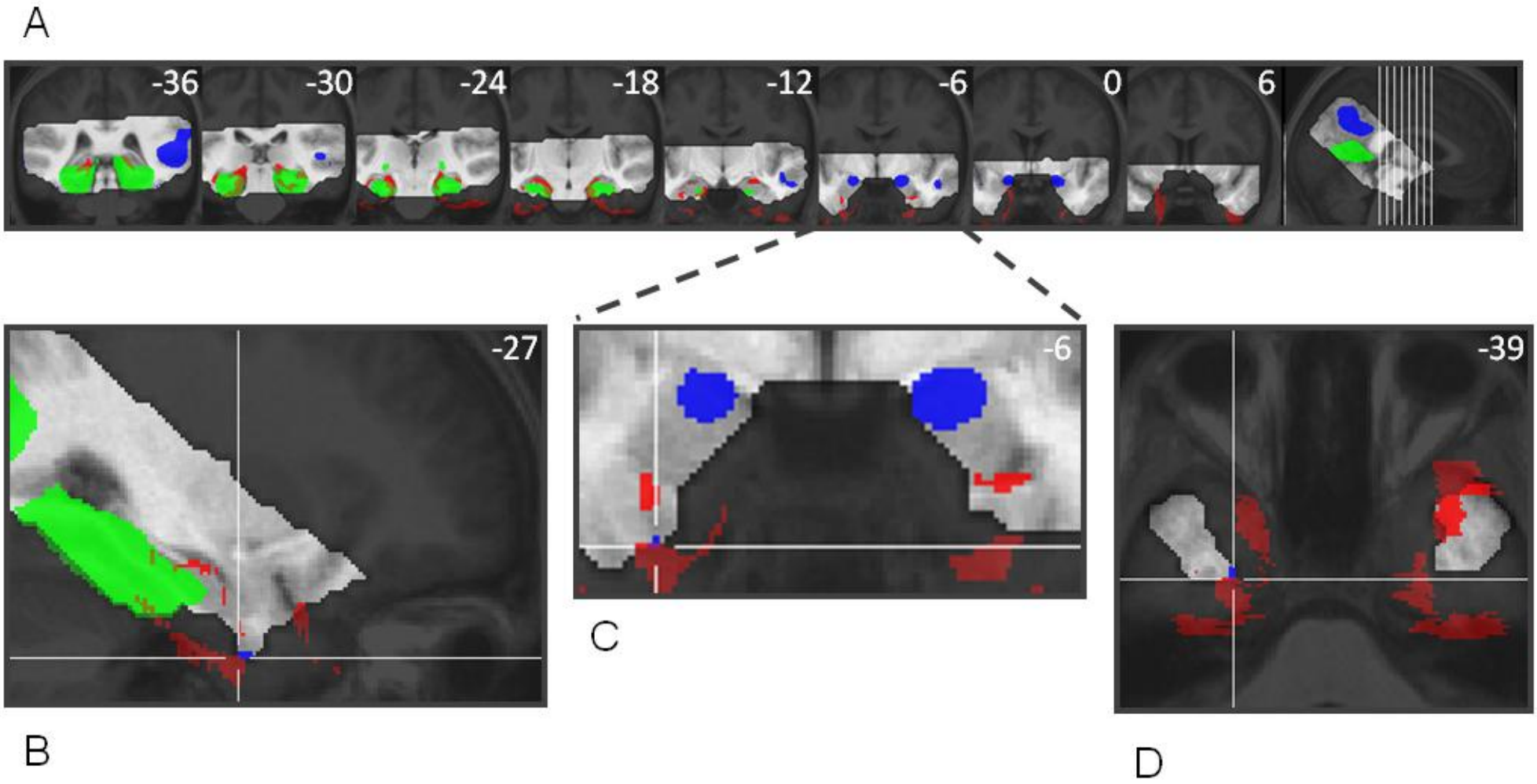


***Figure 5.18 Overlapping regions of atrophy for the MTL patients from Chapter 2 (red), together with main effects of faces > scenes (blue) and scenes > faces (green) from Experiment 2. Panel C illustrates a zoomed in version of a slice from panel A showing overlap (purple) between the lesion and the main effect of faces > scenes. Corresponding sagittal (B) and horizontal (D) slices are also shown. See Figure 5.17 caption for further details.***

# Discussion

The imaging experiments reported in the current chapter are possibly the first to directly compare activations associated with recognition memory for faces and scenes, at either study or test, within the same participants. They were designed to investigate two proposed functional dissociations in the MTL, each of which provide a potential explanation for the pattern of deficits observed across the patient groups reported in Chapters 2 and 3. One possibility, which gained credence from the behavioural findings of Chapter 4, is that recognition memory for scenes depends disproportionately on recollection, which in turn depends on the hippocampus, whereas recognition memory for faces depends disproportionately on familiarity, which in turn depends on the perirhinal cortex. The imaging data provided little support for this possibility: overall, the pattern of activity observed in the perirhinal and parahippocampal cortices, and the hippocampus, could not be distinguished in terms of contributions to recollection or familiarity. Contrasts designed to identify effects of recollection at test revealed significant activations in all of these regions, irrespective of stimulus category, whereas activity in each region at study appeared to predict subsequent levels of familiarity (and potentially also recollection).

A second possibility is that different MTL regions are specialised to support mnemonic and/or perceptual processing of faces and scenes. There was some evidence of stimulus-specific mnemonic processing (i.e., an interaction between the factors stimulus and memory category), although this was limited to the study phase, during which activity in the parahippocampal cortex and hippocampus showed a greater positive correlation with subsequent memory for scenes than for faces. It is possible, therefore, that damage to these regions in the patients reported in Chapter 2 might have led to a deficit in recognition memory for scenes but not faces because they play a greater role, at encoding, in recognition memory for the former relative to the latter stimulus category. When the area of lesion overlap for the HC patients was superimposed on the activation pattern for this interaction, however, no overlap was observed. It seems unlikely, therefore, that this effect was the central cause of the scene recognition memory deficits in these patients. Furthermore, no regions were identified which played a significantly greater role in recognition memory for faces than scenes during either study or test, making the larger impairment in recognition memory for faces than scenes observed in the SD patients in Chapter 3 difficult to explain by this account. The evidence of stimulus-specific mnemonic processing in the MTL obtained

in the current study does not, therefore, provide a very powerful or complete explanation of the dissociations reported in Chapters 2 and 3.

In keeping with previous neuroimaging studies (Kohler et al., 2005; Lee et al., 2008; Pihlajamaki et al., 2004), highly consistent evidence of stimulus-specific activity, that was independent of mnemonic performance, was found during both the study and test phases of both experiments. This could be interpreted as evidence in support of the view that the hippocampus and parahippocampal cortex support the formation of representations of scenes (Buckley et al., 2004 & Gaffan, 2004; Burgess & O'Keefe, 2003; Epstein & Kanwisher, 1998; Lee, Barense et al., 2005), whereas the perirhinal cortex supports the formation of representations of faces (Buckley & Gaffan, 2006; Lee, Barense et al., 2005). It follows that impoverished representations are likely to lead to poor memory performance and so this may explain the stimulus-specific deficits following damage to these regions observed in the patients in Chapters 2 and 3. This account is strengthened by the observation of overlap between the main effect of scenes > faces and regions of atrophy in the HC patients (specifically in the hippocampus and anterior parahippocampal cortex), as well as the observation of overlap between the main effect of faces > scenes and regions of atrophy in the MTL patients (specifically in the perirhinal cortex). These ideas are consistent with previous studies which have revealed perceptual impairments in both humans and non-human primates following damage to MTL regions, with lesions to the perirhinal cortex affecting object and face perception (Barense, Bussey, Lee, Rogers, Davies et al., 2005; Buckley et al., 2001; Lee, Buckley et al., 2006; Lee, Buckley et al., 2005), and lesions to the hippocampus affecting spatial perception (Barense, Bussey, Lee, Rogers, Davies et al., 2005; Buckley et al., 2004; Lee, Buckley et al., 2006; Lee, Buckley et al., 2005).

Several regions of the MTL, including portions of the hippocampus, perirhinal and parahippocampal cortex, exhibited a complex pattern of activity during retrieval. Each of these regions showed significant effects of R > F, but in most cases, there was also a numerical trend towards, or significant effect of CR > F. Similar patterns of activity have previously been observed in the perirhinal cortex (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005) and, as discussed below in more detail, the hippocampus (Yonelinas et al., 2005). This pattern is difficult to interpret in terms of recollection and familiarity. One possibility is that each of these regions simultaneously support familiarity (through a process

of novelty detection, hence the *decrease* in activity for more familiar items) as well as recollection. Another possibility is that the effects of CR > F could signal encoding-related activity (i.e, greater activity for unstudied items than recognised studied items). This is supported by studies which have found that the increased activity seen in MTL regions in response to novel items during a recognition memory test predicts subsequent memory during a second subsequent test (Stark & Okado, 2003). It is difficult to distinguish these possibilities within the current experimental set-up, however, since both processes are equally likely to produce greater activity on CR trials relative to F trials. In fact, it is possible that novelty detection and encoding are merely two behavioural outcomes of a single process. In other words, the brain region in question may detect that an item is novel, stimulating an increase in activity which enables encoding of that item.

Despite these difficulties in interpreting the activation patterns revealed in the present experiments, the fact remains that there was little evidence for a functional division in the contribution of MTL regions to recollection and familiarity. This lack of a dissociation appears to conflict with several neuroimaging studies (see Diana et al., 2007, for a review). As discussed in the introduction to this chapter, however, in contrast to the present experiments, much of the evidence supporting a role for the hippocampus (and perhaps the parahippocampal cortex) in recollection, and for the perirhinal cortex in familiarity, comes from studies involving verbal stimuli (e.g. Davachi et al., 2003; Ranganath et al., 2004). Given the highly significant and consistent effects of stimulus category observed in the MTL in the present experiments, it is not surprising that studies using verbal versus visual modalities might produce different results from one another.

Of the studies that have examined the neural correlates of recollection and familiarity of scenes or faces, some are consistent with the present findings. For example, the pattern of activity observed in the parahippocampal cortex during the study phase of the current experiments was highly consistent with that observed by Brewer et al. (1998), who examined scene recognition memory, i.e. sR > sK/sF > sM. As discussed previously, this pattern is indicative of a role for this region in supporting subsequent familiarity, and perhaps in addition, recollection. The current findings extend those of Brewer et al. by indicating that for at least some regions of the parahippocampal cortex, this effect is specific to scenes and not faces. Similarly to the current experiment, Weis and colleagues observed recollection-

related activity (H+SC > H+SI) in a region which included portions of the hippocampus, amygdala and parahippocampal gyrus. A smaller area of the MTL, which appears to overlap with the area showing an effect of recollection, including aspects of the parahippocampal gyrus and anterior hippocampus, showed an effect of familiarity (H+SI < M). The overlap between these effects is consistent with the observations of the current experiments, in which regions showing a significant effect of recollection (R > F) almost always also showed a trend toward an effect of familiarity (CR > F).

As discussed in the introduction, one study that examined the neural correlates of recollection and familiarity for scenes revealed effects that were highly consistent with the predictions of some dual-process models, with effects of familiarity and recollection being observed in the perirhinal cortex and hippocampus respectively (Montaldi et al., 2006). An important difference between the current experiments and that of Montaldi et al. concerns the nature of the contrasts used to identify effects of recollection and familiarity. It has been argued that since familiarity is thought to be a continuous variable, activity in regions which support this process should be linearly modulated by differing levels of familiarity. As a result, simple categorical contrasts such as those used in the present experiments may not provide the optimal method for identifying effects of familiarity. Montaldi et al. therefore adopted a parametric approach to identifying effects of familiarity, by looking for regions whose activity correlated with familiarity strength. The only MTL region identified using this method was the perirhinal cortex. In addition, since recollected items may be associated with high levels of familiarity, categorical contrasts designed to identify effects of recollection, such as R > F, do not necessarily provide an exclusive measure of recollection-related activity, and may also identify regions which either partially or even exclusively support familiarity, an argument which is wholly accepted here. Montaldi et al. therefore used an additional requirement that regions could only be assumed to exclusively support recollection if their activity was not linearly modulated by differing levels of familiarity. The only MTL region to meet these requirements was the hippocampus.

An important question that follows these points, therefore, is whether the categorical contrasts used in the present experiments may have masked a dissociation between the contribution of MTL structures to recollection versus familiarity, thus explaining the inconsistencies between the current findings and those of Montaldi et al. In other words,

could the same pattern of activity observed in at least one location within all three regions of interest in the current experiments, i.e. R > F < CR, have been produced, in some cases, by processing which exclusively supports recollection, and in others, by processing which exclusively supports familiarity? As discussed previously, this pattern of activity could result from the process of recollection of old items plus encoding of new items, potentially leading to recollection, were an additional memory test performed. The pattern is therefore consistent with an exclusive effect of recollection. It is difficult to see how this pattern of activity could emerge in a region which exclusively supports familiarity, however, since recollected items should be at least as familiar, if not more so, than those given familiar responses, which in turn should be more familiar than correctly rejected items. The activity in a region exclusively supporting familiarity should therefore either positively or negatively correlate across the three response categories in one of the following ways: R > F > CR or R = F > CR. Thus, although a parametric approach may have helped to clarify the nature of these activation patterns, one must conclude that the current findings indicate at least some contribution from the hippocampus, parahippocampal cortex and perirhinal cortex to recollection, although contributions to familiarity may differ.

Interestingly, a recent investigation of verbal recognition memory in which a similar parametric approach to that adopted by Montaldi et al. was used, also produced results which were inconsistent with the dual-process model of MTL function (Yonelinas et al., 2005). The study revealed apparent effects of both recollection (R > 4) and familiarity (1 > 2 > 3 > 4) in the hippocampus, a pattern which maps well onto that observed in several regions in the present experiments. In contrast, no effects of recollection or familiarity were observed in the perirhinal cortex, although this could be due to a number of reasons such as poor signal in the region or insufficient power. Thus, even when more complex measures of familiarity are adopted and verbal stimuli employed, the results of imaging investigations of recognition memory are not always consistent with the predictions of dual-process models.

As highlighted by Montaldi et al., there were some significant differences between the design of their study and that of Yonelinas et al. which may have contributed to the contrasting findings obtained in each case, and these same differences may also explain the inconsistencies between the findings of Montaldi et al. and those of the current chapter. These differences relate to the particular focus given by Montaldi et al. to familiarity rather

than recollection. First, the authors used a longer delay of 2 days between study and test, with the aim being that this would reduce the occurrence of recollection during retrieval. The precise impact of this change is hard to predict but it may well have been significant. Second, in the study by Montaldi et al., a simultaneous match-to-sample task was used at study. Participants were required to match one of two versions of each scene to the sample scene presented above them. The target scene was an exact replica of the sample scene, whereas the foil was shifted slightly either horizontally or vertically. This may have encouraged a very superficial level of processing, with a particular focus on the edges of the scenes where the differences between the targets and foils was apparent, which may in turn have led to the formation of less detailed representations compared to the present experiments. Indeed, the aim was to reduce the type of processing that leads to recollection. Since the processing requirements and the nature of the representations formed in a task are likely to dictate which regions of the MTL play a vital role, this manipulation may also help to explain the differences between the activation patterns observed across the two experiments.

The role of the amygdala is not of central interest in the current thesis. The hippocampal ROI extended into this region in at least some participants, however, and thus several significant effects which were likely to be located in the amygdala were highlighted, and these deserve some discussion. In keeping with the proposed role for the amygdala in the processing of emotionally relevant stimuli (Breiter et al., 1996; Calder et al., 2001; Dolan, 2002), activity in this region was greater in response to faces than scenes during both study and test. Main effects of R > F were observed during test in both experiments, and Experiment 1 also revealed a subsequent memory effect which appeared to predict subsequent levels of familiarity. In addition, a slightly more inferior area closer to the boundary between the amygdala and the hippocampus, was the only region in either experiment in which the effect of CR > F was significant. This effect was significant in both experiments, suggesting that it is highly reliable. The fact that the above effects were not specific to faces is somewhat surprising, since the scenes used in the study are unlikely to carry a particular emotional valence. Like most of the theories explored in the current thesis, dual-process models do not consider the amygdala as a part of the MTL, and it is not thought to play a central role in recollection or familiarity. It is possible, however, that its proposed role in enhancing mnemonic processing (Anderson & Phelps, 2001; Cahill & McGaugh, 1998; Hamann et al.,

1999; Packard et al., 1994; Paz et al., 2006), is not limited to emotionally salient stimuli. Alternatively, given the proximity of these effects to the hippocampus, they may have been produced by some blending of the signal from the hippocampus and the amygdala.

The findings in SD patients reported in Chapter 3 suggested that laterality may be another potentially important factor which influences the contribution of MTL structures to recognition memory. Although this factor was not directly investigated in the analyses reported above, plots for both hemispheres were provided for all significant effects, whether or not they were significant bilaterally, to help identify potential effects of laterality. A large proportion of the observed effects were bilateral, with no obvious trend towards larger or more significant effects of any sort in one or other hemisphere. Where effects were only unilaterally significant, the plots given for the contralateral hemisphere generally revealed a similar pattern of activity in both hemispheres. The findings of the present chapter do not, therefore, shed any light on the laterality effects suggested by Chapter 3.

A final consideration when interpreting the present findings is the incomplete coverage of the MTL obtained in each experiment. Insufficient signal was obtained in Experiment 1, which employed a standard GE sequence, to analyse the neural activity in a large region of the anterior MTL, which included the entire perirhinal cortex. This problem was partially rectified in Experiment 2 which employed a dual-echo sequence consisting of alternating GE and SE acquisitions, and positioned differently to the sequence used in Experiment 1. The GE data provided improved coverage of the MTL, including more anterior inferior portions of the hippocampus and some aspects of the perirhinal cortex. Unfortunately, however, insufficient signal was obtained in a large proportion of the perirhinal cortex. The coverage of the SE data was even better still, but it led to no additional findings due to the low signal-to-noise ratio afforded by this technique. This problem was not helped by the unavoidably small number of participants included in the analysis. A study performed in parallel with Experiment 2, using the same sequence, suggests, however, that even with double the number of participants, the power obtained from SE data is insufficient to detect any but the most robust of effects (Barense, personal communication, 2007).

## Summary

The two experiments reported in the present chapter failed to reveal any evidence for a dissociation in the contribution of MTL structures to recollection versus familiarity. Rather, there was evidence that each region of interest made at least some contribution to both processes. Evidence of stimulus-specific mnemonic processing was also limited. The experiments did reveal consistent evidence, however, that the hippocampus and parahippocampal cortex are preferentially activated by scenes, whereas the perirhinal cortex and amygdala are preferentially activated by faces. Since these effects of stimulus category did not, in general, interact with memory performance, this supports the view that these regions may be involved in building perceptual representations of visual stimuli. The hippocampal and parahippocampal regions which preferentially processed scenes overlapped considerably with the loci of damage in the HC patients exhibiting scene-specific recognition memory deficits reported in Chapter 2. Similarly, the perirhinal cortex region which was more active for faces overlapped with an additional region of damage in the MTL patients who were also impaired in face recognition memory. Together, these findings support the view that different MTL regions are specialised to support processing of different stimulus categories. Dual-process models which propose a functional division in the MTL according to contributions to recollection and familiarity will require significant modification in order to accommodate these novel findings.

# Appendix: Complete breakdown of behavioural results

***Table 5.5 Mean number of each response combination for each category of item in Experiment 1.***

| **Yes/No** | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *No* |
|---|---|---|---|---|---|---|---|
| **R/F** | *R* | *R* | *R* | *F* | *F* | *F* | - |
| **View** | *Same* | *Different* | *DK* | *Same* | *Different* | *DK* | - |
| **Studied Items** | | | | | | | |
| *Same view faces* | 21.8 (12.4) | 2.5 (4.0) | 2.8 (4.2) | 7.1 (5.4) | 5.2 (4.6) | 9.4 (7.5) | 8.8 (5.4) |
| *Different view faces* | 3.1 (2.3) | 5.4 (5.3) | 1.2 (1.4) | 3.9 (4.1) | 8.4 (4.0) | 11.6 (8.2) | 24.2 (9.3) |
| *Same view scenes* | 33.3 (7.5) | 2.8 (1.9) | 2.4 (3.3) | 3.7 (4.1) | 4.3 (2.7) | 4.5 (3.6) | 7.0 (3.8) |
| *Different view scenes* | 6.6 (4.4) | 13.8 (6.9) | 0.8 (1.0) | 2.8 (3.2) | 10.3 (5.2) | 6.4 (4.4) | 16.9 (9.1) |
| **New Items** | | | | | | | |
| *Faces* | 1.2 (2.4) | 0.8 (0.9) | 0.2 (0.6) | 1.7 (1.3) | 4.7 (5.0) | 8.8 (4.6) | 41.3 (8.7) |
| *Scenes* | 0.6 (1.0) | 0.6 (1.0) | 0.3 (0.6) | 1.3 (2.4) | 4.8 (4.2) | 4.4 (2.8) | 46.3 (9.2) |

***Each row sums to a maximum of 60 items[5] (standard deviations presented in parentheses).***

[5] The total of each row is slightly less than 60 due to occasional scanner crashes which cut the length of some blocks for a small number of participants.

***Table 5.6 Mean number of each response combination for each category of item in Experiment 2.***

| **Yes/No** | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *Yes* | *No* |
|---|---|---|---|---|---|---|---|
| **R/F** | *R* | *R* | *R* | *F* | *F* | *F* | - |
| **View** | *Same* | *Different* | *DK* | *Same* | *Different* | *DK* | - |
| **Studied Items** | | | | | | | |
| *Same view faces* | 21.6 (10.0) | 5.5 (6.0) | 2.7 (2.6) | 5.8 (5.4) | 5.8 (4.0) | 8.1 (5.3) | 7.3 (4.2) |
| *Different view faces* | 3.6 (4.9) | 10.9 (8.4) | 1.6 (1.7) | 2.4 (3.1) | 9.6 (6.8) | 7.9 (4.0) | 21.4 (11.4) |
| *Same view scenes* | 26.1 (8.0) | 5.1 (4.6) | 1.9 (2.2) | 6.9 (7.1) | 3.2 (2.0) | 5.6 (4.2) | 8.5 (6.7) |
| *Different view scenes* | 4.3 (3.5) | 15.7 (9.4) | 1.1 (1.6) | 2.7 (3.4) | 8.6 (5.8) | 5.2 (4.1) | 19.5 (10.1) |
| **New Items** | | | | | | | |
| *Faces* | 1.1 (21.8) | 1.9 (3.5) | 0.3 (1.0) | 0.9 (1.7) | 4.8 (4.4) | 4.3 (5.1) | 44.7 (11.6) |
| *Scenes* | 0.2 (0.4) | 1.4 (2.4) | 0.1 (0.3) | 0.4 (0.5) | 3.2 (2.4) | 2.7 (2.9) | 49.1 (6.8) |

***Each row sums to a maximum of 60 items[5] (standard deviations presented in parentheses).***

# Chapter 6
# Conclusions

## Summary of findings

The experiments reported in the current thesis were designed to investigate two groups of theories which have proposed functional dissociations between the hippocampus and surrounding medial temporal cortex. The first group of theories focus on the visual modality and suggest that whereas the hippocampus and/or the parahippocampal cortex support processing of scenes, the perirhinal cortex supports processing of complex objects, particularly those which are configural in nature, such as faces (Buckley & Gaffan, 2006; Lee, Barense et al., 2005; Murray et al., 2007). These ideas were explored in Chapters 2 and 3 by examining the performance of three patient groups with differing profiles of MTL damage on a forced-choice recognition memory test for faces and scenes. Previous studies using non-mnemonic visual discrimination tasks had shown that the same patients were only impaired on conditions involving altered view-points, and not on those in which the view-points of targets and foils remained unchanged (Lee, Buckley et al., 2005). The experiments in Chapters 2 and 3 therefore incorporated trials in which the viewing angle of items was adjusted between study and test, as well as more traditional same-view conditions.

In Chapter 2, patients with focal damage to the hippocampus were impaired on both same- and different-view recognition memory for scenes, but performed within the normal range, relative to age-, education- and sex-matched healthy controls on same- and different-view face recognition memory. In contrast, patients with damage to, but also extending beyond the hippocampus into adjacent MTL structures, including perirhinal cortex, were impaired on all conditions. The differing pattern of impairments between the two groups was confirmed by a significant patient group x condition interaction, providing the first direct evidence for dissociable effects of damage to different MTL structures on recognition memory for different stimulus categories. Although the interaction above included the view factor, there was no evidence that this manipulation had a theoretically significant effect on the outcome of the experiment. This contrasts with previous observations of impaired discrimination of different- but not same-view faces and scenes in focal MTL amnesics (Lee, Buckley et al., 2005). Possible reasons for this discrepancy will be discussed below.

The results of Chapter 2 indicated that whereas the hippocampus is crucially involved in processing scenes, non-hippocampal MTL regions, perhaps the perirhinal cortex in particular, are crucially involved in processing configural objects, such as faces. These conclusions were limited, however, for two reasons. First, the patient sample sizes were small. Second, the observed dissociation may have been confounded by differences in lesion size between the two patient groups, and differences in difficulty between the two stimulus categories. That is, it could be argued that small lesions, such as those in HC group, would only affect the most difficult stimulus category (scenes), whereas larger lesions, such as those in the MTL group, would affect both categories. These issues were dealt with in Chapter 3 by testing a larger group of patients with semantic dementia (SD), a neurodegenerative condition which initially affects the anterior temporal lobe, in particular the perirhinal cortex, before spreading into more posterior MTL regions (Davies et al., 2004; Lee, Buckley et al., 2006; Leow et al., 2005; Whitwell et al., 2004). As a group, and in some cases at an individual level, the SD patients were more impaired on the face conditions than the scene conditions. Crucially, this result challenges the idea that the dissociation observed in Chapter 2 was the result of a difficulty effect, by showing that subtotal damage to the MTL can have a disproportionate impact on either stimulus category, depending on which particular structures are involved. Furthermore, these findings add weight to the idea that the perirhinal cortex, in particular, supports recognition memory for faces. Similarly to the results of Chapter 2, the manipulation of view did not appear to have a significant impact on the pattern of results obtained.

A second group of theories have suggested that MTL structures can be dissociated according to their contributions to recollection versus familiarity. Whereas the hippocampus, and perhaps also the parahippocampal cortex, are thought to support recollection, the perirhinal cortex is thought to support familiarity (e.g. Aggleton & Brown, 1999; Eichenbaum et al., 2007). These theories do not generally predict dissociations in the contribution of MTL structures to recognition memory for different stimulus categories; hence, the results of Chapters 2 and 3 might be difficult to accommodate. One possibility, however, is that recognition memory for scenes and faces depends more on recollection and familiarity respectively, which could explain the contrasting effects of different profiles of MTL damage on each stimulus category. This possibility was investigated behaviourally in Chapter 4 using a yes/no test of recognition memory for faces and scenes, which incorporated a

remember/familiar (R/F) decision. The results revealed that correct recognition of previously viewed scenes in both young and older healthy participants was more likely to be accompanied by an R response than was correct recognition of previously viewed faces. There was also a significant interaction between estimated levels of recollection versus familiarity and stimulus category in younger participants, such that levels of recollection, relative to familiarity, were disproportionately high for scenes relative to faces. Together, these results suggest that participants may, indeed, ordinarily rely on recollection to a greater extent for tests of recognition memory for scenes than for faces. Recognition memory for faces, on the other hand, might be adequately supported by familiarity.

Although the results of Chapter 4 established a way that the stimulus-specific effects observed in Chapters 2 and 3 could be accommodated by dual-process models, they did not rule out the possibility that the contribution made by particular MTL structures to recognition memory might depend exclusively on the category of stimulus involved, regardless of the type of processing being performed. In other words, both recollection and familiarity for scenes might depend on the hippocampus and parahippocampal cortex, whereas recollection and familiarity for faces might depend on the perirhinal cortex. The aim of Chapter 5, therefore, was to investigate the evidence in favour of a functional division of labour within the MTL in terms of (i) stimulus type, and (ii) recollection versus familiarity, using functional MRI. Two experiments were carried out using a similar behavioural paradigm to that used in Chapter 4; the first involved a standard scanning sequence and the second involved a specialised, dual-echo sequence to improve coverage of anterior MTL regions. The patterns of activity observed in the hippocampus, parahippocampal and perirhinal cortices could not be distinguished in terms of mnemonic effects, during either study or test. There was little evidence, therefore, in favour of a functional division in the contribution of these structures to recollection versus familiarity. Rather, activity in all three regions during study appeared to predict subsequent levels of familiarity (perhaps also making some contribution to recollection). Conversely, effects of recollection were observed in all three regions at test, although the overall pattern of activity in most cases indicated a trend towards an additional effect of novelty or possibly encoding of correctly rejected items.

Evidence of stimulus-specific mnemonic processing was limited to effects observed in the hippocampus and parahippocampal cortex, activity within which was positively correlated with subsequent memory for scenes, but not faces, during study. These effects were located

outside the region of damage common to the HC patients reported in Chapter 2, and there is little evidence, therefore, that they can explain the scene-specific mnemonic impairments of these patients. Highly consistent main effects of stimulus were observed, however, across the study and test phases of both experiments. These were interpreted as evidence for a role for the hippocampus and parahippocampal cortex in building representations of scenes, and for the perirhinal cortex, and perhaps the amygdala, in building representations of faces. There was considerable overlap between the regions showing a main effect of scenes > faces and the area of damage common to the HC patients from Chapter 2. Similarly, the region of the perirhinal cortex which showed a main effect of faces > scenes partially overlapped with an area damaged in the MTL patients, although the extent of overlap was difficult to establish due to signal drop-out in the functional imaging data. These findings suggest that the stimulus-specific deficits of the patients reported in Chapter 2, and perhaps also those of the SD patients in Chapter 3, may have been caused by an impaired ability to form visual representations, which had a knock-on effect on tests of recognition memory.

In summary, the findings of the present thesis lead to three main conclusions. First, Chapters 2, 3 and 5 provide converging evidence for a dissociation between different MTL structures according to stimulus category, with the hippocampus and parahippocampal cortex playing an essential role in processing scenes, and the perirhinal cortex playing an essential role in processing faces. The nature of this stimulus-specific processing is open to interpretation, however, and therefore the second conclusion is more speculative: although the stimulus-specific effects reported in the thesis were revealed through tests of recognition memory, it was concluded that they arose from the contribution that the MTL makes to a more fundamental process, such as the building of representations, or the ability to differentiate between similar items within a particular class of stimuli. Finally, each of these regions appears to support both recollection and familiarity in a predominantly non-stimulus-specific manner, at least in the case of the visual stimuli used in the present experiments. The fact that recognition memory for faces was intact in the HC patients in Chapter 2, however, reveals that although the hippocampus and parahippocampal cortex may contribute towards recognition memory for faces in the intact brain, as indicated by the findings of Chapter 5, their contributions are perhaps redundant. The same may be true of the contribution made by the perirhinal cortex to recognition memory for scenes.

## Relation of findings to existing theories of MTL function

The first two conclusions outlined above are incompatible with Squire's declarative memory model of the MTL, which proposes that all subregions of the MTL work together in the exclusive support of declarative memory (Squire et al., 2004; Squire & Zola-Morgan, 1991). Although Squire et al. (2004) stated that visual and spatial memory depend more on the perirhinal and parahippocampal cortices respectively, and based on work in rats (Broadbent, Squire, & Clark, 2004), they have suggested that "less hippocampal tissue is needed to support object recognition than is needed to support spatial learning", these authors have consistently rejected several proposals for functional divisions within the MTL and they would likely argue that every MTL structure plays at least a partial role in long-term memory for all stimulus categories. The finding that damage to particular MTL regions can selectively disrupt memory for some stimulus categories but not others presents a major challenge to this view. This model also assumes that the online formation of stimulus representations is performed by neocortical regions outside the MTL, with the MTL itself simply providing a long-term link between them. The findings of the present thesis are consistent with a growing body of evidence which challenges this view and suggests instead that the MTL plays a much broader role in cognition, including the formation of complex representations of visual stimuli.

The idea that the hippocampus and parahippocampal cortex play a vital role in tests of spatial memory whereas the perirhinal cortex plays a vital role in tests involving memory for objects is supported by an extensive body of literature, as discussed in Chapter 1. The majority of the evidence in support of this view, however, has come from studies which have contrasted the effects of damage to these regions on spatial and object memory using highly dissimilar experimental paradigms. Previous tests of spatial memory have generally involved navigation or memory for the location of objects, whereas recognition memory (or equivalently DMS or in some cases DNMS in animals) has been used to probe object memory. This has made it difficult to identify which of the many differences in processing demands between these paradigms explains the differential effects of damage to different MTL structures. The findings of the current thesis therefore make an important step forward by revealing that functional dissociations between MTL structures can be observed within a single mnemonic paradigm, where the only differences in processing demands are driven by the nature of the stimuli involved. Crucially, it appears that these differences cannot be

attributed to a differing dependence of memory for different stimulus categories on recollection versus familiarity.

This raises the question of why different stimulus categories should be processed by different regions of the MTL. As discussed in Chapter 1, perhaps the most compelling reason for a stimulus-specific division of labour within the MTL is the differing sensory inputs received by each region. The perirhinal cortex is located at the apex of the ventral visual stream or "what" pathway (Ungerleider & Mishkin, 1982), and as such receives high-level visual representations of object features from areas TE and TEO (Suzuki & Amaral, 1994). According to the "Perceptual-Mnemonic/Feature-Conjunction" (PMFC) neural network model (Bussey & Saksida, 2002), this enables the perirhinal cortex to support the formation of complex object representations which can be used in the service of both memory and perception. In contrast, the parahippocampal cortex receives most of its input from the dorsal ventral stream or "where" pathway (Ungerleider & Mishkin, 1982), such as the retrosplenial cortex (Vann et al., 2003), enabling it to form spatial representations. The perirhinal and parahippocampal cortices then provide the major inputs to the hippocampus, via the entorhinal cortex. An interesting question for future research is why, given the combination of inputs relating to both objects and spatial information, the hippocampus seems to play a more dominant and essential role in spatial compared with object processing.

The findings of Chapter 4 indicated that recognition memory for scenes may ordinarily rely more on recollection than memory for faces. This suggests that the scene-specific deficits observed in the HC group in Chapter 2 could have arisen due to a selective impairment in recollection, which had a greater impact on scene relative to face recognition memory. The challenge for dual-process accounts, however, would be in explaining *why* recognition memory for faces and scenes should depend more on familiarity and recollection respectively. One potential explanation is that faces are processed more holistically, as a "gestalt" (Schiltz & Rossion, 2006; Tanaka & Farah, 1993; Young et al., 1987), which may increase reliance upon a signal detection-like familiarity process in the perirhinal cortex (Yonelinas et al., 1999 & Soltani, 1999). Memory for complex scenes, on the other hand, may stress memory for associations between the various elements comprising the scene, which may not be adequately supported by familiarity and may therefore require hippocampally-dependent recollection (Yonelinas, 1997, 2002). Strictly speaking, however,

recollection normally refers to associations between a stimulus and the episodic context in which it was studied, and the question then remains as to why scenes engender stronger item-context associations than do faces. Moreover, the types of associative memory that have been shown to require recollection generally involve pairwise recombinations of studied items, such that familiarity for the two elements of each test item, be it target or foil, should be equivalent (e.g. Mayes et al., 2004; Mayes et al., 2007; Yonelinas, 1997; Yonelinas et al., 1999). Since the scene stimuli used in the current experiment were not recombinations of studied elements, it is not immediately obvious why assessing the relative familiarity of target and foil items would not be sufficient to solve the task.

In light of findings of Chapter 5, the above discussion is a somewhat moot point, since activity in the hippocampus, perirhinal cortex and parahippocampal cortex could not be dissociated in terms of their contributions to recollection versus familiarity. In fact, each of these regions appeared to make some contribution to both processes, a finding which clearly conflicts with most dual-process models. It seems unlikely, therefore, that damage to the hippocampus caused a selective impairment of recollection in the HC group reported in Chapter 2. Not only do these findings question the proposal described above, that dual-process models can explain the stimulus specific deficits reported in Chapters 2 and 3, they also raise the possibility that, in some cases, the reverse could be true, i.e. experimental findings taken as support for dual-process models of MTL function could have sometimes been confounded by the kinds of stimuli involved. In the majority of recognition memory paradigms, familiarity is assessed using memory for discrete items such as objects or words. Recollection, on the other hand, is frequently measured by assessing retrieval of contextual details associated with that item, which might include spatial information (e.g, the location of the item on the screen, or retrieval of a scene that was imagined in response to a target item at study). Since the perirhinal cortex appears to play a vital role in processing objects, whereas the parahippocampal cortex and hippocampus play a vital role in processing spatial information, this may explain why the perirhinal cortex has often been associated with familiarity whereas the parahippocampal cortex and hippocampus have been linked with recollection.

Interestingly, the foundations of one dual-process model, the "binding of item and context" or BIC model, which has recently been described in the literature, are rooted in the differing

types of information processed by the perirhinal and parahippocampal cortex (Diana et al., 2007; see also Eichenbaum et al., 2007). According to the model, the perirhinal and parahippocampal cortex process information relating to objects and (spatial and non-spatial) context information respectively, and the hippocampus provides a link between the two (see also Davachi, 2006). This is thought to explain why, in traditional recognition memory tests, the perirhinal cortex is associated with familiarity for objects, whereas the hippocampus, and sometimes the parahippocampal cortex, are associated with recollection of context information. The model makes the additional prediction that in cases where a context is presented at retrieval to cue recollection of an item, that this may be associated with activity in the perirhinal cortex. Hence the model provides a more flexible account of the involvement of different MTL regions in recollection and familiarity than that proposed previously (Aggleton & Brown, 1999). The findings of the present thesis suggest, however, that the BIC model over-complicates matters by relating the roles of each region to the processing of "items" and "contexts". Instead, it seems that spatial processing relies on the hippocampus and parahippocampal cortex, and so retrieval of both spatial items and contexts will presumably depend on these regions. In contrast, memory for an object will depend on the perirhinal cortex, regardless of whether the object represents an item or a context. A suggestion for how this hypothesis could be tested is described below.

An alternative theory which is closely related to dual-process models of MTL function, the domain dichotomy or DD view, predicts that the roles of the hippocampus and perirhinal cortex can also be dissociated in terms of the kinds of associations they can support. Similarly to other dual-process models, this view assumes that, due to the particular processing algorithms which are supported by the hippocampus and perirhinal cortex, these regions support recollection and familiarity respectively. The model makes the additional prediction that whereas the hippocampus is required for the formation of between-domain associations, such as those between a word and a face, the perirhinal cortex is sufficient for the formation of within-domain associations. This is based on the idea that the information relating to items from the same domain is likely to be processed in close proximity within the perirhinal cortex, thus allowing a link to form between the items. The assumptions that this model shares with dual-process models, e.g. that the hippocampus and perirhinal cortex support recollection and familiarity have clearly been challenged by the current thesis, as outlined above. Although the experiments in the thesis have not directly investigated

memory for associations, the idea that the roles of MTL structures are defined by the information available to them is common to both the DD view and the ideas proposed in the current thesis. Furthermore, it could perhaps be argued that representations of scenes require the association of information from different domains, for example the objects contained within the scene and the spatial locations of those objects. The findings of the current thesis do not, therefore, present a direct challenge to this particular aspect of the DD view.

One finding which was contrary to the predictions made at the outset of this thesis was the observation of deficits on both the same- and different-view conditions in the patients reported in Chapters 2 and 3. In fact, with the exception of the deficits shown by the MTL group on the face conditions in Chapter 2, the impairments shown by each patient group relative to healthy controls were larger on the same- than the different-view conditions. These findings conflict with cognitive map theory (O'Keefe & Nadel, 1978), in which the hippocampus is thought to be involved in allocentric but not egocentric spatial processing, and also with previous observations both from scene recognition memory and non-mnemonic oddity tasks involving faces and scenes. For example, Lee et al. (2005) tested the same patient groups as those reported in Chapter 2 on a non-mnemonic oddity task which required participants to select the odd faces or scenes from a series of four-item arrays. Consistent with the findings of the present thesis, the HC group were impaired on the scene conditions, whereas the MTL group were impaired on both the face and scene conditions. Unlike the findings of the present thesis, however, these impairments were restricted to different-view conditions, in which three different views of a particular item were shown alongside a single view of a different item. Similarly, impaired recognition memory for shifted-, but not same-view scenes has been documented in a patient with bilateral hippocampal damage (King et al., 2002).

As discussed in Chapters 2 and 3, there are several differences in the experimental designs of the tasks used by Lee et al. and King et al. compared with that used in the present thesis which may explain these discrepant findings. First, unlike the experiments reported in the present thesis, the design used by Lee at al. was such that the face task could be solved based simply on the outline of each item (since the target face was always facing in a different direction to the three images of the second face). Second, the scenes used in both Lee et al. and King et al. were of virtual-reality rather than real-world environments. This may have significantly affected the way that they were processed and the availability of cues which

could be used to solve the tasks. Finally, King et al. found that, when the list lengths were increased to greater than 10 items, impairments were found on the same-view conditions. This is indicative of a load- and/or delay-dependent effect. Notably in the paradigm used in the present thesis, the different-view retrieval block always appeared before the same-view retrieval block, which will have increased these effects in the same-view conditions. Further investigation, using small list lengths or perceptual tasks, is therefore required to examine whether view truly is a crucial factor in the involvement of MTL structures in visual memory and perception.

## Future directions

One issue that remains unresolved by the present thesis is the question of which MTL regions play an essential role in recollection and familiarity of faces and scenes. The findings of Chapter 5 did not reveal any evidence in favour of dual-process models of MTL function, since the subregions of the MTL appeared to make equivalent contributions to recollection and familiarity. As discussed in the chapter, however, some of the patterns of activity revealed in the study were difficult to confidently attribute to recollection or familiarity. Some recent studies in the literature have taken advantage of the mathematical characteristics of recollection and familiarity proposed by the dual-process signal detection model of recognition memory (Yonelinas, 1994, 2002) to constrain the identification of neural correlates of these two processes (Daselaar et al., 2006; Montaldi et al., 2006; Ranganath et al., 2004; Yonelinas et al., 2005). According to the model, whereas recollection of each detail associated with an event is characterised as an all-or-none process, item familiarity is modelled as a continuous function which can be described by signal detection theory. Regions which signal familiarity are therefore identified by looking for patterns of activity which correlate with increasing (or decreasing) confidence that an item has been seen before. Regions which support recollection, in contrast, are identified by categorical effects, such as source correct versus source incorrect. The contribution of MTL regions to recollection and familiarity for scenes versus faces could therefore be investigated further using this methodology. This may reveal differences in the contribution of MTL structures to recollection versus familiarity, regardless of stimulus category, which would be in keeping with dual-process models of MTL function. Alternatively, this technique could provide compelling support for the conclusions made in Chapter 5 of the current thesis, i.e. that MTL regions make equivalent contributions to both processes.

Although further neuroimaging studies such as those suggested above could help to clarify the nature of the processing occurring in each MTL region during recognition memory, they would not be able to establish the necessity of each region to successful performance. The necessary contribution of a particular brain region or process can only be established through lesion studies. One limitation of the neuropsychological experiments reported in the present thesis, however, is that they did not measure levels of recollection or familiarity in the participants. Therefore, further studies involving either direct or indirect measures of recollection and familiarity in patients with circumscribed lesions will be needed to establish the regions which are essential to recollection and familiarity for faces and scenes. As discussed in Chapter 1, researchers have often had difficulty in training hippocampal amnesics to understand the remember/know procedure (Baddeley et al., 2001; Barbeau et al., 2005; Bastin et al., 2004) and so the ROC method may provide a more useful way to measure recollection and familiarity in these patients. Since both recollection and familiarity depend on accurate representations, however, the findings of the present thesis lead to the prediction that patients with damage to the hippocampus will show impaired recollection and familiarity for scenes, a pattern which has recently been reported in some amnesic individuals (Bird et al., 2007; Cipolotti et al., 2006). In contrast, patients with disproportionate damage to the perirhinal cortex, such as the high performing SD patients from Chapter 3, may show impaired recollection and familiarity for faces but not scenes.

As discussed in the previous section, some of the evidence which has previously been used as support for dual-process models may have confounded different mnemonic processes (i.e. recollection and familiarity) with different categories of stimuli. This possibility could be tested using experiments which contain conditions in which the "item" to be recognised is spatial in nature, and the "context" to be recollected is a discrete object. For example, in one condition, participants could be scanned using fMRI whilst they study a series of spatial scenes superimposed on one of four possible objects, (which could be made larger than the scenes to ensure they are visible in the background). In another condition, objects could be superimposed onto one of four background scenes. There could then follow a recognition memory test outside the scanner, and for each central item that is correctly recognised, the participant could be asked to decide which of the four background items it had been paired with. If activity in the perirhinal cortex during study was associated with subsequent recollection of the background objects, whereas activity in the parahippocampal cortex and/or

hippocampus was associated with subsequent memory for the background scenes, this would provide strong support for the view that it is the nature of the stimuli rather than the type of process being performed that affects the dependence of recognition memory on particular MTL structures.

The findings of Chapter 5 indicate that, in addition to creating stimulus-specific representations, each MTL region may support recollection and familiarity in a stimulus-independent manner. Presumably, a particular region can only make a useful contribution to mnemonic processing of a stimulus which it does not represent itself, via some form of communication with regions which do represent it. For example, the ability of the perirhinal to contribute towards memory for scenes will presumably depend on communication with the hippocampus and/or the parahippocampal cortex. Our understanding of the nature of this process could be greatly improved through (i) investigation of the temporal dynamics of MTL activity during tests of recognition memory for faces and scenes, and, (ii) estimation of the effective connectivity within the MTL during successful retrieval.

The first investigation would require the use of a technique which retains the spatial resolution of fMRI together with improved temporal resolution. Although magnetoencephalography (MEG) provides good temporal and spatial resolution, source localisation for deep brain structures can be difficult, and therefore differentiation between the hippocampus, perirhinal and parahippocampal cortices might not be possible. An alternative would be to use intracranial electroencephalography (iEEG) in patients with epilepsy in whom depth electrodes have been inserted into the MTL. This technique provides a very high level of temporal resolution and precise localisation, although the readings are obviously limited to the locations of the recording sites of the electrodes. The technique could be used to investigate the spatiotemporal time-course of mnemonic processes, potentially revealing the kinds of information that is processed by each region and the timecourse of information flow through the MTL. The findings of the present thesis might lead to the prediction that immediately following stimulus onset, activity will be greatest in the perirhinal cortex on face trials, and in the parahippocampal cortex and hippocampus during scene trials. These regions may then communicate with adjacent MTL regions, revealing activity throughout the MTL later on in the trial that is associated with recognition accuracy.

The effective connectivity within the MTL in relation to performance and experimental manipulations such as changes in stimulus category could be investigated through use of dynamic causal modelling (DCM) in the analysis of fMRI data, a technique recently developed by Friston Harrison, & Penny (2003). Based on the hypothesis that the involvement of the hippocampus and parahippocampal cortex in recognition memory for faces relies on representations formed in the perirhinal cortex, one would predict that the effective connectivity between these regions will increase on successful relative to unsuccessful trials. Similarly, increased connectivity between the hippocampus and/or parahippocampal cortex and the perirhinal cortex would be predicted during successful relative to unsuccessful scene recognition memory. Such analyses might reveal differences in the direction of the causal relationships between these structures depending on the category of stimulus involved. For instance, successful face recognition memory might be associated with an increasing influence of the perirhinal cortex on the hippocampus and parahippocampal cortex, whereas for scenes, this causal relationship might be reversed. The technique would also help to establish whether particular regions have a direct influence on other regions, or whether their influence is predominantly mediated by a second region. For example, the perirhinal cortex may directly influence the parahippocampal cortex during successful face recognition memory, or its influence may be mediated by the hippocampus. Such investigations would significantly improve our understanding of the precise contribution of each region to performance.

Another limitation of the experiments reported in the present thesis is that they only examined memory for faces and scenes and it is therefore difficult to know to what extent the findings would apply to other categories of stimuli. One particularly interesting question is whether the use of objects instead of faces would have led to equivalent findings. Although faces can be viewed as an example of highly configural objects, it has been suggested that they are processed in a unique way by a specialised network of brain regions, including the occipital face area, superior temporal sulcus, fusiform face area and, notably, the amygdala. As discussed earlier, the amygdala's involvement in face processing is thought to be related to emotional valence. It seems likely, therefore, that neutral objects would not be preferentially processed by the amygdala but rather, may depend more on the perirhinal cortex. This is supported by observations from an fMRI imaging study which compared MTL activity during face and novel object conditions of a perceptual oddity task (Barense,

2006). Whereas activity in the amygdala was greater during face- relative to object-oddity judgement, activity in the perirhinal cortex was greater during object- relative to face-oddity judgement. Repeating the patient experiments and imaging experiments reported in the current thesis, but replacing the face conditions with object conditions, would allow this prediction to be tested directly. Taking this idea further, it would also be interesting to repeat the experiments reported in the present thesis using stimuli from a non-visual modality to investigate how the MTL contributes to recognition memory beyond the visual domain.

Although no effects of laterality were observed in the imaging experiments reported in Chapter 5, the findings of Chapter 3 indicated that recognition memory for both faces and scenes depends on the integrity of the right but perhaps not the left temporal lobe, since performance on both stimulus categories was correlated with the extent of damage to the former but not the latter hemisphere. Together, these results suggest that, although both hemispheres may ordinarily be recruited during performance of these tasks, only the right hemisphere plays an essential role. This possibility could be investigated further in patients with static unilateral lesions to the MTL. It would be important in such studies to perform fMRI analyses during performance of the tasks, to ensure that the contralesional hemisphere was still functioning normally (Sorger et al., 2007). The potential effects of hemispheric re-organisation would also need to be considered.

Finally, it may be worth investigating whether the tasks used in the present thesis could be developed for use in the clinical diagnosis of dementias affecting MTL regions such as SD and Alzheimer's disease (AD). The findings of Chapter 3 revealed that impaired recognition memory for faces seems to be a particularly sensitive marker of the type of cognitive decline observed in SD, which is known to affect anterior temporal regions in its early stages. Imaging studies in AD have revealed a different pattern of pathology in early stages of the disease, however, with more symmetrical involvement of the MTL, in particular the hippocampus and entorhinal cortex (Braak & Braak, 1991; Chan et al., 2001,; Fox et al., 1996; Galton, Patterson et al., 2001; Juottonen et al., 1998; Killiany et al., 1993; Whitwell et al., 2007). Given the pattern of performance in the HC group in Chapter 2, AD might therefore be more likely to affect recognition memory for scenes during its initial stages.
Prior to the development of full-blown AD, patients will normally experience a period of gradual cognitive decline, which has a notable effect on memory in particular (Hodges,

2006). Since such impairments are often observed before patients reach the full criteria for a diagnosis of AD, the term mild cognitive impairment (MCI) was coined, in an attempt to capture this pro-dromal stage. As discussed by Hodges (2006), in practice, it can be difficult to distinguish patients who will go on to develop AD from those who will not. A sensitive behavioural test which can distinguish patients with MCI who will go on to develop AD from those who will not could help ensure that treatments developed to combat AD can be directed to the appropriate patients at a much earlier stage of the disease.

# Conclusion

In conclusion, the present thesis provides clear, converging evidence for specialisation in the MTL according to stimulus type. Although the stimulus-specific processing that is supported by different MTL regions may not be mnemonic in nature, disruption to these processes can have a stimulus-specific effect on mnemonic functions, as evidenced by findings from patients with incomplete damage to the MTL. These findings have major implications for current models of long-term memory, several of which have neglected the importance of this factor. Further investigations may confirm that stimulus-specific processing represents the dominant organisational principle within the MTL, and could perhaps underlie many of the effects which have previously been taken as support for some dual-process models of MTL function. It seems likely, however, that it will only be possible to fully characterise the role of the MTL in cognition by considering both the effects of stimulus category, and the capacity of particular MTL subregions to support distinct types of mnemonic (and possibly perceptual) processes.

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