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# Medial Temporal Lobe contributions to Visuospatial Memory and Cognition

Chris Bird

Thesis submitted to University College London for
the Degree of Doctor of Philosophy in Neuroscience

I, Chris Bird, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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# 2 Abstract

The contributions of human medial temporal lobe (MTL) structures to perceiving and remembering visuospatial features of the environment were investigated from the perspective of human cognitive neuropsychology. The experimental chapters focussed on three main issues: the contribution of the right-sided MTL to spatial awareness; the roles of the right MTL and hippocampus in spatial and non-spatial scene perception and memory; and the role of the hippocampus in anterograde memory for different types of memoranda.

Visual neglect (a failure of spatial awareness), was investigated after lesions of the right medial occipitotemporal lobe. Lesion analyses and diffusion tensor imaging demonstrated that the lesions associated with neglect interrupted a white matter pathway connecting the parahippocampal gyrus with the parietal lobe. The interaction of these areas may be critical to subserve normal spatial awareness.

Perception and short-term retention of spatial and non-spatial aspects of visual scenes were investigated using a new task – the 4 Mountains Test. Right MTL damage impaired both spatial perception and memory. Hippocampal damage impaired spatial memory but had little impact on scene perception. Damage to these areas did not affect non-spatial perception or memory, suggesting a role for the hippocampus in the short-term retention of allocentric spatial information. A rather similar pattern of performance was documented in patients with possible Alzheimer's disease.

The role of the hippocampus in anterograde memory was investigated in two patients using recognition tests for words, scenes and faces. Receiver operating characteristics analyses were used to assess the contribution of recollection and familiarity to performance. Hippocampal damage impacted upon scene and word recognition but not face recognition. In terms of scene recognition, the hippocampus may be critical to make recognition judgements based on both recollection and highly confident feelings of familiarity.

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# 1 Chapter 1: General Introduction

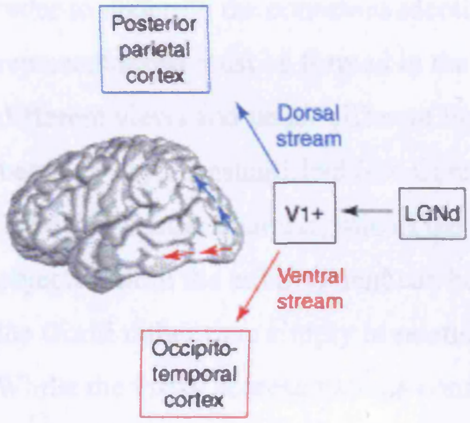
The ability to move through and interact with our environment is a prerequisite of independent living. To do this it is necessary to perceive the locations and orientations of objects around us, relative to ourselves (i.e. forming "egocentric" representations). To revisit these locations or recall what happened when we were there, allocentric representations of our environments are required (representing locations relative to the environment). The understanding of these processes and the elucidation of the neural systems that underpin them is a flourishing branch of cognitive neuroscience. Whilst researchers are beginning to reach consensus on some key points, many theoretical issues are unresolved, and remain controversial. The aim of this thesis is to address some of these latter issues from the perspective of human cognitive neuropsychology.

The experimental chapters in this thesis (Chapters 2-7) report discrete, but related investigations. As such, they all have Introductions and Discussions relating directly to the experimental data contained therein. The aim of this General Introduction is to put into context the experimental investigations that form the bulk of this thesis. First, the organisation of the cortical visual system is discussed, with particular reference to Milner and Goodale's (1995) influential characterisation of the two visual processing streams. Following this I shall review the neuroanatomy of the medial temporal lobes, since the majority of this thesis focuses on the roles of these areas (and in particular the hippocampus) in perceptual and mnemonic processing. I shall then briefly and selectively review the current state of our knowledge regarding the roles of the right hemisphere in general, and the medial temporal lobes in particular, in visuospatial cognition and memory. In the last section I discuss the strengths and weaknesses of the neuropsychological methodology. This section includes a summary of a series of investigations I carried out into the psychometric properties of some commonly used cognitive tests.

## 1.1 Cortical visual processing

It is well established that primates have two distinct cortical visual processing streams (Mishkin, Ungerleider, & Macko, 1983; Milner & Goodale, 1995). These visual streams have been well mapped in non-human primates by anatomists using retrograde tracers to ascertain where the axons of cells in a particular area terminate – or “project to”. Both streams originate in the primary visual cortex in the calcarine sulcus of the occipital lobe. From here, one flows dorsally (including the visual area V5 or MT) to the posterior parietal lobe, including the intraparietal sulcus. The other flows ventrally (including the visual area V4) to the temporal lobe where the progressively “higher-order” visual areas TEO and TE have been characterized in non-human primates. Figure 1-1 shows these streams in the human brain.

**Figure 1-1: Dorsal and ventral visual processing streams**



**Legend:** Diagram showing the two cortical visual streams in the human brain. Figure taken from Goodale & Westwood (2004)

Data from a variety of sources suggests the information carried in these two streams is qualitatively different. Thus, single-cell recording in non-human primates has identified neurons in the dorsal stream that appear to encode where objects are with reference to the body and the directions in which they are moving. Responses of neurons in this pathway are often modulated by motor responses or intentions such as arm reaches or saccades. By contrast, neurons in the ventral visual stream have been identified that respond preferentially to particular classes of visual stimuli such as hands or faces but not necessarily to where they are in the visual field. It has been further shown that these neurons maintain their selectivity irrespective of the viewpoint of the stimulus. Functional brain imaging studies have revealed similar properties of the two visual streams in humans. For example, James et al., (2003) demonstrated viewer-independent visual representations in a visual area of the ventral stream but only viewer-dependent representations in visual areas in the dorsal stream.

In the light of observations such as these, Milner and Goodale proposed that the dorsal stream mediates the visuomotor control of behaviour, whilst the ventral stream mediates conscious visual perception.

Central to Milner and Goodale's model of visual processing is the proposal that the two visual streams are specialized according to what the information they carry is to be used for. Thus, in order to control visuomotor behaviour, the dorsal stream encodes the current positions of objects in order for an animal to be able to grasp or fixate them. These representations must be constantly updated as the animal moves through the environment and often appear to be unavailable to consciousness. By contrast, in order to underpin the conscious identification of visual stimuli, object-centred representations must be formed in the ventral stream (to allow recognition from different views and under different lighting) and the relative spatial relationships between objects established (see Carey, Dijkerman, Murphy, Goodale, & Milner, 2006). The latter characteristic of the ventral stream means that the locations of objects within the environment can be recalled according to where they are situated in the world rather than simply in relation to the observer, i.e. in *allocentric* coordinates. Whilst the visual representations constructed in the ventral visual stream are probably required for numerous cognitive processes (naming, planning, decision making, etc.), I will focus on one process that they are essential for, that of forming stable, long-term memories. The characteristics of both visual streams are summarised in Table 1-1.

**Table 1-1: Summary of Milner & Goodale's dual process theory of vision**

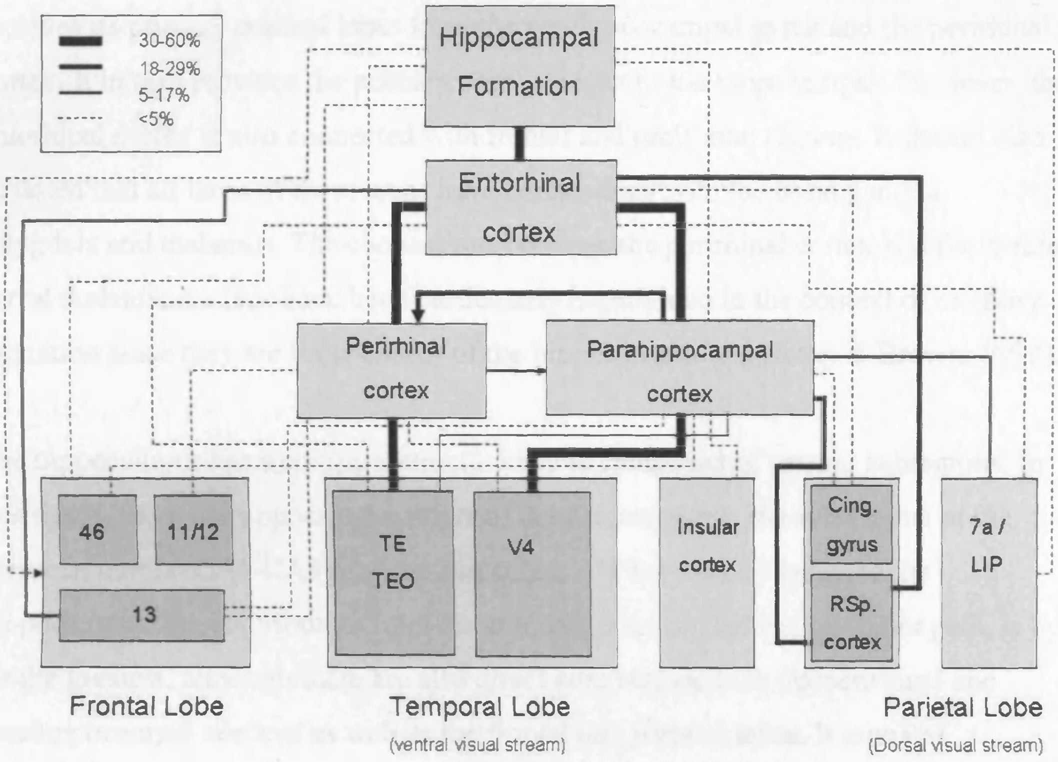
| | **Ventral stream** | **Dorsal Stream** |
|---|---|---|
| **Coding** | Viewer independent | Viewer dependent |
| **Robustness of representation** | Persistent | Transient |
| **Co-ordinate system** | Allocentric | Egocentric |
| **Purpose** | Conscious visuospatial perception | Visuomotor control of goal-directed behaviour |
| **Output** | Includes long-term memory systems | Motor effector systems |

The boundaries between brain areas that might be conceptualised as "perceptual" and "mnemonic" respectively, are somewhat blurred. Thus, perceptual priming – the phenomenon whereby behaviour elicited by a (visual) stimulus can be modulated by prior exposure to that stimulus may be completely underpinned by unimodal sensory areas (Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995). In addition, areas that receive polymodal sensory information and have been thought of as primarily mnemonic, may nevertheless underpin some aspects of perception (Murray & Bussey, 1999; Buckley & Gaffan, 2006; Lee et al., 2005b). In order to understand the functional roles of the different anatomical regions comprising the medial temporal lobe, it is useful to consider where these areas receive most of their inputs from and to which areas they project. This is covered in the next section.

## 1.2 Neuroanatomy of the Medial Temporal Lobe

The cortical and subcortical connectivity of the parahippocampal gyrus, perirhinal cortex, entorhinal cortex and the hippocampus have been investigated in rats and non-human primates (see Burwell & Witter, 2002). These studies have shown considerable correspondence between the connectivity of these structures across species. Thus, whilst the connections are not well characterised in the human brain, the general pattern of connectivity is likely to be similar. In some cases, this has been ascertained using diffusion tensor imaging (DTI) tractography techniques (e.g. Rushworth, Behrens, & Johansen-Berg, 2005). I will therefore review the findings based on studies of non-human primates. The cortical connections of the main structures of the medial temporal lobe are shown schematically in Figure 1-2.

**Figure 1-2: Cortical connections of MTL structures**



**Legend:** Diagram showing the major cortical inputs to the monkey hippocampal formation, entorhinal, perirhinal and parahippocampal cortices. The connections between the superior temporal gyrus and dorsal and ventral parts of the superior temporal sulcus are not shown here. Different line widths represent the percentage of cortical inputs to these areas. Three areas of the frontal lobes are distinguished; area 46 is in the dorsolateral frontal lobe, areas 11/12 and 13 are in the lateral and medial orbitofrontal cortex. In the temporal lobe, TE, TEO and V4 are higher cortical visual areas in the ventral visual processing stream. Area 7a/LIP is in the lateral parietal lobe and may correspond to the angular gyrus in humans (Rushworth et al., 2005). Adapted from Suzuki and Amaral, (1994) and also Burwell & Witter, (2002) and Rockland & Van Hosen, (1999). Abbreviations: Cing. = cingulate, RSp = retrosplenial, LIP = lateral intraparietal area.

The parahippocampal gyrus and the perirhinal cortex can both be conceptualised as lying at the end of the ventral visual stream as they both have strong reciprocal connections with higher cortical visual areas in the temporal lobe. However, both structures also receive additional inputs from polymodal association areas (such as regions of the frontal lobes) and have strong connections with the entorhinal cortex (and each other). The parahippocampal gyrus also has reciprocal connections with the cingulate gyrus and retrosplenial cortex as well as the posterior parietal cortex which lies in the dorsal visual stream. These areas have been particularly implicated in spatial processing (Burgess, 2002). The perirhinal cortex receives a higher proportion of its input from higher-order visual areas than the parahippocampal gyrus (well over one half) and has fewer connections with the parietal lobe. The entorhinal cortex receives its primary cortical input from the parahippocampal gyrus and the perirhinal cortex. It in turn provides the primary cortical input to the hippocampus. However, the entorhinal cortex is also connected with frontal and prefrontal regions. It should also be noted that all three of these areas have connections with the basal ganglia, amygdala and thalamus. The connections between the perirhinal cortex and the medial dorsal thalamic nucleus have been particularly highlighted in the context of memory formation since they are independent of the hippocampus (Aggleton & Brown, 1999).

The hippocampus has a complex structure and is composed of several subregions. In this thesis, the term hippocampus refers to the dentate gyrus, the subregions of the cornu ammonis (CA1-CA4) and the subiculum. Of the cortical inputs to the hippocampus, the contribution from the entorhinal cortex, via the perforant path, is by far the greatest, although there are also direct connections with the perirhinal and parahippocampal cortices as well as the frontal and parietal lobes. It terms of subcortical connections, the major efferent pathway from the hippocampus is the fornix, a large white matter fibre bundle that connects the hippocampus with the septal nuclei, the mammillary bodies and the anterior thalamic nucleus. Thus, the hippocampus receives converging inputs of highly processed polymodal sensory information and has extensive cortical and subcortical connections. This is consistent with its proposed role in underpinning the formation of contextually rich episodic memories (e.g. Baddeley, Conway, & Aggleton, 2002).

## 1.3 Literature Review

It is now well established that the right hemisphere has a specialized role in spatial thought (De Renzi, 1982). Historically, the bulk of the evidence that supports this position comes from the study of patients with disorders of spatial cognition. Probably the first such case was reported by Hughlings Jackson in 1876. In this classic study, Jackson describes a 59 year old woman who “did not know objects, persons or places”. Her first clinical sign was noted when she was walking to a local park. She was unable to find the park, and had to ask directions “although the park gates were just in front of her" and "when she wished to return she was utterly unable to find her way". Her deficit appeared to be primarily a disturbance of visuospatial perception rather than of memory and led Jackson astutely to describe "imperception" as "a deficit as special as aphasia". Post mortem analysis of the patient's brain revealed "a large gliomatus tumor in hinder part of the right temporo-sphenoidal lobe".

Jackson's case highlighted several of the deficits that can follow unilateral right sided brain damage, including visuospatial disorientation (or at least, hemispatial neglect), agnosia for objects, faces and landmarks, and topographical disorientation. One of the first major studies to highlight the link between visuospatial disorientation and right hemisphere lesions was carried out by Brain (1941), some 70 years after Jackson's case report. Brain described two groups of neurological cases. The first group had problems with localizing objects on the contralesional side of space. Only two of the three patients had right sided lesions, suggesting to Brain that "the central process through which objects are localized visually is organized in each hemisphere independently". The second group of three patients all had large right lesions in the parieto-occipital lobe resulting in a left hemianopia as well as "inattention to or neglect of the left half of external space" (p257). All three patients had difficulty in finding their ways about familiar and non-familiar environments.

Brain ascribed a key role for the right hemisphere in spatial awareness since all three patients with "agnosia for the left half of space" (now termed "visual neglect") had large right-sided lesions. In particular, he proposed that a lesion of the right parietal lobe was responsible. Subsequent group studies have confirmed that neglect is far more common after right-sided brain injury than left (see De Renzi, 1982). Nevertheless, the neuroanatomy of visual neglect is a hotly debated topic. Earlier studies emphasized a critical role of the posterior parietal lobe (Bisiach, Luzzatti, & Perani, 1979; Vallar & Perani, 1986). Whilst lesions to this area remain those most commonly associated with neglect, many other areas have also been implicated. These include the inferior frontal lobes, superior temporal gyrus, and subcortical structures such as the thalamus and putamen, in most cases on the right (Husain & Kennard, 1996; Karnath, Fruhmann, Kuker, & Rorden, 2004; Vallar & Perani, 1986; Watson, Valenstein, & Heilman, 1981).

Identification of the brain lesions critical for causing neglect offers important insight into the neural underpinnings of spatial awareness. However, the fact that so many candidate areas for the lesion site "critical" to cause neglect have been identified, suggests that spatial awareness arises from interactions between more than one anatomically distinct area. One of the first studies to explicitly test this hypothesis was carried out in non-human primates (Gaffan & Hornak, 1997b). The authors demonstrated that disconnection of one hemisphere from its visual inputs results in neglect-like behaviour. Recently, some studies in humans have argued that neglect may arise due to disconnections of anatomically separate areas (e.g. Doricchi & Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005; Park et al., 2006). It is therefore clearly desirable that a complete investigation of the anatomy of neglect in patients should attempt to include an analysis of which cortical or subcortical connections may be interrupted by common regions of brain damage between patients.

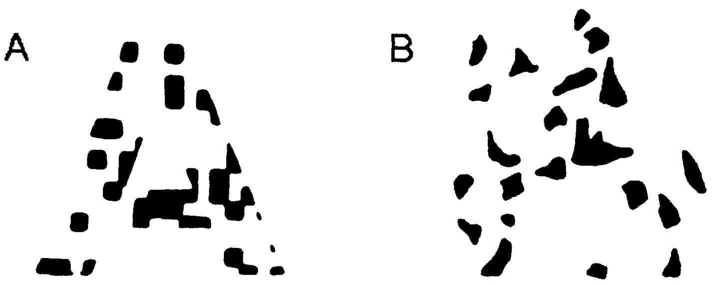
It has been proposed that visual neglect is likely to arise through disruption of information in the ventral visual stream, despite its frequent association with posterior parietal damage (Milner & Goodale, 1995). Compelling evidence for this is the fact that neglect can operate in object-centred coordinates (Behrmann & Tipper, 1999; Driver & Halligan, 1991). Thus, some authors have proposed that there exists a representational area in the inferior parietal lobule of the human brain, which integrates at a high level, information derived from both visual streams (Milner, Dijkerman, & Carey, 1999; Turnbull, Carey, & McCarthy, 1997). This area may be able to put together and manipulate information about perceptually segregated elements of a visual display in order to construct abstract spatial representations (Milner et al., 1999).

Chapter 2 of this thesis reports an investigation of visual neglect in a group of patients with lesions to the medial occipitotemporal lobe, following infarction in the territory of the posterior cerebral artery (PCA). Damage to these regions is not widely recognized to result in neglect (but see Mort et al., 2003). The results presented in Chapter 2 suggest that disruption of a white matter tract that carries projections between the parahippocampal gyrus and the posterior parietal lobe may be sufficient to cause visual neglect. To relate this to Milner et al.'s (1999) proposal, disruption of this tract would substantially disconnect the inferior parietal lobe with highly processed visual information from the ventral stream.

Whilst the neglect syndrome demonstrated a primary role for the right hemisphere in spatial awareness, neuropsychological research has also highlighted its pre-eminence in two other areas of visual and spatial cognition: perception and memory. I shall first consider visual and spatial perception.

Although full-blown agnosias are rarely reported in the context of unilateral brain lesions, group studies have identified a greater role for the right hemisphere in visual perception. Warrington & James (1967) demonstrated that right hemisphere lesions were associated with poorer performance on a range of tasks involving the identification of visually degraded stimuli (Figure 1-3). Such stimuli included fragmented pictures of objects and letters, silhouettes of objects rotated around a major axis and photographs of objects taken from unusual views (see Warrington, 1985). Within the patient groups, those with right-sided parietal lobe damage were most consistently impaired, both in comparison to patients with left-sided parietal lobe damage and with right-sided non-parietal lobe damage.

**Figure 1-3: Examples of visually degraded stimuli**



**Legend**: A: Fragmented Letter stimuli used by Warrington & James (1967) and B: stimuli from the Street Test used by De Renzi & Spinnler (1966) and Orgass et al., (1971) to reveal perceptual deficits in patients with posterior right hemisphere lesions.

Similar results were obtained by De Renzi & Spinnler (1966), Orgass and colleagues (1971), and Riddoch & Humphreys (1993). Orgass et al., (1971) administered three perceptual tasks to a series of patients with posterior hemisphere lesions. On two of the tests (Form Perception and the Street Test, see Figure 1-3) there was a significant interaction between damaged hemisphere and visual field deficit; patients with right hemisphere damage and a visual field deficit were significantly poorer. Since the presence of a visual field deficit was not related to poor performance per se, this result implies that the lesion responsible for poor performance on these tests corresponds closely to the visual pathways of the right hemisphere.

These group studies of perception suggested that visual processing areas in the left hemisphere are sufficient to perceive objects when seen from prototypical viewpoints. However, the right hemisphere may either store representations of non-prototypical viewpoints of objects, or underpin processes whereby objects are mentally rotated to a familiar viewpoint in order to allow recognition. It may also be that the right hemisphere is able to integrate fragmented stimuli into a coherent percept. This would be consistent with the greater role of the right hemisphere in global versus local processing (Robertson, Lamb, & Knight, 1988). A similar proposal to this was made by Turnbull et al., (1997) who suggested that the posterior parietal lobe was necessary to perform these transformations, thus accounting for Warrington's finding that perceptual deficits were associated with right parietal lobe damage. However, it remains an open question whether damage to the right ventral visual stream is sufficient to cause deficits in object processing of degraded visual stimuli. Preliminary data addressing this issue is presented in Chapter 2 of this thesis. The results suggest that such deficits can be observed following damage to ventral occipitotemporal areas.

Whilst severe visual perceptual impairments do not generally follow unilateral right hemisphere damage, perceptual deficits for particular classes of visual stimuli have been documented. Both prosopagnosia and landmark agnosia (or topographagnosia) have been documented following right sided medial occipital and temporal lobe damage, following PCA stroke (Landis, Cummings, Benson, & Palmer, 1986; Mendez & Cherrier, 2003; Takahashi & Kawamura, 2002; Habib & Sirigu, 1987). With respect to the discrimination of large-scale environments, determination of the specific spatial relationships between objects and landmarks is necessary. It may be that this level of spatial analysis is dependent upon the right hemisphere. With regards to the specific areas underpinning place perception, neuroimaging studies have suggested that the parahippocampal gyrus and the lingual gyrus are critical (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998b; Epstein, Graham, & Downing, 2003). Neuropsychological data support this position, with reports of landmark agnosia often implicating these areas (Takahashi & Kawamura, 2002; Habib & Sirigu, 1987). However, it is not always clear whether the patients in these studies have a problem at the level of perception or of memory (or representation) of topographical information. This issue is addressed in Chapter 3 of this thesis. A novel task – the 4 Mountains Test - is used that tests perception of visual (non-spatial) and spatial aspects of scene processing. Participants are tested using concurrent match-to-sample (perceptual) and delayed match-to-sample (memory) procedures. A patient with extensive right-sided medial occipitotemporal damage, including the parahippocampal and lingual gyri was shown to be profoundly impaired at perceiving the spatial but not the non-spatial aspects of scenes.

The remaining experimental chapters of my thesis (Chapters 3-7) address the roles of the medial temporal lobes and particularly the hippocampus in perception and memory. I will discuss the role of these areas in long-term memory below. There is a large body of experimental evidence suggesting that the hippocampus plays a major role in representing spatial information, particularly allocentric spatial information (Burgess, Maguire, & O'Keefe, 2002; O'Keefe & Nadel, 1978; Burgess et al., 2002). Thus, "place cells", identified in the rat hippocampus appear to code where the rat is situated in relation to its environment. Similar cells have also been identified in monkeys and humans (Ono, Tamura, & Nakamura, 1991; Ekstrom et al., 2003). Neuroimaging studies have also identified a primary role for the hippocampus when wayfinding in large-scale environments (Maguire et al., 1998; Hartley, Maguire, Spiers, & Burgess, 2003). Furthermore, a patient with selective bilateral hippocampal damage was shown to be disproportionately impaired when trying to recall the locations of objects from a shifted viewpoint (requiring an allocentric representation of where the objects were in the environment: King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004). If the hippocampus is critical for representing spatial information concerning the locations of objects in allocentric coordinates, then impairments in tasks that tap this ability should be observed, even when the information needs only to be retained for very short periods. In fact, recent neuropsychological evidence suggests that the hippocampus may be necessary even for the perception of such information (Lee et al., 2005b; Lee et al., 2005a). To investigate this, four patients with hippocampal damage were administered the 4 Mountains Test (Chapter 3). The results are consistent with the view that the hippocampus is necessary to represent and/or retain spatial information over very short delays. However, its role in the perception of spatial relationships was equivocal. Interestingly none of the hippocampal patients were impaired in their ability to remember the non-spatial visual attributes of the scenes, which argues against a broader role for the hippocampus as being necessary to represent configural information, at least over short intervals (Eichenbaum & Cohen, 2001; Wallenstein, Eichenbaum, & Hasselmo, 1998).

The data presented in Chapter 3 demonstrated that the 4 Mountains Test is very sensitive to hippocampal damage. The purpose of the investigation reported in Chapter 4 was to ascertain whether patients likely to develop Alzheimer's disease would perform similarly to the patients with hippocampal damage. Alzheimer's disease is progressive in nature and is characterised by deterioration in multiple modules of cognition. However, the very early stages are characterised by relatively selective memory deficits and neuropathology in the medial temporal lobes, particularly the entorhinal cortex and the hippocampus. The preliminary data presented in this chapter suggests that the 4 Mountains Test may prove to be sensitive to early cognitive changes associated with Alzheimer's disease, although important limitations were also noted.

Structures within the medial temporal lobe, particularly the hippocampus, are well known to play a crucial role in the formation of new memories (Spiers, Maguire, & Burgess, 2001c; Squire, Stark, & Clark, 2004). As can be seen from Figure 1-2, the hippocampus and the entorhinal cortex are particularly well placed to receive the highly processed polymodal sensory information that would necessarily have to be bound together to form context-rich episodic memories. The cellular structure of different regions of the hippocampus may be specialised to carry out this binding process. For example, the long-range recurrent connections between pyramidal cells in area CA3 of the hippocampus have long been interpreted as enabling this region to work as an auto-associative neural network, by which episodic memories with a "snapshot" quality can be formed and later retrieved by means of pattern completion (see e.g. Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Rolls, 1996).

Neuropsychological studies have demonstrated the importance of the medial temporal lobes in memory, with bilateral damage resulting in devastating memory impairment (Scoville & Milner, 1957). Bilateral hippocampal damage alone is sufficient to cause profound anterograde amnesia (e.g. Rempel-Clower, Zola, Squire, & Amaral, 1996; Squire, 1982).

Since the structures in the medial temporal lobe receive much of their cortical inputs from the ipsilateral ventral visual stream, it is unsurprising that the laterality effects that are found in the domain of perception are also found in memory. Thus, important studies by Brenda Milner and colleagues and Warrington demonstrated that right hemisphere lesions are more associated with deficits in spatial memory and face recognition (Milner, 1971; Smith & Milner, 1981; Warrington, 1984). In a series of elegant studies by Morris and colleagues with temporal lobe epilepsy patients, it was demonstrated that both spatial and visual memory deficits are associated with right-sided TL lesions (Abrahams, Pickering, Polkey, & Morris, 1997). Furthermore, the spatial memory impairment in these patients may be dissociated from that related to object recall or visual memory for abstract designs (Nunn, Polkey, & Morris, 1998; Nunn, Graydon, Polkey, & Morris, 1999). The latter of these studies reported a correlation between the extent of right hippocampal removal and performance on the spatial memory task (Nunn et al., 1999). Since no such correlations were found for other MTL structures, this suggested a critical role for the right hippocampus in spatial memory.

More direct evidence for a role for the right hippocampus in spatial memory (recall of object-locations) was provided by Stepankova and colleagues (Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004). In this study, small thermocoagulation lesions to the right hippocampus were sufficient to impair object-location memory and additional damage to the right perirhinal or parahippocampal cortices did not add to the impairment. Interestingly, similar lesions to the left hippocampus also disrupted performance on the task, although less consistently. A previous study by the same authors suggested that when a spatial task could be solved through simply remembering a single viewpoint, performance was impaired by right parahippocampal gyrus lesions rather than right hippocampal lesions (Bohbot et al., 1998). It is worth mentioning that whilst there is ample evidence that deficits in face recognition memory are predominantly lateralized to the right temporal lobe (Morris, Abrahams, & Polkey, 1995; Baxendale, 1997; Warrington, 1984), the role of the right hippocampus in face recognition memory is not well established.

Despite these well documented laterality effects in memory, they are very rarely included in the dominant theories of memory processing (Eichenbaum & Cohen, 2001; Squire et al., 2004). Thus, bilateral hippocampal damage is usually considered to impair (or spare) memory processes irrespective of the precise nature of the to-be-remembered material (e.g. words, faces or buildings), and the effects of unilateral hippocampal damage are scarcely considered. The data presented in Chapters 6 & 7 suggests that the nature of the to-be-remembered material can have a profound effect on memory performance. Specifically, when damage is limited to the hippocampus, recognition memory for faces can be spared, even when recognition memory for another type of non-verbal memoranda (outdoor scenes) is impaired. Furthermore, a striking laterality effect was demonstrated in a patient with right-sided hippocampal damage; recognition for topographical materials was impaired but recognition memory for verbal materials (words) was preserved. The investigation of material specific memory deficits following MTL damage forms a major focus of this thesis.

The other focus of Chapter 6 is the role of the hippocampus in recollection and familiarity. These terms derive from the experimental psychology literature and refer to two putative processes by which items can be judged as having been encountered previously (Tulving, 1985; Jacoby & Dallas, 1981; Mandler, 1980). Recollection is the conscious retrieval of information about an encoding event, whilst familiarity is the feeling that something has been encountered before, in the absence of retrieval of other related information. Some researchers propose that both of these processes are part of a general "declarative" memory system that is dependent, in part, upon the hippocampus (Squire et al., 2004). Another view holds that only recollection is hippocampal dependent, and that familiarity can be adequately subserved by extrahippocampal areas such as the perirhinal and entorhinal cortices (Aggleton & Brown, 1999; Rugg & Yonelinas, 2003).

Inspection of Figure 1-2, which shows the anatomical connections of the medial temporal lobe structures, makes clear why the two distinct memory systems position is plausible. The parahippocampal gyrus, perirhinal cortex and entorhinal cortex all receive convergent polysensory inputs from several cortical areas and are therefore theoretically be in a good position to either store this information or consolidate it via their reciprocal connections. In particular, the perirhinal and entorhinal cortex project to the medial dorsal thalamus and from there to the frontal lobes in a pathway that by-passes the hippocampus. This pathway has been particularly emphasised as a plausible circuit to underpin familiarity processing (Aggleton & Brown, 1999; Rugg & Yonelinas, 2003). Nevertheless, the evidence distinguishing these theoretical positions is equivocal. The data in chapter two suggest that whilst familiarity may underpin residual recognition abilities in two patients with hippocampal lesions, overall performance on item recognition tasks was impaired.

## 1.4 Neuropsychology as a tool for investigating brain and behaviour relationships

All the experimental work in this thesis employs a neuropsychological methodology. The strengths and weaknesses of this approach are discussed extensively elsewhere and will only be briefly reviewed here (see Shallice, 1988; Kolb & Wishaw, 1996; McCloskey, 2001). Detailed neuropsychological assessment can reveal how cognitive processes fractionate following brain injury. If the question to be asked is simply "are certain cognitive processes dissociable?" it is not necessary to have detailed anatomical data, or for brain lesions to be focal in nature. However, when the aim is to establish which brain areas underpin particular cognitive processes, relatively focal lesions as well as high resolution neuroanatomical data are required.

A major advantage of neuropsychology over other techniques for establishing cognitive neuroanatomy is that it is possible to establish which brain areas are necessary for particular cognitive processes (unlike, for example, functional neuroimaging). In particular, large scale group studies of patients with similar aetiologies are the most powerful approach. By testing such patients on the same cognitive tasks, performance can be related to lesions in a particular area, whilst at the same time areas not involved in performing the task can also be identified (Stuss et al., 2002; Burgess, Veitch, de Lacy, & Shallice, 2000; Mort et al., 2003).

Unfortunately, this approach is not always practical, as damage to some areas of the brain is very uncommon. In some cases, single patients with very focal and well characterised brain lesions can show specific impairment of a cognitive process, allowing strong structure-function relationships to be proposed (e.g. Husain, Parton, Hodgson, Mort, & Rees, 2003). However, this method of investigating structure-function relationships becomes problematic when patients with lesions that are very similar, have different cognitive profiles. A clear example of this is patients who are reported to have selective hippocampal damage (e.g. Cipolotti et al., 2001; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Vargha-Khadem et al., 1997). I shall argue that in these cases identifying the consistent findings across patients is particularly important.

Whilst neuropsychology can inform which brain areas are necessary to perform particular cognitive functions, the reverse is also true. When a patient with extensive brain lesions can be demonstrated to have no impairment in a cognitive domain, this implies strongly that the damaged areas are not necessary to carry out these cognitive processes. For example, several neuroimaging studies have implicated the medial frontal lobes in "mentalizing" (Gallagher & Frith, 2003). However, a patient with very extensive bilateral medial frontal lobe lesions was shown to perform normally on a large range of the same tasks that were used in the original imaging studies (Bird, Castelli, Malik, Frith, & Husain, 2004). Used in this way, neuropsychology can be used to constrain the hypotheses of structure-function relationships generated by less powerful cognitive neuroscientific techniques.

In addition to neuropsychology another technique can be used to assess whether particular brain regions are necessary to perform cognitive functions – transcranial magnetic stimulation (TMS). This technique can be used to create a reversible brain lesion in healthy adults. However, this technique is only able to affect processing in brain areas close to the scalp. It is therefore not possible to create reversible lesions in the medial brain areas that are the focus of this thesis. Cognitive processes and their underlying neuroanatomy can also be investigated in animals. Such studies have proved very influential in guiding theories about perception and memory in humans. When similar tasks can be used with both animals and humans, e.g. as in spatial memory tasks, clear parallels between species have been documented (e.g. Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Hartley, Trinkler, & Burgess, 2004). However, for other cognitive domains, such as verbal memory, generalization is not possible, and consequently, issues such as laterality of function cannot be investigated satisfactorily in animals.

There are some weaknesses of the neuropsychological approach. It is always possible that following brain injury, some degree of compensation will have taken place. Compensation can take the form of functional reorganisation, where brain areas not normally involved in performing a task are recruited following damage to areas that would typically subserve the task in healthy adults. When aiming to categorise the enduring deficits that may follow brain damage consequent to a stroke or tumour, very rapid functional reorganisation will not generally concern the investigator. If, however, one is investigating a cognitive process in patients with very longstanding neurological conditions such as epilepsy or developmental amnesia, and one intends to extend the findings to healthy adults, the problem of functional reorganization may be of more concern. If possible the findings of such studies should be corroborated with data from other sources, such as adults with lesions acquired later in life. Compensation can also mean the use of strategies to perform tasks in a qualitatively different way than usual. The most efficient way to ensure that a patient cannot use alternative strategies to perform a task is to design tests that can only be efficiently solved in one way.

An issue that is essential to bear in mind whenever using neuropsychology in either research or purely clinical settings is that of variability in test performance. Thus, performance on a cognitive task, although typically thought of as an "objective" measure of ability, may be affected by a number of factors, with brain injury being only one of those. Other factors include motivation, mood, fatigue, concentration, etc. as well as noise associated with the test itself. One way of investigating how much these factors contribute to variability in test performance is to have participants undertake the same test on two occasions. If the variability between test sessions is large, then the test will have poor test-retest reliability and large changes in scores will be necessary to conclude that there has been a significant change in cognitive status. By extension, when using such tests, caution should be exercised before placing particular emphasis on the results from just one test session.

In a series of studies I investigated the issue of variability in test performance over time for a selection of cognitive tests (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2003; Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004; Bird & Cipolotti, 2005). In a large sample of healthy adults it was shown that a test of semantic memory (the Graded Naming Test, McKenna & Warrington, 1983), and a test of visual perception (the Silhouettes Test, Warrington & James, 1991) were associated with little variability between test sessions and were highly reliable (Bird et al., 2004). A small but significant practice effect (an increase in the mean score at retest) of approximately 1 point was observed on both tests. In a further study, the reliability of the GNT was assessed retrospectively in neurological patients with either acute or degenerative conditions. Interestingly, the variability in both populations was also small and identical test-retest reliabilities as those in healthy adults were documented. Analysis of intra-subject variability suggested that changes in scores of 5 points or more were diagnostic of clinically relevant change in such populations. These findings suggest that performance on visual perceptual and nominal tasks is not overly affected by day-to-day fluctuations in factors such as mood, concentration, etc. and therefore scores obtained on such tests are good indicators of an individual's current level of functioning.

I also investigated the psychometric properties of a commonly used test of long-term memory for words and faces – the Recognition Memory Test (RMT: Warrington, 1984). In the first study, 206 healthy adults were administered twice either the same version or two different versions of the RMT. In contrast to both the Silhouettes Test and the Graded Naming Test, the test-retest reliability was found to be rather poor. Modest practice effects were found on the faces subtest when using the same version of the RMT at both assessments. When using the same version of the words subtest, practice effects were found in lower scoring individuals, but may have been masked by ceiling effects in higher scoring individuals. The use of alternative forms of the RMT at retest abolished the practice effect. This suggests that the small but significant practice effects reflect a degree of retention of the specific test items over the one month interval. Although the mean group changes in scores were small, the standard deviations of the mean changes were large. This reflects the large intra-subject variability in performance between test sessions. For an individual's change in score to exceed the "normal" variability associated with the healthy populations, a change in score of 5-8 points needed to be documented, depending on the age and subtest of the RMT. To give a specific example, if an individual aged 55-70 years scores at the 75th percentile on the faces subtest of the RMT, their score must drop to the 10th percentile before it can reliably be considered to have declined. This seriously hampers the usefulness of the RMT in monitoring individuals with changing neuropsychological profiles, such as neurodegenerative conditions.

There is evidence that intra-subject variability on some cognitive tests is greater in patients with neurological conditions than healthy adults (Stuss, Murphy, Binns, & Alexander, 2003). I therefore also investigated variability on the RMT in two populations of neurological patients (with either acute or degenerative brain damage). Patients were selected retrospectively if the time between test and retest was under 2 years and if it could be demonstrated by their performance on other cognitive tests, that their neuropsychological profile had remained relatively unchanged. The test-retest reliability of both subtests was actually *greater* than in the healthy adults. However, this reflects the greater range of scores (between-subject variability) obtained in the neurological patients than in the healthy adults, as it is well established that increasing the range of two datasets will increase any correlation between the datasets (Anastasi, 1988). As predicted, intra-subject variability in both populations exceeded that of the healthy adults. Thus, in both populations and on both subtests of the RMT, changes of at least 6-8 points were needed to exceed normal variability.

It is clear from these results that performance on tests of long-term memory is subject to significant variability between test sessions. Consequently, unusual findings from a specific test cannot necessarily be taken at face value as they may not reflect an individual's "true" level of competence. There are various ways in which his potential problem can be circumvented. The first is to repeat the test on a different occasion to check consistency in performance. Another method is to corroborate the findings with a separate test that is presumed to require the same cognitive process. In order to ascertain that the individual is not simply having a "bad day" it is useful to administer similar tests that are matched in difficulty and tax similar but subtly different cognitive processes. In this case, performance can be compared between the test of primary interest and the "control" test. Lastly, replicability of findings across patients with similar anatomical lesions is desirable before making strong claims about structure-function relationships.

### 1.4.1 Summary

This Introduction has briefly reviewed our current state of understanding of visuospatial perceptual and mnemonic processing in the human brain. Some areas of controversy have been highlighted and I have mentioned the experimental chapters where these issues have been addressed. I have also reviewed some of the strengths of and weaknesses of neuropsychology as a tool for investigating structure-function relationships. In particular, I have drawn attention to some of the considerations that must be borne in mind whilst both designing neuropsychological investigations and interpreting the data.

# 2 Chapter 2: Visual neglect and visual perception following posterior cerebral artery stroke

## 2.1 Background

The data in this chapter was collected in collaboration with Prof. Masud Husain and his research group at the Institute of Cognitive Neuroscience, UCL. Paresh Malhotra, Andrew Parton and Elizabeth Coulthard were involved with data collection and Paresh Malhotra and Elizabeth Coulthard demarcated the patients' lesions. Matthew Rushworth (Oxford University) made available to us the diffusion tensor imaging data published by Rushworth et al., (2005) and created Figure 2-4. The data have been published by the Journal of Neurology, Neurosurgery and Psychiatry in a manuscript by Bird, Malhotra, Parton, Coulthard, Rushworth and Husain (2006).

## 2.2 Introduction

Hemispatial neglect is a frequently observed syndrome following unilateral brain damage, especially of the right hemisphere, characterized by a failure to respond to contralesional stimuli (Stone et al., 1991; Vallar & Perani, 1986). The study of neglect offers an opportunity to characterize which areas of the brain are necessary to represent objects and their locations in the world. Neglect is a multi-component syndrome which can operate across different sensory modalities and in different body-centred (egocentric) and object-centred references frames (Driver & Halligan, 1991; Beschin, Cubelli, Della, & Spinazzola, 1997; Behrmann & Tipper, 1999). It is therefore unsurprising that neglect has been associated with damage to a large number of brain regions. The aim of this chapter is to investigate visual neglect in a rather poorly characterised population of patients, those with infarction in the territory of the posterior cerebral artery (PCA).

The cortical branches of PCA supply the posterior medial parietal lobe and the splenium of the corpus callosum, the inferior and medial part of the temporal lobe including the hippocampus, and the medial and inferior surfaces of the occipital lobe. Subcortically, branches of the PCA innervate the thalamus and subthalamic nucleus.

In contrast to the rather modest territory supplied by the PCA, the middle cerebral artery (MCA) is by far the largest of the cerebral arteries and supplies most of the outer convex brain surface, nearly all the basal ganglia, and the posterior and anterior internal capsule. It is also the vessel most commonly affected by stroke. Neglect is particularly prevalent acutely following stroke and it is now well established that most patients with the syndrome have damage to brain areas in the territory of the MCA, although the critical lesion areas responsible for causing neglect are controversial. Candidate areas include the posterior parietal lobe (including the angular gyrus and supramarginal gyri), the anterior superior temporal gyrus, and the inferior frontal lobe (Hillis et al., 2002; Husain & Kennard, 1996; Karnath et al., 2004; Mort et al., 2003; Vallar & Perani, 1986). Neglect has also been reported after lesions of the thalamus (Schmahmann, 2003; Vallar & Perani, 1986; Watson et al., 1981), but it is less well documented that the syndrome can follow lesions that lie within the wider territory of the superficial PCA. Although a few recent reports have documented neglect following PCA infarction (Cals, Devuyst, Afsar, Karapanayiotides, & Bogousslavsky, 2002; Mort et al., 2003; Park et al., 2006), important questions remain about which anatomical areas within the PCA territory are specifically associated with the syndrome and the characteristics of neglect following PCA infarction.

By comparison to strokes in the MCA territory, PCA infarction is relatively rare, representing only 5-10% of all strokes (Brandt, Steinke, Thie, Pessin, & Caplan, 2000). Visual field defects are by far the most common neurological sign documented after either left or right hemisphere damage in such patients (Binder & Mohr, 2004; Chaves & Caplan, 2001). These are caused by damage to cortical visual areas or damage to the optic radiations that send information from the lateral geniculate nucleus to the primary visual cortex. In addition, a broad spectrum of cognitive deficits - including amnesia, agnosia and alexia - are known to occur following left-sided PCA infarction, particularly when the lesions are large and extend beyond the occipital lobe (Binder & Mohr, 2004; Chaves & Caplan, 2001; De Renzi, Zambolin, & Crisi, 1987; Kinsbourne & Warrington, 1962).

The cognitive deficits following right-sided PCA infarction have generally received much less attention. The first study to attempt to systematically document the clinical presentation of patients PCA infarction was carried out by Cals and colleagues (2002).

The authors reported that in a small minority of patients, right-sided PCA infarction could be associated with prosopagnosia, palinopsia, visual hallucinations, dyscalculia, constructional apraxia, agitated confusion, disorientation and memory impairment. Importantly, in the context of the present study, 16% of patients with right-sided lesions were considered to have visual neglect. In 80 % of these patients, the lesion involved not only the occipital lobe but also extended into the medial parietal or temporal lobe.

The anatomy of visual neglect following PCA infarction was first directly addressed by Mort and colleagues (2003). Visual neglect was associated with lesions that extended from the occipital lobe anteriorally to the parahippocampal region and centred in the white matter of the ventromedial temporal lobe in the parahippocampal gyrus. The authors raised the possibility that disruption of the parieto-temporal white matter tracts may explain the presence of neglect in these patients. Interestingly, in this context, a very recent study using diffusion-weighted imaging and probabilistic tractography in healthy humans has documented robust projections between the parahippocampal gyrus and the angular gyrus of the parietal lobe, homologous to the tract that connects the same regions in non-human primates, which takes a very similar route (Rushworth et al., 2005; Seltzer & Pandya, 1984). Thus, it is possible that the reciprocal connections between these areas play an important role in spatial awareness.

A second study addressing the anatomy of visual neglect following PCA infarction has been very recently reported by Park et al., (2006) who assessed 45 patients with both left and right-sided brain lesions. Overall, 42% of the patients demonstrated some degree of visual neglect (48% of right hemisphere lesions and 38% of left hemisphere patients). The severity of neglect was greater following right hemisphere damage. The authors reported a number of areas as being associated with visual neglect including the parahippocampal gyrus and the thalamus. However, multiple regression analyses revealed that the only combination of lesions to contribute significantly to the frequency and severity of neglect were damage to both the occipital lobe and the splenium of the corpus callosum. They argued that this pattern of damage results in deafferentation and disconnection of visual information to one hemisphere, which can cause neglect (see also Gaffan & Hornak, 1997b); for a similar proposal). However, this is unlikely to be a complete explanation for all cases of PCA neglect, since 57% of their left hemisphere neglect patients and 33% of their right hemisphere neglect patients had no involvement or only partial involvement (in 1 patient) of the splenium. Furthermore, two patients with occipital lobe damage and complete lesions of the splenium did not have neglect.

PCA infarction frequently involves damage to those areas characterised as the ventral visual pathway (Milner & Goodale, 1995). Neuroimaging studies have identified areas within the pathway that respond preferentially to different classes of visual stimuli (Epstein & Kanwisher, 1998a; Kanwisher, McDermott, & Chun, 1997; Kourtzi, Erb, Grodd, & Bulthoff, 2003). These studies normally suggest little division of labour between the hemispheres. By contrast the neuropsychological data suggest a greater role of the right hemisphere is visual processing, particularly for visually degraded objects (De Renzi & Spinnler, 1966; Orgass, Poeck, Kerschensteiner, & Hartje, 1971; Warrington & James, 1967). However, deficits in visual perception of degraded objects are normally associated with right parietal damage (Warrington, 1985). Visual perceptual deficits following damage to areas in the ventral visual stream on the right are usually documented only in the context of category specific agnosias such as prosopagnosia or landmark agnosia (or topographagnosia: Habib & Sirigu, 1987; Landis et al., 1986; Landis, Cummings, Christen, Bogen, & Imhof, 1986; Takahashi & Kawamura, 2002; Tohgi et al., 1994). It therefore remains an open question whether damage to the ventral medial temporal and occipital cortices results in more general perceptual impairments.

The present study had several aims. First, to examine the characteristics of neglect and perceptual deficits following PCA infarction by assessing patients with right-sided PCA infarction on a battery of neglect tests and a subgroup on tests of visual perception. Second, to investigate which anatomical areas are most commonly damaged in PCA neglect paying particular attention to those areas previously implicated in previous studies (the thalamus, parahippocampal gyrus and the splenium of the corpus callosum). Third, we aimed to explore whether disconnection is a likely cause of neglect following PCA infarction.

## 2.3 Methods

### 2.3.1 *Participants*

15 patients were recruited for this study who all gave informed consent to participate, according to the Declaration of Helsinki. The study was approved by the relevant hospital research ethics committees. All patients had been admitted to hospital with acute right hemisphere stroke, subsequently confirmed to involve infarction in the territory of the PCA. All patients were assessed within 31 days of stroke (mean interval between stroke and assessment = 9.7 days, SD = 8.4). Visual fields were assessed clinically using a confrontation technique, by experienced examiners. See Table 2-1 for further details.

### 2.3.2 *Cognitive Assessment*

#### 2.3.2.1 Neglect battery

A comprehensive battery of tests was administered to assess various aspects of neglect. We used three tests of "peripersonal" neglect. These were: Line Bisection (mark the midpoint of three 18cm lines: neglect cut-off = 0.5cm rightward deviation: Manning, Halligan, & Marshall, 1990); Mesulam's Shape Cancellation test (search for target symbols embedded among distractors on a sheet of A4 paper: Mesulam, 1985); the Star Cancellation test from the Behavioural Inattention Test (search for target stars embedded among distractors on a sheet of A4 paper: BIT: Wilson, Cockburn, & Halligan, 1987). "Extrapersonal neglect" was assessed by asking the patients to report objects from around the room (Stone et al., 1991). The patient is required to point to and/or name all the objects they could see in the room, whilst the examiner stands directly behind them and marks on a semicircular piece of card all the objects identified and their approximate positions. The number of degrees omitted is calculated (cut-off point = 50 deg). We used the comb-razor test to detect the presence of "personal neglect" (Beschin & Robertson, 1997). In this test the subject is asked to

**Table 2-1: Participant details**

| ID | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| imaging protocol | CT | MRI | CT | CT | CT | CT | MRI | MRI | CT | CT | CT | MRI | CT | MRI | MRI |
| Age (years) | 75 | 95 | 61 | 66 | 71 | 77 | 75 | 67 | 77 | 63 | 74 | 83 | 67 | 59 | 63 |
| Sex | M | M | M | M | M | F | F | F | F | F | F | F | M | F | F |
| Handedness | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| Interval (days)[A] | 10 | 2 | 9 | 6 | 8 | 25 | 4 | 15 | 0 | 4 | 11 | 31 | 5 | 7 | 8 |
| Constructional apraxia[B] | + | + | + | + | - | n.t. | + | + | n.t. | n.t. | - | + | n.t. | + | - |
| Visual field deficit | LH | LH[C] | LH | LH | LH | LH | LH | LSQ | LH | LSQ | LIQ | LH[C] | LH | LH | LH |
| Lesion volume (cc) | 67.3 | 13.6 | 56.2 | 44.7 | 21.7 | 52.6 | 5.9 | 29.4 | 11.5 | 31.0 | 25.0 | 6.4 | 10.5 | 6.1 | 7.1 |

**Legend**: A = Interval between stroke and assessment; B = As tested by the ability to draw a copy of a three dimensional cube; C = initially an apparent hemianopia which resolved to an upper quadrantanopia; cc = cubic centimetres; + = evidence of constructional apraxia, - = no evidence of constructional aparaxia comb his/her hair for a 30 second period during which time the examiner categorizes each stroke according to whether it was applied to the left or right side of the head, or was ambiguous. A similar procedure is used for shaving (men) or facial compact use (women). Results were analyzed according to the procedure of McIntosh et al., (2000). There was one test of representational drawing (Clock drawing from the BIT).

#### 2.3.2.2 Additional tests of visual perception

Six patients were administered a selection of tests of visual perception. These were chosen to encompass aspects of visual processing from the basic level (figure-ground segregation) to complex visual identification (recognition of visually degraded objects). The Shape Detection Test from the Visual Object and Spatial Perception Battery (VOSP: Warrington & James, 1991) involves identifying the presence or absence of a fragmented letter "X" upon a fragmented background. Basic visual identification was assessed using the Fragmented Letters Test from the VOSP. The patient must identify large reproductions of capital letters which are degraded by 70% using a random pattern. The Silhouettes Test from the VOSP is a stringent test of visual perception that requires the identification of 15 animals and 15 objects from the outline of each object that has been rotated around the lateral axis.

Care was taken to ensure that the presence of neglect would not impact on performance of these tasks. Patients were tested several days after the initial screening for neglect was carried out (Table 2-1 and Table 2-3), by which time neglect had improved in most cases. All test materials were presented ipsilesionally and attention was drawn to the whole of the stimulus.

### *2.3.3 Anatomical Assessment*

Brain lesions were imaged by CT or MRI and plotted using MRICro software (www.mricro.com) using a graphics tablet (WACOM Intuos A6). A T1 weighted template consisting of 12 axial slices was used to demarcate the lesions for all patients. Lesion volumes were computed using MRICro software tools. MRICro was also used to analyze the degree of overlap of lesions in the two patient groups and to make comparisons between them.

## 2.4 Results

### 2.4.1 Results of cognitive tests

#### 2.4.1.1 Neglect battery

The performance of the patients on these tests is shown in Table 2-2. The patients have been split into two groups according to whether or not they demonstrated any evidence of neglect (patients N1-N8 and patients C1-C7 respectively). There were no significant differences between the two groups in terms of age or interval between stroke and assessment [Age; N1-N8 mean (sd) = 73.4 (10.2), C1-C7 mean (sd) = 69.4 (8.8), t = 0.79, d.f. = 13, P>0.1: Interval; N1-N8 mean (sd) = 9.9 (10.1), C1-C7 mean (sd) = 9.4 (10.1), t = 0.1, d.f. = 13, P>0.1].

The range of severity of neglect was large. For example, N1 and N2 presented with clear evidence on neglect on almost all of the tests. On the other hand, N8 passed all the neglect tests except Mesulam's Shape Cancellation task, on which she was mildly impaired. Nevertheless, N8 invariably started from the right side on cancellation tasks and worked leftwards, which has been considered to be a very sensitive marker for neglect (Azouvi et al., 2002; Wilson et al., 1987).

All of the patients (N1-N8) demonstrated evidence of visual neglect for peripersonal space, failing at least one of the cancellation tasks. On the line bisection test, 5 patients (N1-N5) showed a clear rightward deviation. However, patient N6 showed a very large leftward deviation, a phenomenon which has been documented in acute patients with hemianopia (Barton & Black, 1998). Personal neglect was rare, with only two patients failing the razor test (N1 & N2) and only one of these also failing the Comb test (N1). Finally, three patients (N1-N3) were impaired at drawing objects from memory, which may reflect an impairment of visual representation.

**Table 2-2: Results of the neglect battery**

| ID | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Line bisection (cm)$^A$ | 7.5 | 6.5 | 1.7 | 3.5 | 1.3 | -6.2 | 0.4 | -0.5 | -0.6 | -0.4 | -1 | -0.7 | -1.6 | -0.8 | 0 |
| L (Mes) /30 | 0 | 0 | n.a. | 7 | 25 | 0 | 1 | 22 | 26 | n.a. | 26 | n.a. | 30 | 29 | 29 |
| R (Mes) /30 | 2 | 2 | n.a. | 17 | 28 | 11 | 22 | 25 | 25 | n.a. | 28 | n.a. | 30 | 28 | 29 |
| Total (Mes) /60 | 2 | 2 | n.a. | 24 | 53 | 11 | 23 | 47 | 51 | n.a. | 54 | n.a. | 60 | 57 | 58 |
| L (BIT) /27 | 0 | 0 | 4 | 19 | 19 | 13 | 0 | 26 | 26 | 25 | 27 | 26 | 27 | 26 | 27 |
| R (BIT) /27 | 10 | 7 | 15 | 20 | 25 | 14 | 23 | 25 | 25 | 24 | 27 | 24 | 27 | 25 | 27 |
| Total (BIT) /24 | 10 | 7 | 19 | 39 | 44 | 27 | 23 | 51 | 51 | 49 | 54 | 50 | 54 | 51 | 54 |
| Copying shapes | n/a | + | + | + | + | n.t. | n/a | - | - | n.t. | - | - | - | - | - |
| Reporting Objects | n.t. | + | + | - | - | + | n.t. | - | - | n.t. | - | - | - | - | - |
| Comb test | + | - | - | - | - | n.t. | - | - | - | n.t. | n.t. | - | - | - | - |
| Razor test | + | + | - | - | - | n.t. | - | - | - | n.t. | n.t. | - | - | - | - |
| Drawing | + | + | + | - | - | - | - | - | - | - | - | - | - | - | - |

**Legend:** A = mean rightward deviation; n.t. = not tested; n/a = patient unable to compete test, + = evidence of neglect, - = no evidence of neglect

**Table 2-3: Performance on tests of visual perception**

| ID | N2 | N3 | N4 | N5 | N8 | C2 |
|---|---|---|---|---|---|---|
| Interval (days) | 44.00 | 14.00 | 196.00 | 19.00 | 60.00 | 22.00 |
| Shape detection | 19/20<br>(pass) | n.t. | n.t. | 20/20<br>(pass) | 20/20<br>(pass) | 20/20<br>(pass) |
| Fragmented letters | 7/20<br>(<5 %ile) | 2/20<br>(<5 %ile) | 15/20<br>(<5 %ile) | 10/20<br>(<5 %ile) | 18/20<br>(pass) | 20/20<br>(pass) |
| Silhouettes | 4/30<br>(<5 %ile) | 14/30<br>(<5 %ile) | 9/30<br>(<5 %ile) | 12/30<br>(<5 %ile) | 8/30<br>(<5 %ile) | 16/30<br>(5-10 %ile) |

### 2.4.1.2 Visual Perceptual Tests

The results of the three visual perceptual tests are shown in Table 2-3. There was clear evidence for higher level visual perceptual deficits in five of the six patients. Interestingly, of the four patients that were administered the Shape Detection test, all four passed it (N2, N4, N8, C4), indicating that they had no impairment of early visual processing abilities. Nevertheless, patients N2-N5 were impaired on a relatively easy test of visual form perception – the Fragmented Letters test from the VOSP. The same patients, as well as patient C4, were impaired on the Silhouettes test from the VOSP, a more stringent test of visual object perception. The latter test was passed by patient N8, although her score fell below the 10th percentile for her age group. In sum: there was a range of severity of visual perceptual deficits in the patients; broadly speaking, pre-categorical visual processes appeared to be intact in these patients, but failures were noted at the level of perceptual categorization.

Figure 2-1: Lesions of the patients with neglect

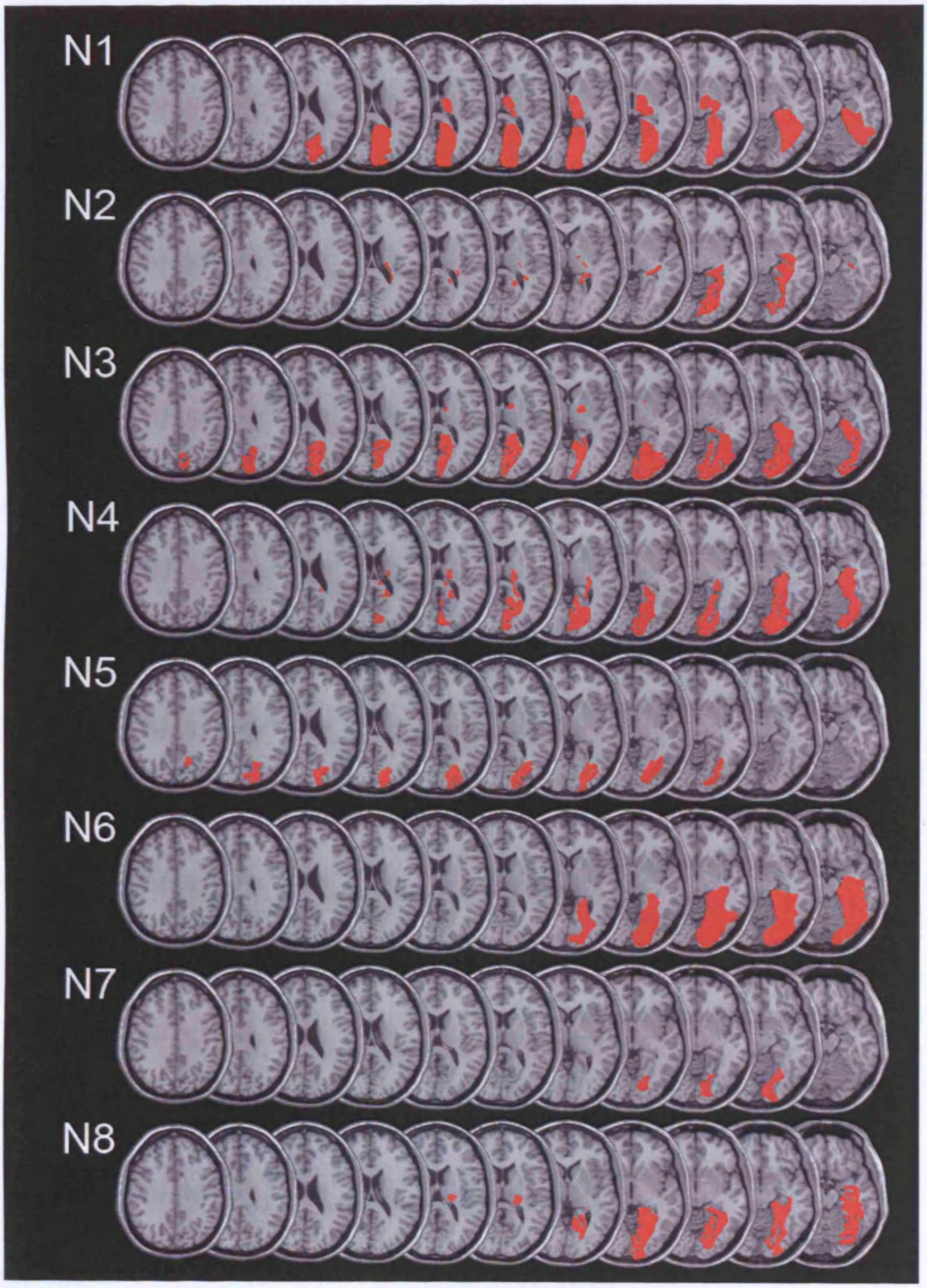
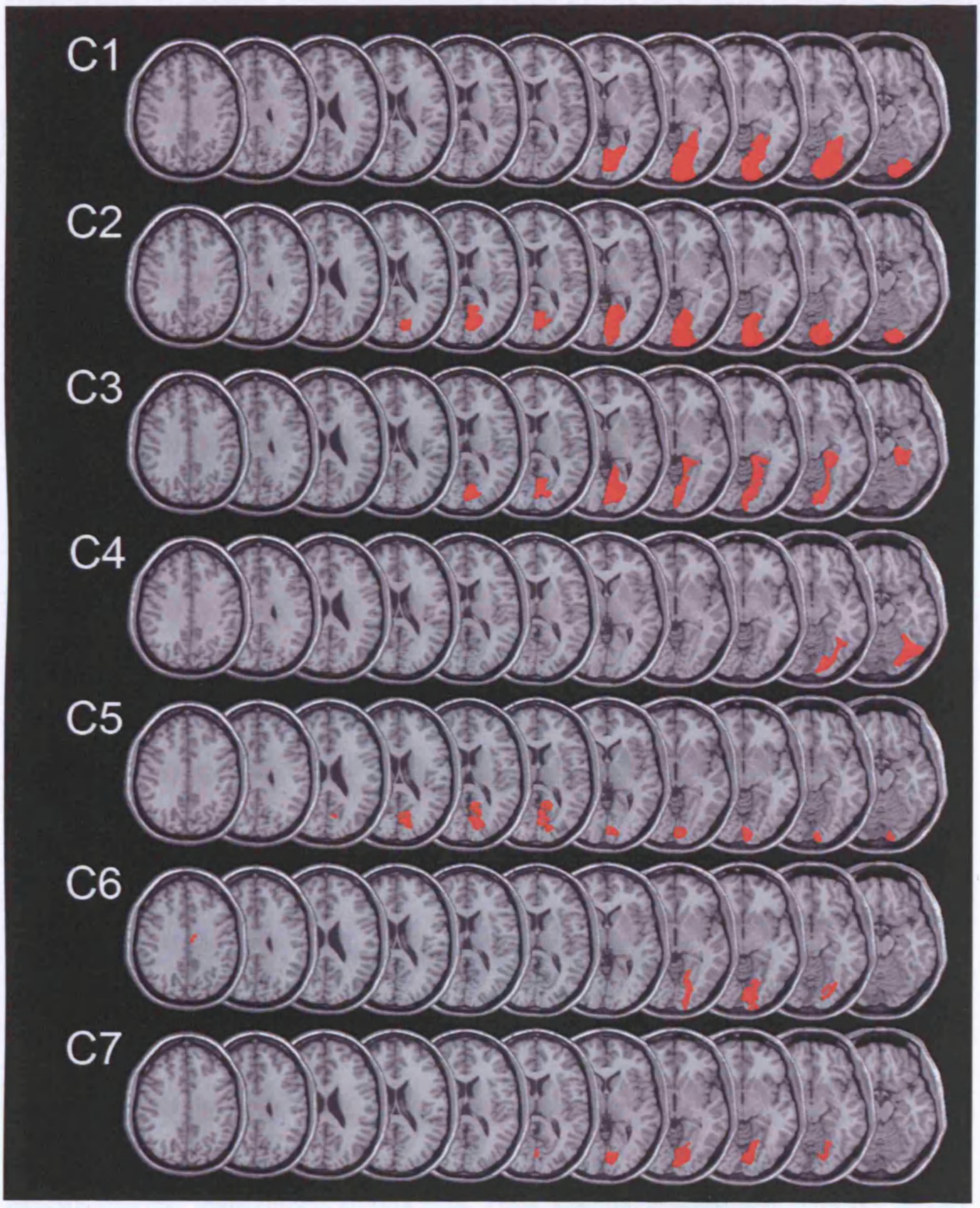


**Figure 2-2: Lesions of the patients without neglect**



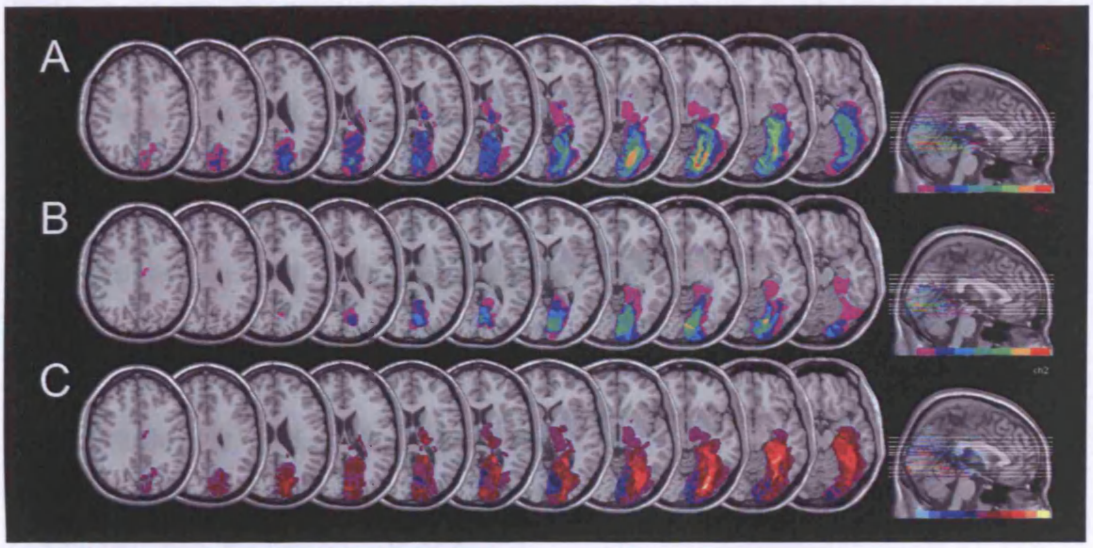
### 2.4.1.3 Anatomical data

All patients had lesions within the territory of the posterior cerebral artery, involving the occipital lobe in all cases (Figure 2-1 and Figure 2-2). Neglect was generally associated with larger lesions that extended beyond the occipital lobe, with a significant difference between the lesion volumes of patients N1-N8 and patients C1-C7 (volume in cc; N1-N8 mean (sd) = 36.4 (22.0), C1-C7 mean (sd) = 13.9 (10.0), t = 2.5, d.f. = 13, $P<0.05$). Six patients in the neglect group had lesions extending into the medial temporal lobe, involving the fusiform gyrus, lingual gyrus, parahippocampal gyrus and hippocampus (N1, N2, N3, N4, N6, N8). Another had a lesion that extended into the parietal lobe (N5) and patient N7's lesion was restricted to the occipital lobe. Among the control non-neglect patients, the lesion extended anteriorally as far as the parahippocampal gyrus in only two patients (C1 and C3). Of these two patients, only C3 had fairly extensive involvement of the parahippocampal gyrus.

Five of the neglect patients had some degree of thalamic involvement (N1, N3, N4, N8 and to a very limited extent, N2). The damage was most extensive in patient N1, who also presented with the densest neglect of any of the patients. However, the extent of thalamic damage did not predict severity of neglect. For example, N5 demonstrated clear evidence of neglect despite no thalamic involvement, whilst N8 who showed only very subtle signs of neglect, had moderate damage to this structure. None of control patients C1-C7 had any involvement of the thalamus.

Since Park et al., (2006) noted that damage to the splenium was associated with visual neglect, we paid particular attention to this area. Half of the neglect patients had damage to the splenium (N1-N4), but neither patients N5-N8 nor any of the control patients had any involvement of this area. Thus, splenial involvement does not appear necessary to cause neglect.

**Figure 2-3: Areas associated with neglect**

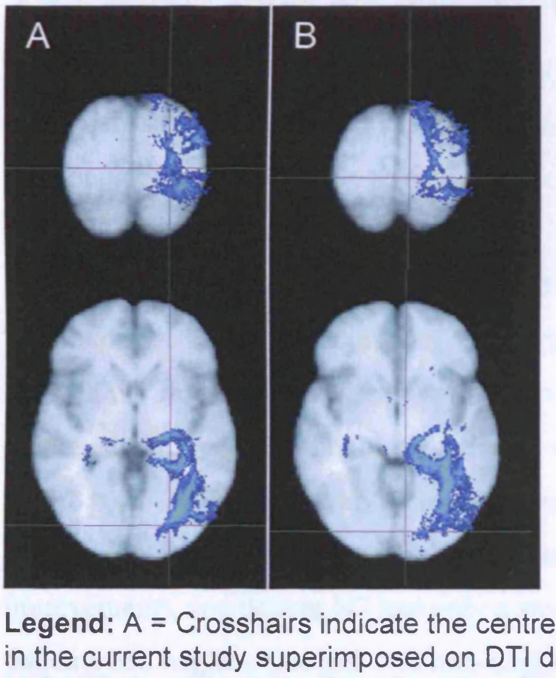


**Legend:** A = overlap of lesions of patients with neglect (N1-N8); B = overlap of lesions of patients with no neglect (C1-C7); C = subtraction plot showing areas most associated with neglect (A-B)

In order to determine which anatomical regions were most associated with neglect, we compared the lesions of the patients with neglect to those of the patients without neglect. In the neglect patients, there was maximal overlap of lesions in the white matter of the occipital lobe, although there was also a high degree of overlap extending anteriorally into the ventral medial temporal lobe (Figure 2-3A). In the patients with no neglect there was also an area of common damage in the occipital lobe close to the region most frequently damaged in the neglect patients (Figure 2-3B), reflecting the fact that both groups of patients have infarction in the same vascular territory. However, in the patients without neglect, there were no other common areas of damage apart from this area in the occipital lobe. Figure 2-3C shows the key direct comparison between the two groups of patients. Importantly, this demonstrates an area within the white matter of the occipital lobe which is damaged in all the neglect patients but none of the patients without neglect. This region is slightly lateral to the occipital region that was maximally damaged in the patients without neglect. Additionally, there are large regions of the ventral medial temporal lobe which show a high degree of association with neglect.

In healthy humans, diffusion tensor imaging (DTI) has identified a white matter tract coursing between the parahippocampal gyrus and the angular gyrus (Rushworth et al., 2005). In terms of the position and connections of this tract, it is homologous to the inferior longitudinal fascicle, identified in the macaque (Seltzer & Pandya, 1984). Both of these areas have been associated with visual neglect (Mort et al., 2003). Whilst we found no area of overlap in our study close to the parahippocampal gyrus, it is possible that lesions within the white matter of the occipital lobe disrupt the tract identified by Rushworth and colleagues. Figure 2-4A shows the area maximally associated with neglect in our study with the DTI data (from Rushworth et al., 2005) showing the probable course of the white matter tract from the parahippocampal gyrus to the angular gyrus. Interestingly, it appears that the area of maximal lesion overlap does indeed lie within this tract. Critically, the area most commonly damaged in the non-neglect patients lies outside of it.

**Figure 2-4: The association of white matter tracts between the parahippocampal gyrus and posterior parietal lobe and lesions responsible for causing neglect**



**Legend:** A = Crosshairs indicate the centre of the area most associated with neglect in the current study superimposed on DTI data from healthy adults showing the probabilistic white matter tract from the parahippocampal gyrus to the angular gyrus (inferior longitudinal fascicle). [DTI data from Rushworth et al. 2005]; B = Crosshairs indicate the area of maximal overlap in the non-neglect patients superimposed on DTI data from healthy adults showing the probabilistic white matter tracts from the parahippocampal to the angular gyrus. [DTI data from Rushworth et al. 2005]

## 2.5 Discussion

There have been very few group studies of visual neglect in the acute stage following right-sided PCA infarction (Mort et al., 2003; Park et al., 2006). In our study, eight of the fifteen patients demonstrated evidence of visual neglect of varying severity. In general, these patients had relatively large lesions that extended from the occipital lobe into the medial temporal lobe. In some, but not all cases, the thalamus was also involved. In addition, half of the patients with neglect had damage to the splenium. However, neither of these areas was critical in causing neglect. In contrast, an area of white matter in the occipital lobe did appear to be damaged in the neglect patients but not in the non-neglect controls. A lesion in this area may disrupt white matter projections between the parahippocampal gyrus and the angular gyrus of the parietal lobe. Lastly, visual perceptual processing was also found to be compromised in a subgroup of patients.

### *2.5.1 Which areas are most associated with neglect?*

It is important to note that the brain regions damaged in the patients with neglect are quite distinct from the lateral parietal and frontal regions most commonly associated with neglect which lie in the territory of the MCA (Husain & Kennard, 1996; Mort et al., 2003; Vallar & Perani, 1986). In our PCA group, neglect was most frequently associated with larger lesions that extended beyond the occipital lobe into the medial temporal lobe, up to, and including the hippocampus (Figure 2-3A). In this general respect, our results are in agreement with those of a previous study, which documented an area of maximal overlap in white matter of the parahippocampal gyrus (Mort et al., 2003). However, there are some caveats to be made. First, patient N5 had no temporal lobe involvement (although there was a degree of parietal lobe involvement), and patient N7 had only a small occipital infarct, yet both of these patients had neglect. Second, two non-neglect control patients had lesions that extended into the temporal lobe up to and including the parahippocampal gyrus. The subtraction of the areas damaged in the control group from those of the neglect group are shown in Figure 2-3C. These findings reveal how important it is to perform a direct contrast between the two patient groups. Figure 2-3C demonstrates the tendency for medial temporal areas to be associated with neglect. However, in the current study the region most associated with neglect lay in the white matter of the occipital lobe, where damage co-occurred in all neglect patients but was spared in the patients without neglect.

Previous reports have documented neglect following isolated thalamic lesions (Schmahmann, 2003; Vallar & Perani, 1986; Watson et al., 1981). Thalamic damage was present in two patients with very dense neglect (N1 & N2). However, taking the series as a whole, damage to the thalamus did not appear to be necessary to cause neglect. A recent study highlighted the association between damage to the splenium of the corpus callosum and visual neglect (Park et al., 2006). Four patients in our study had lesions to these areas and all four had neglect. Nevertheless, there were four neglect patients who had no involvement of the splenium (neglect without splenial damage was also reported in the Park et al. study). Thus, similarly to the thalamus, damage to the splenium does not appear necessary to cause neglect.

### *2.5.2 Possible causes of neglect following PCA infarction*

Since all the patients with neglect had a visual field deficit and were tested in the acute stage, could it be that these patients were simply unable to compensate for their visual field loss? The data from the patients with no neglect convincingly argues against this proposal. Half of these control patients had complete homonymous hemianopias and yet demonstrated no signs of neglect. Therefore, damage to areas of the occipital lobe sufficient to cause hemianopia, cannot on its own, explain the presence of neglect.

Park and colleagues argued that PCA stroke may cause neglect through combined damage to the occipital lobe, and the splenium of the corpus callosum as this would result in deafferentation and disconnection of one hemisphere from visual information about the contralesional side of space (Park et al., 2006). A rather similar argument was also proposed by Gaffan and Hornak (1997b) and equivalent proposals have been used to explain pure alexia following left-sided PCA infarction (Binder & Mohr, 1992). This explanation is partially supported by our data, since four patients with rather severe neglect also had splenial involvement. Therefore, although not necessary to cause neglect, this pattern of disconnection may influence the severity of neglect manifested in PCA patients.

Our data, point towards a critical role for white matter in the occipital lobe, while the study by Mort et al. another study identified an area of white matter in the parahippocampal gyrus that was most associated with neglect (Mort et al., 2003). A recent investigation using diffusion tensor imaging in healthy humans has shown that the parahippocampal area has strong reciprocal connections with the angular gyrus – an area strongly associated neglect (Rushworth et al., 2005). This tract resembled the inferior longitudinal fascicle, a well categorized white matter tract connecting these areas in the macaque (Seltzer & Pandya, 1984). Critically, the fibres appear to course through the white matter of the posterior occipital lobe including the region identified to be associated with neglect in the current study (Figure 2-4A). Importantly, the areas most commonly damaged in the non-neglect control patients do not lie within this tract (Figure 2-4B).

The parahippocampal gyrus receives the bulk of its cortical inputs from visual areas in the ventral visual processing stream (Suzuki & Amaral, 1994). Functional neuroimaging in humans and electrophysiological studies with non-human primates have shown that the parahippocampal gyrus plays a role in supporting large-scale representations of the environment and objects in the periphery of both hemispheres (Epstein & Kanwisher, 1998a; Levy, Hasson, Avidan, Hendler, & Malach, 2001; Sato & Nakamura, 2003). In comparison, the posterior parietal lobe has been conceived as a functional nexus which cannot be strictly placed in either the dorsal or the ventral stream (Milner et al., 1999), and may be responsible for constructing abstract spatial representations of the visual world. Consequently, disconnection of the white matter tract linking these areas may be a mechanism underpinning our patients' visual neglect. It should be noted that disconnection has also been discussed in the context of mechanisms underlying MCA neglect (Doricchi & Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005).

### 2.5.3 Visual perception following PCA infarction

Six of the patients were assessed on additional tests of visual perception. There was no evidence of impairment in figure-ground segregation, which is considered to be an early (pre-categorical) visual process (Warrington, 1985). However, there was evidence for impairment at the level of perceptual identification (Table 2-3). Since all stimuli were presented ipsilesionally, and there was no left hemisphere damage, it demonstrates the privileged role of the right hemisphere in visual processing – left hemisphere visual areas alone, were insufficient to perceive the test items. As reviewed in Chapter 1, there is ample evidence that the right hemisphere plays a greater role in the perception of visually degraded object. However, impairment on the tests used in the present study is usually ascribed to damage to the lateral aspect of the right parietal lobe – not the medial occipitotemporal regions damaged in these patients (Warrington & James, 1967; Warrington & Taylor, 1973).

It is unclear what the likely causes of visual processing deficits in these patients are. One possible reason is that the ventral visual stream in the right hemisphere plays a greater role than the left hemisphere stream in perceiving complex visual stimuli. This claim is made by Milner and Goodale (1995). However, functional imaging studies usually find little evidence for hemispheric differences in object perception (Grill-Spector & Malach, 2004). An alternative suggestion proposed by Turnbull and colleagues (1997) is that the posterior parietal lobe (in the right hemisphere) is necessary for the perception of such stimuli. The authors suggest that it is involved in image manipulation and re-organisation strategies; for example, to "clean up" a degraded image during object recognition as part of a process of visual "problem-solving" (Farah, 1990). Disconnection of visual input to this area would therefore impair the recognition of such stimuli. Both of these positions may be partially true, although our data perhaps favour the latter. For example, Patient N5 (with severe perceptual problems) did not have very extensive lesions to ventral visual processing areas, but did have extensive white matter damage in the occipital lobe which may have disconnected visual inputs from the posterior parietal lobe. On the other hand, Patient C2 (who had a questionable perceptual impairment) had more damage to the ventral visual areas, but less white matter involvement of the white matter. Further studies are necessary to clarify the roles of these areas in visual perception for complex stimuli.

### 2.5.4 Conclusions

This study contributes to the recent literature on a relatively unexplored phenomenon – visual neglect following PCA stroke. We documented a range of severity of neglect that followed PCA stroke in an unselected group of patients. Although lesions of the thalamus and combined lesions of the splenium of the corpus callosum and the occipital lobe were associated with neglect, damage to these areas was not necessary to cause neglect. By contrast, careful comparison of the patients with and without neglect, revealed an area of white matter in the occipital lobe was consistently associated with neglect. We suggest that damage to this area may disrupt white matter tracts connecting the parahippocampal gyrus in the temporal lobe and the angular gyrus in the parietal lobe. It is possible that the interaction of these areas is necessary to subserve awareness for the contralateral side of space. Visual perceptual deficits were also associated with PCA stroke. Interestingly, the pattern of perceptual deficits we report has only previously been documented in the context of right-sided parietal damage.

In Chapter 4 I will return to investigate perception following brain damage. One of the patients (MH) has a chronic lesion involving the posterior cerebral artery, similar to the patients with large medial occipitotemporal lesions included in this study. Although this patient has no neglect and only very mild perceptual problems, his ability to perceive the spatial layouts of outdoor scenes is profoundly impaired – providing a plausible reason why patients with right-sided PCA lesions often have topographical disorientation. I also investigate the role of the hippocampus in perceiving and representing this type of spatial information over very short intervals. The following chapter details the case reports of the patients that take part in the experimental investigations in Chapters 4, 6 and 7.

# 3 Chapter 3: Case reports

## 3.1 Introduction

Chapter 4, 6 and 7 report experimental data from six neurological patients as well as healthy controls. For clarity, full details of all six patients are reported here rather than in the experimental chapters themselves. Thus, in this chapter the case descriptions, neuroanatomical data and the results of neuropsychological assessments are reported for all patients. Tables with the results of cognitive tests and neuroanatomical figures are presented at the end to preserve continuity.

Patients MH, and RH had unilateral right hemisphere lesions, whilst the remaining patients had bilateral lesions (Jon, KE, VC and JC). Patients MH, RH, Jon, KE and VC all took part in the investigation reported in Chapter 4. Patients RH, VC and JC took part in the investigation reported in Chapter 6. Chapter 7 reports preliminary data from Patient Jon's performance on the same tasks as those reported in Chapter 6.

## 3.2 Participant details

## 3.3 Patient MH

### *3.3.1 Case description and neuroanatomical results*

MH is a 70 year old male, who formally worked as an airport terminal duty officer. In August 2000, he had a sudden onset of dizziness and mild weakness in his left arm. Subsequently he was disorientated and had difficulty walking as he started bumping into objects. A neurological examination in February 2003 revealed a left homonymous upper quadrantanopia. The only other neurological sign was a mild postural tremor.

Following discharge, MH complained of difficulty in recognizing famous people's faces on television, although friends and family never presented a problem. He has experienced several episodes of topographical disorientation, although he is able to live independently. He was also concerned that his quadrantanopia was expanding although this was found not to be the case.

MH underwent a dedicated high resolution structural MRI scan, which comprised one 256 slice T1- weighted acquisition performed in the coronal plane, on a 1.5 T MRI scanner. Within- and between-slice resolution was 1 mm, giving an isotropic voxel dimension of 1 $mm^3$. This showed right-sided occipital and temporal lobe infarction in the territory of the posterior cerebral artery (Figure 3-1). The lesion involved the fusiform, lingual and parahippocampal gyri and extended into posterior portions of the hippocampus.

### *3.3.2 Performance on general cognitive tests*

MH's performance on a range of cognitive tests is summarized in Table 3-1. His verbal and performance IQ's were found to be in the average range which is in keeping with premorbid estimates. There was no evidence of nominal or reading difficulties as indexed by the Graded Naming Test and the National Adult Reading Test (GNT: McKenna & Warrington, 1983; NART: Nelson & Willison, 1991). There was no evidence of visual neglect on cancellation (Mesulam, 1985) or line bisection tasks (Manning et al., 1990) and his spatial span was normal (5 items). In addition, MH's performance on a stringent test of auditory selective attention was flawless (Elevator Task with Distraction, from the Test of Everyday Attention).

MH's visual perceptual abilities were compromised, as evidenced by his performance on various subtests of the VOSP (Warrington & James, 1991). His performance was weak on an easy test of perceptual identification (Fragmented Letters) and impaired on two more stringent tests of object perception (Object Decision and Silhouettes). However, visuospatial perception was unimpaired (he scored in the normal range on Dot counting, Number Location and Cube Analysis subtests of the VOSP).

Despite his complaints of poor face recognition, there was no clear evidence for an impairment in face perception. His performance on the Benton Face Recognition Test was in the normal range (42/54 (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). In addition he was able to name 10/12 and recognize 12/12 photographs of famous faces and on a further test asking him to assess the age of unfamiliar faces, his performance was flawless (subtest from the Cortical Vision Screening Test: James, Plant, & Warrington, 2001).

### *3.3.3 Performance on Episodic Memory Tests*

MH's performance on various tests of episodic memory is summarized in Table 3-2. Verbal memory was intact as assessed by the RMT and the recall and recognition subtests of the Doors and People Test (DPT: Baddeley, Emslie, & Nimmo-Smith, 1994). Visual recall (Shapes subtest of the DPT) was in the normal range, although somewhat weaker than his performance on most of the other memory tests. Visual recognition as assessed by the Topographical Recognition Memory Test (Warrington, 1996) and the Doors subtest of the DPT was intact. However, his performance on the Faces subtest of the RMT was impaired (Warrington, 1984). This was confirmed at a second assessment, where he performed at the 5th percentile on an alternative version of the RMT (35/50).

### *3.3.4 Summary*

MH is a 70 year old man who suffered a right-sided posterior cerebral artery stroke. This resulted in medial occipitotemporal lobe infarction, extending into the posterior portions of the hippocampus and involving the lingual, fusiform and parahippocampal gyri. He complains of occasional difficulty with recognizing people on television and topographical disorientation. His neuropsychological profile is unremarkable apart from mild visual perceptual problems.

Chapter 4 reports MH's performance on tasks requiring the perception and short-term retention of spatial and non-spatial aspects of outdoor scenes.

## 3.4 Patient RH

### *3.4.1 Case description and neuroanatomical results*

RH is a 58 year old, female, housewife. In 1996, she developed sudden onset tingling and weakness in the left arm. Subsequent to this event, she noticed an impairment in remembering events, appointments and conversations. She also began to notice a difficulty with her sense of direction particularly when walking in unfamiliar places. Neurological examination was entirely normal. Given the sudden onset of her symptoms and her static neuropsychological profile (see below), a vascular aetiology was suspected (ischaemia).

RH's scans have been qualitatively assessed by three independent, experienced neurologists, blind to any of the experimental investigations carried out in this thesis. Axial T2-wighted and coronal T1-weighted scans covering the whole brain were obtained from RH. A few peri-ventricular non specific white matter abnormalities were detected on the T2-weighted scan. On T1-weighted images there was a selective atrophy of the right hippocampal formation (Figure 3-2). Volumetric analysis of both hippocampi from two scans 1 year apart consistently revealed a 59% volume reduction in the right hippocampus compared with the left. Consistent with such focal volume loss, there was an enlargement of the right lateral ventricle, prominently involving its temporal horn. No abnormalities were noted in the left hippocampus. Unfortunately, detailed volumetric analyses to ascertain whether there is volume loss to structures outside of the hippocampus have not been performed. However, qualitatively the appearances of the left and right entorhinal cortex, parahippocampal gyrus, fusiform gyrus and other temporal lobe areas were normal according to three experienced neurologists.

### 3.4.2 Performance on general cognitive tests

RH was administered a full neuropsychological assessment twice, one year apart. The experimental investigations that will be described took place around the time of the second assessment. The results of the most recent assessment are shown in Table 3-1.

When assessed on the WAIS-R in the two assessments, RH obtained similar verbal and performance IQ scores (previous VIQ = 109, PIQ = 101), which were in keeping with premorbid estimates based on educational level and occupational background, but somewhat lower than the level predicted by her performance on the NART. Nominal skills as assessed by the GNT were above the 75th percentile at both assessments. Similarly, visual and visuospatial perception was normal (Object decision, Cube Analysis and Position Discrimination subtests of the VOSP). RH's performance on several tests of executive processing was found to be normal. At the first assessment her interpretations of proverbs were sensible and she provided good cognitive estimates. She passed the Modified Card Sorting Test (MCST: Nelson, 1976) quickly and easily on the first assessment. At the second assessment her verbal fluency was good and she obtained scores in the average range on the Hayling and the Brixton Tests (Burgess & Shallice, 1997).

RH was also administered a comprehensive assessment of her semantic memory at the time of the experimental investigations. Her performance was well within the normal range on all subtests of a stringent test of picture naming (Category Specific Names Test: Animals = 21/30, Fruit/vegetable = 25/30, Objects part 1 = 26/30, Objects part 2 = 25/30: McKenna, 1998). Three tests of comprehension were administered; The Graded Synonyms Test; the Camel and Cactus Test; the Cambridge Category Comprehension Test (Warrington, McKenna, & Orpwood, 1998; Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Hodges & Patterson, 1995). She performed all three tests entirely satisfactorily (Concrete synonyms = 25/25, Abstract Synonyms = 24/25, Cambridge Category Comprehension Test = 64/64, Camel and Cactus Test, Words subtest = 63/64, Faces subtest = 63/64). RH's category fluency was normal for 8 semantic categories (animals = 19, birds = 13, dogs = 10, fruits = 20, tools = 9, vehicles = 10, boats = 9, and household objects = 20) and three phonemic categories ("F" = 21, "A" = 18 and "S" = 25). Her naming of 12 famous landmarks was flawless.

### 3.4.3 Performance on Episodic Memory Tests

RH underwent two detailed assessments of her anterograde memory functions. The results of her most recent assessment are shown in Table 3-2. On tasks of verbal recall, her performance was rather mixed. Her performance on story recall tests was somewhat weak. At the first assessment, she obtained comparable scores for both immediate and delayed recall, which were at the 10th percentile. At the second assessment her immediate recall was somewhat better, but her delayed recall was impaired. Her performance on another test of verbal recall memory (Paired Associate Learning: PAL: Warrington, 1996) was better, being within the lower end of normal performance at the first assessment (PAL time 1: 11/24, time 2: 19/24; both 10-25 %ile), but at the upper end of the average range at the second. The DPT was only administered at the second assessment. RH performed well on both the verbal recall and recognition subtests of the DPT. It should be noted that her verbal delayed recall on the DPT was poor. Lastly, her performance on the verbal subtest of the RMT was unimpaired at the first assessment (44/50; 50-75 %ile) and flawless at the second.

In contrast to her generally good verbal memory, visual memory functions were less well preserved. At the second assessment, her visual recall as tested by using the Rey-Osterreith complex figure (Osterrieth, 1944) was weak (below the 10th %ile), and her performance on the Shapes subtest of the DPT was clearly impaired. Turning to recognition memory, her performance on the non-verbal subtest of the RMT was normal, suggesting preserved recognition memory for unfamiliar human faces. She also performed within the normal range on the visual recognition subtest of the DPT (although her level of performance was markedly lower than on the verbal subtest of the DPT). However, her performance on the Topographical Recognition Memory Test was poor at both assessments (first assessment = 16/30; 5th %ile).

### 3.4.4 Summary

RH is a 58 year old woman who suffered a presumed ischaemic incident which resulted in right-sided hippocampal damage. The appearance of extrahippocampal areas appear to be normal. Although it is somewhat circular to resort to neuropsychological data to infer the integrity of cortical areas, the fact that RH's cognitive profile was completely normal apart from her memory impairments, is suggestive of highly selective lesions. Thus, cognitive modules requiring frontal, occipital, parietal and lateral and anterior temporal areas were functioning normally and repeated assessments demonstrated no evidence of progressive cognitive decline. Perhaps most importantly, RH performed entirely normally on a range of stringent tests of semantic memory. Neuroimaging tasks have indicated that semantic memory is underpinned by a neuronal network based upon temporal lobe structures (e.g. Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Patients with semantic dementia, who typically show a severe impairment on these tasks, present with clear cut damage in many anterior temporal areas (Chan et al., 2001; Mummery et al., 2000; Galton et al., 2001; Rosen et al., 2002). Thus, there appears little evidence to suggest that the neuroanatomical data should not be taken at face value, i.e. limited to the right hippocampus.

Chapter 4 reports RH's performance on tasks requiring the perception and short-term retention of spatial and non-spatial aspects of outdoor scenes. Chapter 6 reports an investigation of RH's recognition memory for words, outdoor scenes and unfamiliar faces, including estimation of the relative contribution of recollection- and familiarity-based memory processes to her performance on the tasks.

## 3.5 Patient Jon

### *3.5.1 Case description and neuroanatomical results*

Jon is a 26 year old, male, whose medical and neuropsychological history are described extensively elsewhere (Gadian et al., 2000; Maguire, Vargha-Khadem, & Mishkin, 2001; Vargha-Khadem et al., 1997). He was born prematurely after 26 weeks of gestation. He initially suffered apnoeic attacks and at the age of 3 years 10 months he had an unconfirmed convulsive episode. No hard neurological signs were apparent, but at the age of about 5 years his parents first noticed he had memory difficulties. Despite considerable problems with episodic memory, he attended mainstream school and achieved near-normal levels of general knowledge.

Vargha-Khadem et al., (1997) reported three neuroradiological investigations of Jon's hippocampal damage. Volumetric MRI demonstrated bilateral shrinkage of approximately 50% along the whole length of the hippocampus (Figure 3-3). T2 relaxometry, showed elevated T2 values from the hippocampus bilaterally, suggesting that the remaining hippocampal tissue in Jon is compromised. Finally, MR Spectroscopy was used to detect neuronal loss or damage outside of the hippocampus. The $^{1}H$ MRS values obtained for Jon were in the normal range on the left and marginally below on the right, suggesting that the extrahippocampal regions sampled were largely preserved. Subsequently, a functional MRI study by Maguire et al., (2001), demonstrated bilateral hippocampal activation whilst Jon recalled autobiographical memories. This indicates that some remaining tissue within Jon's hippocampi may, in fact, be functional.

### 3.5.2 Performance on general cognitive tests

A detailed description of Jon's neuropsychological profile is available elsewhere (Baddeley, Vargha-Khadem, & Mishkin, 2001). Neuropsychological assessments have found Jon's verbal IQ to be in the average range, whilst his performance IQ has risen over serial assessments. At the age of 19, he had a performance IQ of 120. At the age of 22 years, he achieved a score on Raven's Advanced Matrices (Set 1) equivalent to a performance IQ at the 90th percentile. His semantic knowledge was found to be unimpaired on several measures although his spelling is somewhat weak (Baddeley et al., 2001). Jon performs adequately on tests of executive function. In 1991, Jon was administered the Wisconsin Card Sorting Test and performed within the normal range (Baddeley et al., 2001). In 1997 he was administered the Behavioural Assessment of the Dysexecutive Syndrome Battery (BADS: Wilson, Alderman, Burgess, Emslie, & Evans, 1996). He obtained an overall profile score of 21/24 which is entirely satisfactory. However, Jon was noted to be easily distracted and have some trouble with decision making. His performance on verbal fluency tasks was normal on both these occasions (Baddeley et al., 2001). These results are summarized in Table 3-1.

### 3.5.3 Performance on Episodic Memory Tests

The data presented in Table 3-2 were collected when Jon was 20 years old except for the Paired Associate Learning Test and the Topographical RMT, which were administered when Jon was 22 years old. Jon has consistently been shown to be impaired on tests of recall but show preserved recognition memory (Table 3-2, but see also Vargha-Khadem et al., 1997; Gadian et al., 2000; Baddeley et al., 2001). His impairment of recall memory encompasses both verbal and non-verbal memoranda.

### *3.5.4 Summary*

Jon is a 27 year old male who has had profound memory problems since an episode of peri-natal anoxia. His hippocampi are markedly shrunken bilaterally, but extrahippocampal areas, including other structures in the medial temporal lobe, appear normal. Some remaining tissue in Jon's hippocampi may be functionally intact. Jon's day-to-day memory deficits are characterized by problems in spatial memory (including navigation and remembering the locations of objects), temporal memory (including orientation in time and date and remembering appointments, etc.) and episodic memory (remembering telephone conversations, television programmes, holidays, etc.). His neuropsychological profile is generally unremarkable apart from a selective memory impairment that encompasses tests of verbal and non-verbal recall but not recognition.

Chapter 4 reports Jon's performance on tasks requiring the perception and short-term retention of spatial and non-spatial aspects of outdoor scenes. Chapter 7 reports a preliminary investigation of Jon's recognition memory for outdoor scenes and unfamiliar faces, including estimation of the relative contribution of recollection- and familiarity-based memory processes to his performance on the tasks.

## 3.6 Patient KE

### *3.6.1 Case description and neuroanatomical results*

KE is a 57 year old, male, who worked as a market trader. His first language is Italian. He left school aged 11 years, but underwent further schooling and completed a Classics degree in the 1990s. Six months prior to the present investigation KE began to experience "panic attacks" manifested as episodes of anxiety, with no obvious triggers. The following month he continued to experience frequent daily panic attacks and began to notice some problems with episodic memory that rapidly became more severe. In addition, KE began to get lost when driving along a route from home to work upon which he had traveled three times a week for over twenty years. General neurological examination was entirely normal, although discussions relating to his symptoms would often precipitate a "panic attack".

A diagnosis of autoimmune encephalitis associated with anti-voltage gated potassium channel (anti-VGKC) antibodies was made and subsequently confirmed (the anti-VGKC antibody titre was markedly raised, see Vincent et al., 2004). Video EEG telemetry revealed that the "panic attacks" were partial seizures arising from the right temporal lobe. KE received immunomodulatory therapy in the form of plasma exchange and subsequent oral corticosteroids, and he was also started on anti-epileptic therapy, with complete cessation of his "panic attacks". After treatment there was subjective recovery of episodic memory function, although he continued to experience topographical disorientation.

A volumetric MRI brain scan revealed abnormal high signal restricted to the hippocampi and amygdalae with no abnormality elsewhere in the temporal lobe (Figure 3-4). There was mild associated atrophy within these affected medial temporal lobe structures but no atrophy affecting the remainder of the brain. There were no significant white matter lesions indicative of ischaemic vascular disease.

### 3.6.2 Performance on general cognitive tests

KE's performance on a range of cognitive tests is summarized in Table 3-1. A neuropsychological assessment was carried out 2 months prior to the present investigation. KE completed a 7-subtest version of the WAIS-R. Verbal and performance IQ was in the average range, although his rather low performance on the latter is partly due to a borderline defective score on the Block Design subtest. These scores may represent some degree of intellectual underfunctioning in view of his estimated high average premorbid IQ based upon educational level. He was only able to name four of the first ten words from the GNT, although this may partly be attributable to English not being his first language. He performed adequately on the easy Oldfield Picture Naming Test (28/30: Oldfield & Wingfield, 1965). KE performed adequately on several tests of visual and visuospatial perception (Object Decision, Number Location, Cube Analysis subtests of the VOSP). His performance on two tests of verbal fluency was poor, although this again may be confounded by the fact that English is his second language.

### *3.6.3 Performance on Episodic Memory Tests*

KE's performance on various tests of episodic memory is summarized in Table 3-2. He performed within the normal range on all tests of anterograde memory. Thus, verbal and non-verbal recall and recognition memory was consistently unimpaired. There was evidence from additional testing that retrograde memory was compromised (Chan & Warrington, in prep).

### *3.6.4 Summary*

KE is a 57 year old male who suffered autoimmune encephalitis which responded well to steroids. Abnormal signal return and some atrophy were noted in the hippocampi and amygdalae bilaterally. At the time of testing he was experiencing infrequent seizures and, at a cognitive level, topographical disorientation and retrograde memory problems. A standard neuropsychological assessment did not reveal clear impairment in any cognitive domain.

Chapter 4 reports KE's performance on tasks requiring the perception and short-term retention of spatial and non-spatial aspects of outdoor scenes.

## 3.7 Patient VC

### *3.7.1 Case description and neuroanatomical results*

VC, is a 74 year old, male, who worked as a chief engineer in large ships such as liners (for details see Kartsounis, Rudge, & Stevens, 1995; Cipolotti et al., 2001). In May 1992 he developed an apparent severe migraine attack followed by a seizure. In September 1993 he had two further seizures four days apart with a tachyrhythmia requiring cardioversion. Following these episodes, at the age of 67, he was left profoundly amnesic. Since then he had no further epileptic episodes. Apart from VC's dense amnesia, neurological examination was unremarkable except for a minor but variable impairment of pain assessed by pin prick over the left hand and foot.

The results of extensive neuroradiological investigations carried out with VC are reported elsewhere (Cipolotti et al., 2001; Cipolotti et al., 2006; Kapur, Thompson, Kartsounis, & Abbott, 1999; Kartsounis et al., 1995; Maguire, Frith, Rudge, & Cipolotti, 2005). Kartsounis et al., (1995) first reported VC as a single case study and documented MRI data suggesting that his lesions were confined to the CA1 and CA2 fields of the hippocampus. An FDG PET scan of VC detected evidence of hypometabolism in right thalamic and possibly right parietal areas as well as in both hippocampi (Kapur et al., 1999). Subsequent static radiological techniques have failed to discern any structural abnormalities in these areas. Qualitative MRI data reported in Cipolotti et al., (2001) noted increased signal return throughout the length of both hippocampi as well as abnormal signal return from the left amygdala. The same study reported volumetric MRI data showing the hippocampi to be significantly reduced in volume by 47% on the left and 44% on the right (Figure 3-5). The only other finding of note was reduction in volume of the left parahippocampal gyrus by 31%, which lies between 2-3 standard deviations below controls. Cipolotti et al., (2001) argued that this may reflect loss of efferent white matter fibres from the hippocampus which comprise, in part, the white matter of the parahippocampus. A functional MRI study found no hippocampal activation using the same paradigm that had revealed hippocampal activation in Jon (Maguire et al., 2005). Nevertheless, adjacent areas such as the parahippocampal gyrus were activated in VC. Lastly, Cipolotti et al., (2006) reported VBM and MR spectroscopy analyses which documented no significant abnormalities beyond the hippocampus. The selective nature of VC's hippocampal damage was hypothesized to be due to ischaemia coupled with a high energy requirement due to concurrent epilepsy (Kartsounis et al., 1995).

### 3.7.2 Performance on general cognitive tests

VC was first assessed in 1993 and was subsequently reassessed on 5 occasions. The results of his first four assessments, together with experimental investigations are reported elsewhere (Cipolotti et al., 2001; Kartsounis et al., 1995). The experimental investigations that will be described later took place following a fifth assessment (April 2000). The results of this assessment are reported in Table 3-1.

VC's Verbal IQ was in the upper end of the average range while his Performance IQ was at a very superior level, having improved consistently across assessments. Nominal skills as assessed by the GNT were at a high average level. His perceptual abilities have been consistently unimpaired. On three tests of frontal 'executive' skills (MCST, Hayling Test, Cognitive estimates: Shallice & Evans, 1978) his performance was entirely satisfactory. In particular on the MCST he obtained the 6 categories rapidly and made no perseverative errors. His attention and concentration abilities were clearly completely intact.

Cipolotti et al., (2006) reported a detailed investigation of VC's semantic memory skills using the same tests that were administered to RH (see above). VC's performance on stringent picture naming tasks, semantic and phonemic category fluency tasks and three comprehension tasks was entirely satisfactory.

### 3.7.3 Performance on Episodic Memory Tests

Throughout the five neuropsychological investigations, VC was assessed on a variety of anterograde memory tests involving both recognition and recall paradigms. The results of the most recent are shown in Table 3-2. It is worth mentioning that on any delayed recall test, VC is unable to score, since he invariably cannot remember the initial presentation of the materials. Verbal recall and recognition memory has been consistently impaired as assessed by Story recall, Paired-Associate learning, the verbal subtest of the RMT and the DPT. Visual recall memory was assessed using the Rey-Osterreith complex figure and the DPT. Performance on both tests was impaired. On two tests of non-verbal recognition memory (the Topographical RMT and the Doors subtest of the DPT), his performance was also impaired on every assessment. At the first two assessments, VC obtained impaired scores on the faces subtest of the RMT. Interestingly, however, his performance on latter assessments has been within the normal range (see Cipolotti et al., 2006).

### 3.7.4 Summary

VC is a 74 year old male who suffered an anoxic stroke due to a heart attack. Several neuroanatomical investigations have documented bilateral hippocampal damage, but no clear-cut evidence for anatomical or functional abnormalities elsewhere. VC presents with completely intact intellectual, nominal, perceptual, attentional and executive abilities. However, he has a very severe and global anterograde amnesia, the only exception being his face recognition abilities which may be somewhat better preserved. Similarly to RH, VC's performance on a comprehensive battery of semantic memory tests was completely normal, and suggests that anterior temporal lobe regions are functionally intact.

Chapter 4 reports VC's performance on tasks requiring the perception and short-term retention of spatial and non-spatial aspects of outdoor scenes. Chapter 6 reports an investigation of VC's recognition memory for words, outdoor scenes and unfamiliar faces, including estimation of the relative contribution of recollection- and familiarity-based memory processes to his performance on the tasks.

## 3.8 Patient JC

### *3.8.1 Case description and neuroanatomical results*

JC is a 60 year old, male, who worked as a safety advisor. In 2004 he sustained a prolonged ventricular fibrillation arrest and was resuscitated after 6 DC shocks. He remained in an intensive therapy unit for 3 days and upon reduction of sedation was noted to have cognitive problems, particularly in the memory domain. Neurological examination was completely unremarkable apart from brisk reflexes in the upper and lower limbs, which were symmetrical.

Using a scanner operating at 1.5 T, axial T2-wighted and coronal fluid attenuated inversion recovery (FLAIR) scans covering the whole brain were obtained from JC. A qualitative review of the images was independently performed by three expert neuroradiologists blinded to the purposes of the experimental investigations. Increased signal return was observed in the hippocampus bilaterally (Figure 3-6), consistent with ischaemia caused by a significant period of paraparesis. There was no evidence of abnormal signal return from any other part of the brain. In particular, no abnormalities were observed in the thalamus, temporal poles, anterior middle temporal and anterior parahippocampal gyri of both sides.

### 3.8.2 Performance on general cognitive tests

JC underwent a neuropsychological assessment in 2004, at the time of the experimental investigation reported in Chapter 6. When assessed on the WAIS-R, JC's verbal IQ was in the average range, whilst performance IQ was in the low average range. This may reflect a mild degree of underfunctioning on the performance subtests, since premorbid IQ based on educational and occupational level, and as estimated by the NART, was average. Nominal skills for common nouns were profoundly impaired. Thus, he failed to name any items on the GNT, and he only named 13 of the 30 items on the easy Oldfield Picture Naming Test. In contrast, naming of proper nouns was relatively spared. For example, he achieved an average score on a stringent naming test of proper nouns (McKenna & Warrington, 1980). JC's visual perception was normal (Fragmented Letters and Object Decision subtests of the VOSP). JC was impaired on several tests of executive functioning. He provided concrete interpretations of proverbs, and he failed an easy version of the Stroop Test, despite having no difficulty reading the colour words. Similarly, his phonemic fluency was severely reduced. Nevertheless, he was able to provide both solutions to the Weigl test (Weigl, 1941). These results are summarized in Table 3-1.

### 3.8.3 Performance on Episodic Memory Tests

Results from several recall and recognition tests are shown in Table 3-2. Similarly to VC, when assessed on a test of delayed recall, JC failed to remember the original presentation of the materials. Verbal recall was gravely impaired, as measured by a test of story recall and his performance on the Names subtest of the DPT. Similarly, visual recall was also very impaired as indexed by the Rey-Osterreith Complex Figure and the Shapes test of the DPT. JC's recognition memory was also severely impaired. Thus, his performance on both the words and the faces subtests of the RMT as well as the Topographical Recognition Memory Test was below the 5th percentile.

### 3.8.4 Summary

JC is a 60 year old male who suffered a prolonged period of ventricular fibrillatory arrest. Consistent with this, neuroradiological investigations detected abnormal signal return denoting ischaemic changes from his hippocampi bilaterally. Neuropsychological assessment revealed disruption of multiple modules of cognition. Although verbal intellectual and perceptual abilities were largely intact, impairment of nominal and executive abilities were noted. Most striking however, was his profound anterograde memory problems which affected recall and recognition for all types of materials. This profile is strongly suggestive of damage not only to bilateral medial temporal lobe areas but to other cortical areas as well.

Chapter 6 reports an investigation of JC's recognition memory for words, outdoor scenes and unfamiliar faces, including estimation of the relative contribution of recollection- and familiarity-based memory processes to his performance on the tasks.

## 3.9 Overall Summary

All of the patients described above have reasonably focal cerebral lesions and have been well characterized from a neuropsychological perspective. Whilst several have common regions of brain damage (e.g. Jon, KE, VC and to a certain extent, RH), it would be inappropriate to group them together and make comparisons with a control group since this assumes that the patients are homogenous with respect to their deficits (McCloskey, 2001). In fact, it is clear that important differences exist between the patients. Therefore, the investigations in the following chapters all utilize a multiple case study methodology, where each patient's performance is considered separately.

It has been suggested on the basis of both patient data and animal data that ischaemia does not result in selective hippocampal lesions (Markowitsch et al., 1997; Mumby et al., 1996; but see Rempel-Clower et al., 1996; Zola-Morgan, Squire, Rempel, Clower, & Amaral, 1992). This issue is clearly of relevance to patients RH, Jon and VC who are argued to have relatively selective hippocampal damage. Given the scarcity of patients with apparently selective hippocampal lesions it would seem sensible to characterize the cognitive deficits in these patients, whilst accepting that some of these impairments may be due to undetectable damage outside of the hippocampus. However, strong assertions about structure / function relationships should only be made when findings across patients are broadly consistent, and understandable with reference to data from other sources (e.g. functional neuroimaging, animal studies).

**Table 3-1: Cognitive test scores**

|  | MH |  | RH |  | Jon |  | KE |  | VC |  | JC |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Intelligence** |  |  |  |  |  |  |  |  |  |  |  |  |
| VIQ | 106 | Ave | 109 | Ave | 108 | Ave | 99 | Ave | 107 | Average | 100 | Ave |
| PIQ | 93 | Ave | 101 | Ave | 120 | Sup | 92 | Ave | 138 | Very Sup | 86 | Low ave |
| Matrices | n.t. |  | 6/12 | 50-75 %ile | 11/12 | >75 %ile | 7/12 | 50-75 %ile | 8/12 | >75 %ile | n.t. |  |
| NART | 105 | Ave | 126 | Sup | n.t. |  | n.t. |  | 116 | High ave | 105 | Ave |
| **Semantic memory** |  |  |  |  |  |  |  |  |  |  |  |  |
| Graded Naming Test | 17/30 | 25-50 %ile | 27/30 | >75 %ile | n.t. |  | 4/10 | <5 %ile | 24/30 | 75 %ile | 0/30 | <5 %ile |
| **Object Perception** |  |  |  |  |  |  |  |  |  |  |  |  |
| Fragmented letters | 16/20 | 5 %ile | n.t. |  | n.t. |  | n.t. |  | 20/20 |  | 18/20 | >5% cut |
| Silhouettes | 12/30 | <5 %ile | n.t. |  | n.t. |  | n.t. |  | n.t. |  | n.t. |  |
| Object decision | 12/20 | <5 %ile | 19/20 | >5% cut | n.t. |  | 17/20 | >5% cut | 18/20 | >5% cut | 16/20 | >5% cut |
| **Spatial Perception** |  |  |  |  |  |  |  |  |  |  |  |  |
| Number Location | 10/10 | >5% cut | 9/10 | >5% cut | n.t. |  | 8/10 | >5% cut | n.t. |  | n.t. |  |
| Cube Analysis | 8/10 | >5% cut | 10/10 | >5% cut | n.t. |  | 10/10 | >5% cut | 10/10 | >5% cut | n.t. |  |
| **Executive functioning** |  |  |  |  |  |  |  |  |  |  |  |  |
| Verbal fluency (fas) | n.t. |  | n.t. |  | 50 | 75 %ile | n.t. |  | n.t. |  | n.t. |  |
| Verbal fluency (s) | n.t. |  | 18 | 50-75 %ile | n.t. |  | 8 | 5-10 %ile | 17 | 50-75 %ile | 2 | <5 %ile |
| Verbal fluency (animals) | n.t. |  | 19 | 25-50 %ile | 20 | 25-50 %ile | 11 | 5% ile | 14 | 25-50 %ile | 3 | <5 %ile |

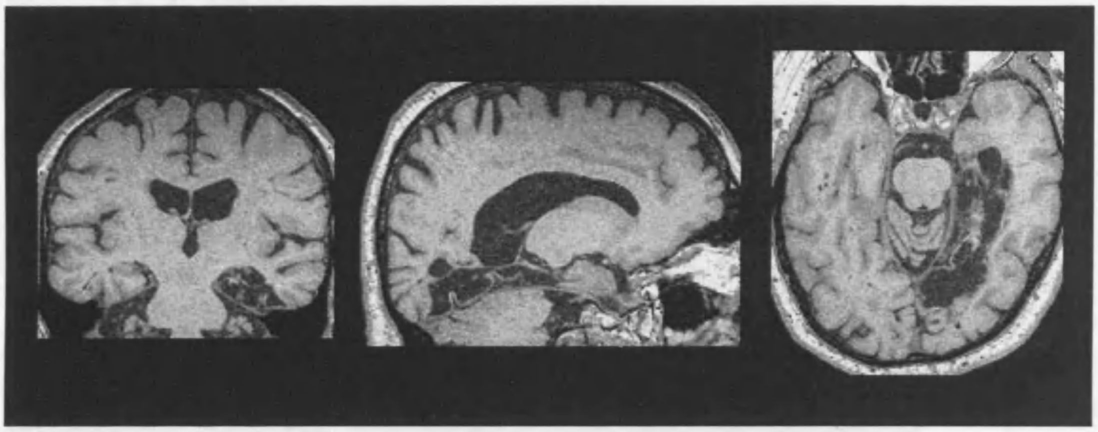
**Legend**: Ave = average; Sup = superior; n.t. = not tested; %ile = percentile; cut = cutoff

**Table 3-2: Memory test scores**

| | MH | | RH | | Jon | | KE | | VC | | JC | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Story recall** (imm) | n.t. | | 18 | 10-25 %ile | n.t. | | n.t. | | 6 | <10 %ile | 7 | <10%ile |
| **Story recall** (del) | n.t. | | 9 | <5 %ile | n.t. | | n.t. | | 0 | <10%ile | 0 | <10%ile |
| **Paired associate Learning** | | | | | | | | | | | | |
| Time 1 | n.t. | | 16/24 | 25-50 %ile | 16/24 | 10-25 %ile | n.t. | | 3/24 | <5 %ile | n.t. | |
| Time 2 | n.t. | | 24/24 | >75 %ile | 16/24 | <5 %ile | n.t. | | 7/24 | <5 %ile | n.t. | |
| **Rey Figure** (copy) | n.t. | | 33/36 | >75 %ile | n.t. | | n.t. | | 35/36 | 90 %ile | 35/36 | 50-75 %ile |
| **Rey Figure** (imm recall) | n.t. | | 8/36 | <10 %ile | n.t. | | n.t. | | 3/36 | <5 %ile | 0/36 | <5 %ile |
| **RMT** Words | 47/50 | >75 %ile | 50/50 | >75 %ile | 45/50 | 25 %ile | 46/50 | 75 %ile | 35/50 | 5 %ile | 28/50 | <5 %ile |
| **RMT** Faces | 30/50 | <1 %ile | 39/50 | 25 %ile | 41/50 | 25 %ile | 44/50 | 50-75 %ile | 39/50 | 25 %ile | 34/50 | <5 %ile |
| **Topographical RMT** | 27/30 | >75 %ile | 18/30 | 5-10 %ile | 25/30 | 25-50 %ile | 22/30 | 25-50 %ile | 12/30 | <5 %ile | 14/30 | <5 %ile |
| **Doors & People** | | | | | | | | | | | | |
| Verbal Recall | 28/36 | 75 %ile | 30/36 | 75 %ile | 6/36 | <5 %ile | 21/36 | 10-25 %ile | 7/36 | <10 %ile | 1/36 | <5 %ile |
| Verbal Recall (del) | 10/12 | | 7/12 | | n/a | | 7/12 | | 4/12 | | 0/12 | |
| Verbal Recognition | 17/24 | 50-75 %ile | 21/24 | >75 %ile | 19/24 | 50 %ile | 16/24 | 25 %ile | 7/24 | <5 %ile | 11/24 | <5 %ile |
| Visual Recall | 24/36 | 10-25 %ile | 10/36 | <1 %ile | 6/36 | <1 %ile | 33/36 | 50-75 %ile | 12/36 | <5 %ile | 8/36 | <1 %ile |
| Visual Recall (del) | 9/12 | | 6/12 | | n/a | | 12/12 | | 4/12 | | 0/12 | |
| Visual Recognition | 18/24 | 50-75 %ile | 17/24 | 25 %ile | 20/24 | 50-75 %ile | 18/24 | 50 %ile | 10/24 | <5 %ile | 12/24 | <5 %ile |
| **Famous Faces** | 10/12 | n/a | 9/12 | n/a | n.t. | | n.t. | | 3/12 | n/a | 8/12 | n/a |

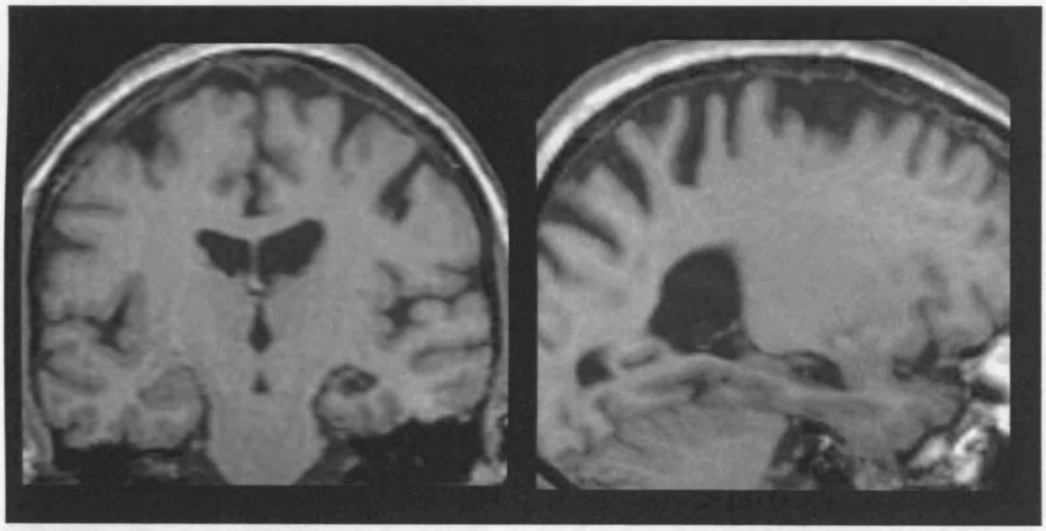
**Legend**: imm = immediate; del = delayed; n.t. = not tested; %ile = percentile; n/a = not available

**Figure 3-1: MH's lesions**



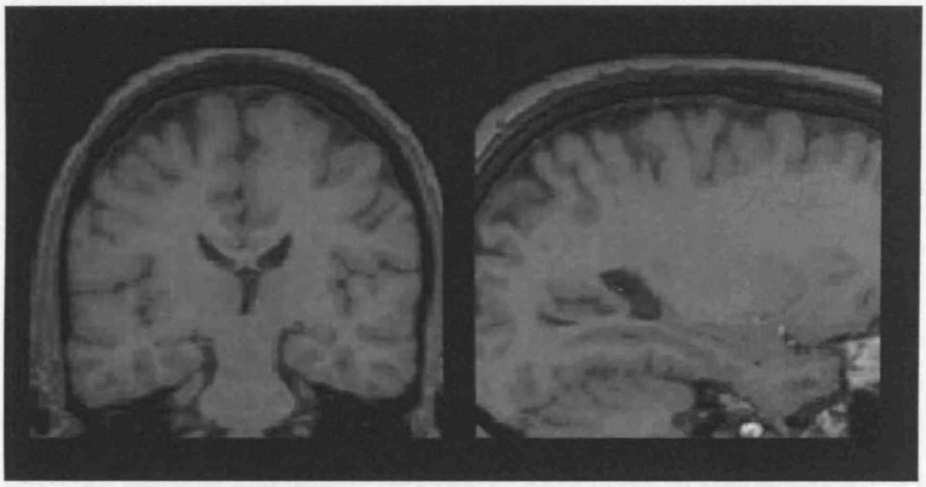
**Legend**: Coronal, sagital and axial sections of MH's brain, showing medial occipital and temporal infarction including posterior portions of the hippocampus.

**Figure 3-2: RH's lesions**



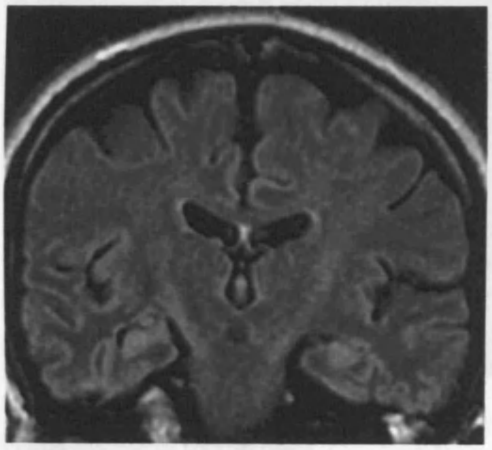
**Legend**: Coronal and sagital sections of RH's brain, showing shrinkage of the right hippocampus.

**Figure 3-3: Jon's lesions**



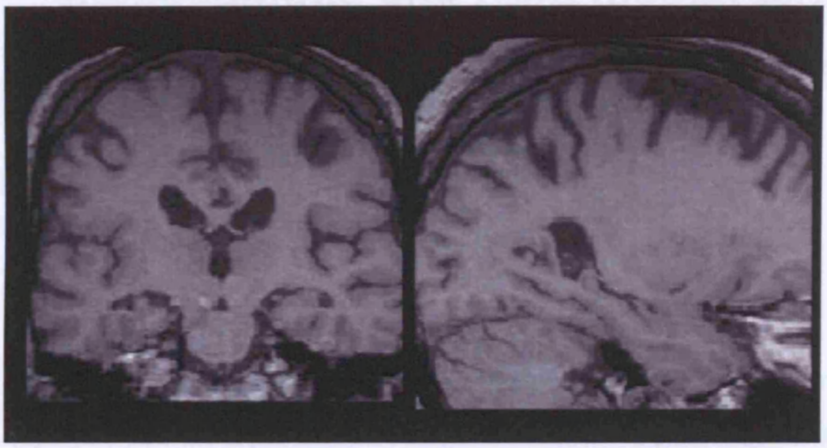
**Legend**: Coronal and sagital sections of Jon's brain, showing shrinkage of the hippocampus bilaterally.

**Figure 3-4: KH's lesions**



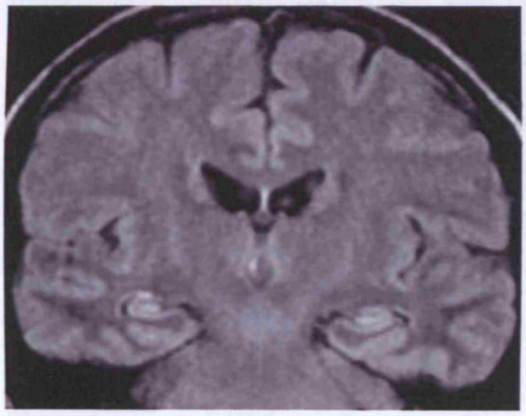
**Legend**: Coronal section of KE's brain, showing abnormal signal return from the hippocampus bilaterally.

**Figure 3-5: VC's lesions**



**Legend**: Coronal and sagital sections of VC's brain, showing shrinkage of the hippocampus bilaterally.

**Figure 3-6: JC's lesions**



**Legend**: Coronal section of JC's brain, showing abnormal signal return from the hippocampus bilaterally.

# 4 Chapter 4: The involvement of the hippocampus and right medial temporal lobe in the perception and short-term retention of topographical information

## 4.1 Background

In Chapter 2 it was demonstrated that the perception of visually degraded single objects could be impaired by damage to medial occipitotemporal structures on the right. The focus of this chapter is the perception and short-term retention of another type of visual material – outdoor scenes. This investigation was carried out with Tom Hartley (TH), Neil Burgess (NB) and various clinical collaborators. The study was initially conceived by TH and NB, and TH designed and constructed the experimental materials. I undertook all of the data collection reported in this chapter, and was involved in developing and refining the experimental tests as well as data analysis and interpretation. A manuscript reporting our results has been submitted for publication by Hartley et al., and this manuscript forms the backbone of this chapter.

## 4.2 Introduction

Since the case of HM was first described (Scoville & Milner, 1957) the human medial temporal lobe (MTL) has been implicated in the formation of new long-term memories. All forms of consciously accessible long-term memory are at risk from MTL damage (Squire et al., 2004). Where this includes extensive bilateral damage to the hippocampus, memory deficits are invariably marked by anterograde amnesia for personally experienced events (Spiers et al., 2001c).

Short-term memory (STM) is traditionally assumed to rely on distinct processes from long-term memory (LTM: e.g. Atkinson & Shiffrin, 1971). In terms of neural systems, some neuropsychological patients show spared LTM and impaired STM (Saffran & Marin, 1975; Shallice & Warrington, 1970) and others show impaired LTM but spared STM (e.g. Baddeley & Warrington, 1970; Cave & Squire, 1992; Drachman &

Arbit, 1966; Milner, 1971) However, these dissociations do not necessarily imply separate neural substrates specialized for short- and long-term memory per se. In particular, short-term memory performance in different tasks relies on different neural substrates, often reflecting strategic rehearsal or reactivation of domain-specific sensory and motor resources (Baddeley, 1986; Baddeley & Hitch, 1974). Thus the multiple neural systems supporting STM overlap with those supporting online processing of specific types of stimuli (e.g. speech perception/production or visuo-spatial sensorimotor control). Similarly, although declarative LTM depends on the medial temporal lobe (Squire et al., 2004), the exact role of the hippocampus within this remains the subject of much debate, and may not be restricted to LTM. Here we examine the hippocampal contribution to perception and STM, using stimuli explicitly designed to require hippocampal processing on theoretical grounds described below.

Many argue that the unique anatomy of the hippocampus enables the rapid formation of cross-modal associations (Marr, 1971; McClelland et al., 1995; Rolls, 1996), and that this gives it a crucial role in encoding personally experienced events and their context ("episodic memory", see e.g. Aggleton & Brown, 1999; Gaffan & Hornak, 1997a; Mayes et al., 2002; O'Keefe & Nadel, 1978; Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997). Related proposals for hippocampal function seek to further constrain the nature of hippocampal processing as encompassing the formation of configural associations between otherwise independent elements (Rudy & Sutherland, 1989; Rudy & Sutherland, 1995), or of flexible relations between discontiguous stimuli (Eichenbaum & Cohen, 2001; Wallenstein et al., 1998). Here we focus on another such proposal, namely that the hippocampal role in episodic memory evolved out of an ability to support a flexible allocentric representation of environmental spatial relationships or 'cognitive map' (O'Keefe & Nadel, 1978), which can be seen as implementing a specifically spatial form of flexible relational processing (Eichenbaum & Cohen, 2001). Although this type of representation would be well suited to LTM, for instance permitting a place to be recognized when later encountered from a novel perspective (Burgess, 2002; Milner et al., 1999) or contributing to the memory for the spatial context of an event (O'Keefe & Nadel, 1978), it would also imply a role in on-line processing of location and orientation relative to the environment. Accordingly, we sought to investigate hippocampal involvement in processing environmental spatial relationships (or 'topography').

Evidence for the cognitive map theory comes from neurophysiological experiments showing striking spatial correlates of neuronal firing in freely moving rats. “Place cells” in the hippocampus fire whenever the rat is at a particular location (O'Keefe & Dostrovsky, 1971), as determined by the geometry of the environment (O'Keefe & Burgess, 1996) and regardless of the presence or absence of particular subsets of cues (Muller, 1996; O'Keefe, 1976) or the animal's orientation (at least in open environments, Muller, Bostock, Taube, & Kubie, 1994). “Head-direction cells"”, with a compass-like representation of heading (Taube, Muller, & Ranck, Jr., 1990), and very recently “grid cells”, whose firing shows a remarkably regular grid-like spatial pattern (Hafting, Fyhn, Molden, Moser, & Moser, 2005), have been found in the regions providing input to the rat hippocampal formation. Neurons with similar properties to place cells have now been found in primates (Ono et al., 1991; Rolls, Robertson, & Georges-Francois, 1997) and in humans (Ekstrom et al., 2003). Neuropsychological experiments have also shown the hippocampus to be specifically required when a flexible or allocentric representation of spatial layout is required. For instance in recognizing object locations when tested from a new viewpoint (Abrahams et al., 1997; Holdstock et al., 2000; King et al., 2002) and in large-scale navigation (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001a). In addition, functional neuroimaging studies indicate the specific involvement of the hippocampus in accurate navigation (Hartley et al., 2003; Maguire et al., 1998) and allocentric spatial processing (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). Finally, some lateralization of function is indicated by studies of unilateral temporal lobectomy, with right-sided damage specifically impairing spatial tasks such as object-location memory, navigation and map drawing (Abrahams et al., 1997; Bohbot et al., 1998; Nunn et al., 1999; Pigott & Milner, 1993; Smith & Milner, 1981; Spiers et al., 2001b; see Burgess et al., 2002 for a review). In summary, environmental spatial relationships (or 'topography') at the very least provide a particularly clear cut example of stimuli that require processing by the hippocampus.

Whilst the cognitive map theory proposes that the hippocampus is necessary for flexible allocentric representations of the environment, it may not be required for the perceptual processing of scenes. The bulk of the experimental evidence suggests that ability is underpinned by extrahippocampal areas. For example, topographical disorientation – a relatively selective impairment in the ability to use landmarks for the purpose of wayfinding – has been associated with damage to the parahippocampal gyrus (Habib & Sirigu, 1987; Takahashi & Kawamura, 2002; Epstein, Deyoe, Press, Rosen, & Kanwisher, 2001). A related disorder – the failure to recognize familiar buildings and landscapes – has been associated with damage to the lingual gyrus (Takahashi & Kawamura, 2002). Unfortunately, these studies rarely contrasted perceptual versus mnemonic processing of scenes directly and often the photographs of scenes or buildings could be recognized by the identification of distinctive local features. Nevertheless, imaging studies are in broad agreement with the neuropsychological data, also implicating the posterior parahippocampus and lingual gyrus in the perceptual processing of spatial scenes (Epstein et al., 2003; Epstein & Kanwisher, 1998a) and buildings (Aguirre et al., 1998).

The hippocampal contribution to processing over short timescales has been investigated previously (see Ranganath & Blumenfeld, 2005 for a brief review). Cave and Squire (1992) examined immediate memory performance on spatial and non-spatial tasks, finding no impairment. Ryan and colleagues (Ryan, Althoff, Whitlow, & Cohen, 2000; Ryan & Cohen, 2004) investigated the effects of hippocampal damage on implicit memory by monitoring eye movements as participants looked at spatial scenes. Healthy participants sampled repeated scenes less thoroughly than novel scenes, while showing more intensive sampling of locations in repeated but modified scenes where elements had been added, deleted or moved. Hippocampal patients showed similar effects after short delays but did not show the increased sampling of modified locations after long delays, indicating impaired implicit LTM (but not STM) for the composition of scenes. However, the stimuli used in these experiments (2-D designs and scenes presented from a single point of view) may have allowed successful performance on the basis of visuo-spatial STM, without requiring access to an allocentric topographical representations in the hippocampus. Very recently, evidence for a relatively specific role of the hippocampus in STM for *relational* information has been reported (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). The authors argued that hippocampal damage impaired the ability to maintain object-location conjunctions in STM, but not the ability to remember either objects or locations themselves. Unfortunately, the performance of the individual hippocampal patients is not reported and nor is it directly contrasted with the healthy controls, so the degree of impairment is unclear. Additionally, this form of relational memory clearly has a substantial spatial component, although not necessarily requiring allocentric processing. It therefore remains unclear whether the hippocampus is required for all aspects of relational or configural STM.

Another recent study, using topographical stimuli (comparison of images of irregularly shaped rooms seen from shifted viewpoints) suggested that the human hippocampus does play a role in allocentric processing and/or storage over short timescales. Lee et al. (2005a) examined performance in a range of 4-alternative odd-one-out tasks designed to tax perceptual processing for different types of material. They found that patients with focal hippocampal damage were specifically impaired on spatial scene oddity whereas patients with larger MTL lesions showed a greater range of perceptual deficits including problems with face and object processing. This study appears to implicate the hippocampus with aspects of scene processing over short durations. However, there are a number of important caveats to bear in mind. First, it is arguable that the odd-one-out paradigm involves a significant memory load (because of the large number of comparisons that must be borne in mind during performance of the task). Second, it is not clear that the short duration deficit is specifically spatial due to a ceiling effect in the non-spatial stimuli. Third, the impairment of the hippocampal group was rather modest. For example, despite being significantly impaired when compared to aged matched controls (47 years old), the patients were well within the range of healthy adults aged 66 years old. One might therefore question the functional relevance of the group's impairment. In an earlier paper, Lee et al. (2005b) used morphing to create a range of visually similar stimuli (including faces, objects and scenes) which subjects learned to discriminate or match with a sample image. Hippocampal patients were found to be impaired in learning the scene discrimination. The authors attributed this to a perceptual failure. However, because both tasks involved learning with feedback over several presentations of the same stimuli it could be argued that the task was not purely perceptual.

A study by Shrager et al., (2006) failed to replicate the findings of Lee et al., (Lee et al., 2005b; Lee et al., 2005a), not only in patients with selective hippocampal damage, but also in two patients with more extensive MTL lesions. These latter two patients had very extensive lesions involving complete destruction of the perirhinal, entorhinal cortices and much of the parahippocampal gyri bilaterally. None of the patients performed differently from healthy controls on any of the perceptual tasks, including a task involving the matching of scenes. However, the latter test involved morphed images of similar scenes, without manipulating viewpoint, and therefore could be solved without allocentric representations (as was also the case for the stimuli used by Lee et al., 2005b). These results indicate that further investigation of the time course of the involvement of MTL structures in perception and memory is warranted.

In the current study we examined the hippocampal contribution to perception and short-term memory for the topographical and non-spatial information in spatial scenes. Inspired by Piaget and Inhelder (1967), we used computer-generated landscapes containing 4 mountains in which the topography of the landscape (i.e. the geometry of the surface) and its non-spatial visual features could be independently varied. See Figure 4-1 and Figure 4-2. Perception was tested by 4-alternative match to sample, to minimize any memory load (cf. odd-one-out procedures), while memory is tested by 4-alternative delayed match to sample (delay=2s). In topographical tests, participants matched a sample scene to the target (the same place from a different viewpoint) rather than three foil scenes with different topography. In non-spatial tests, participants matched global non-spatial properties of the scene reflecting the "prevailing conditions" when the picture was taken (i.e., weather, time-of-day and time-of year as reflected by the conjunction of parameters such as lighting, cloud cover and vegetation color). In both tests, the non-tested (spatial/non-spatial) attributes were the same for the 4 choices but different from the sample. The changes in both the viewpoint and the non-spatial properties between sample and target serve to make the topographical tests dependent on matching the allocentric topographical information in the scenes, and less susceptible to solution by visual pattern matching. The similarity of the targets and foils was varied to ensure that the performance of healthy young participants did not differ significantly across the 4 tasks (place perception, place memory, non-spatial perception, non-spatial memory) to avoid any non-specific effects of difficulty.

## 4.3 Methods

### *4.3.1 Participants*

#### 4.3.1.1 Neurological patients

Five neurological patients took part in the study. These were, KE, VC, RH, Jon, and MH. Their detailed case reports and results of neuroimaging and neuropsychological assessments are all reported in the previous chapter. Selected demographical information for each patient is shown in Table 4-1.

#### 4.3.1.2 Healthy adult controls:

28 healthy adults were recruited to serve as a control group. 20 of these were older adults selected to be representative of the older patients in the study (RH, VC, KE and MH). 8 of these were young adults selected to match patient Jon. The demographics of both control groups are shown in Table 4-1.

### *4.3.2 Materials*

Landscape stimuli were based on a height field (a 2D array of altitudes) constructed using MATLAB 6.1 (Mathworks Inc.). Each stimulus heightfield (see Figure 4-1a) was built by summing six 256x256 height fields: four hills of varying shapes and sizes (Figure 4-1b), placed at different locations around the centre, a semicircular range (in the background of the stimulus images) and a smoothed interpolated 2D noise field. The noise served to add realism and additional unique small scale topographical features.

The heightfields were rendered with realistic lighting and texture (Terragen v0.9 Planetside Software). Parameters supplied to the rendering software could be used to determine the location and orientation of a virtual camera. In addition sunlight direction (elevation), cloud cover, atmospheric conditions and surface texture parameters were varied. Eight different combinations of these parameters were used to produce eight distinct sets of "prevailing conditions" under which each height field could be rendered (Figure 4-1c).

Each scene was rendered from a virtual camera facing the origin and placed at one of seven predefined viewpoints, at an altitude of 30 units and spaced at fifteen degree intervals around the origin at a radius of 128 units (as indicated in Figure 4-1a).

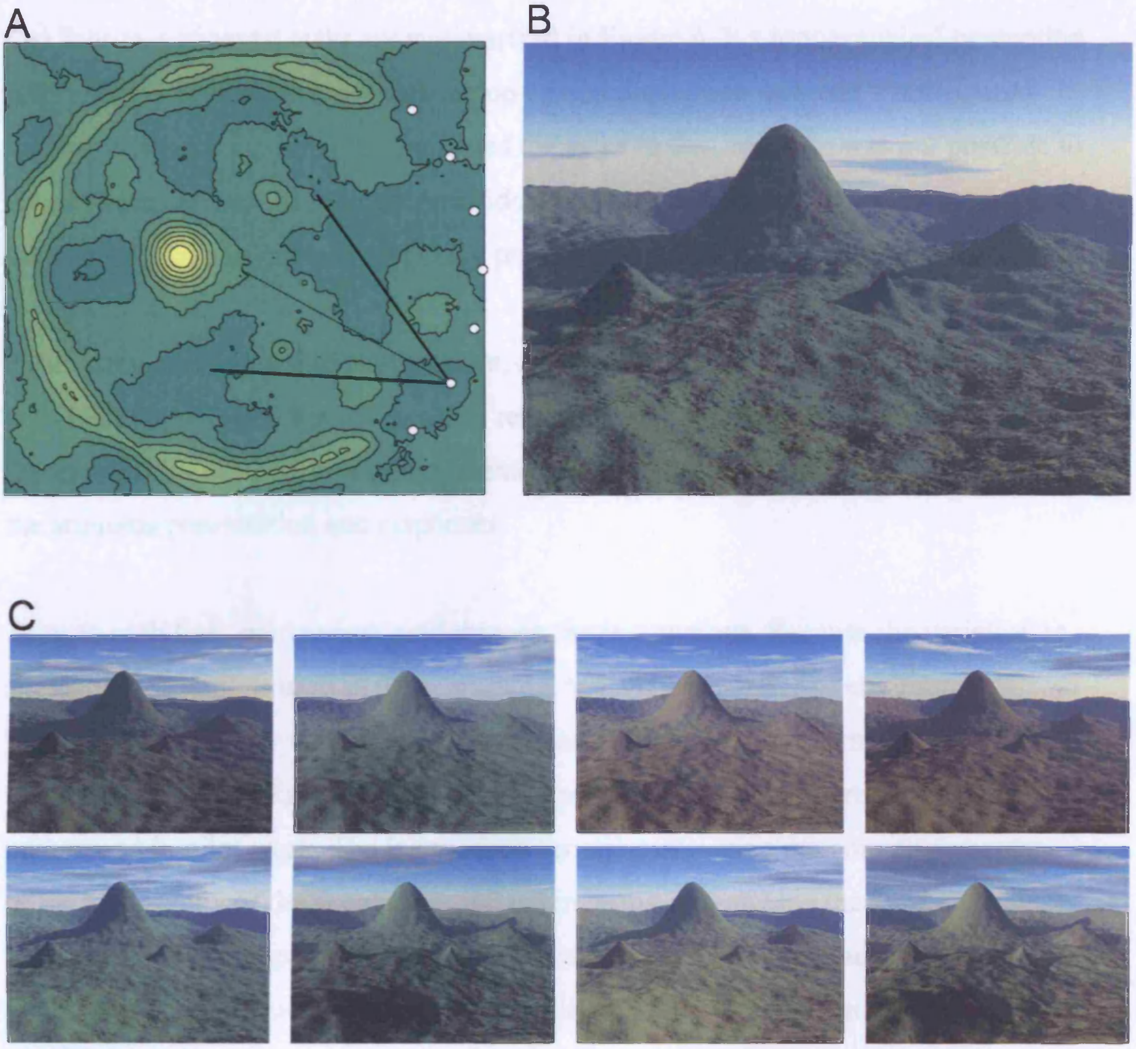
Stimuli were systematically generated to fit the constraints described below, while ensuring that the peaks of all four hills were clearly visible in each rendered scene. The four experimental tasks detailed below were pilot tested in a group of elderly women. This, and other pilot data from younger volunteers, was used to select the final set of stimulus items from a larger set generated at random, and to modify items where necessary, with the objective of matching performance across the four experimental tasks.

**Table 4-1: Control group demographics and comparison of control participant and patient scores on measures of IQ, mental rotation and scene recognition memory.**

| **Subject/Group** | **Sex** | **Age** | | **Matrices**[a] | | **Flags Test**[b] | | **Topographical RMT**[c] | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| Young Controls | ♂8:0♀ | 28.4 (2.9) | 24-33 | 10.9 (1.5) | 8-12 | 9.8 (0.5) | 9-10 | 26.6 (4.2) | 18-30 |
| Jon | ♂ | 26 | | 11 | | 10 | | 25 | [normal range] |
| Old Controls | ♂11:9♀ | 65.2 (6.9) | 51-80 | 8.9 (1.7) | 6-12 | 9.7(0.5)[d] | 9-10 | 28.5 (1.4)[e] | 24-30 |
| KE | ♂ | 57 | | 7 | | 10 | | 22 | [normal range] |
| VC | ♂ | 78 | | 8 | | 10 | | 12 | [<5%ile] |
| RH | ♀ | 58 | | 6 | | 8 | | 16 | [5%ile] |
| MH | ♂ | 70 | | n.t.[f] | | 10 | | 27 | [normal range] |

**Legend**: a = Raven's Advanced Progressive Matrices Set I (Raven, 1976); b = a simple 10-item test of planar mental rotation using flags, based on Thurstone and Jeffreys, (1956); c =from Warrington (1996); d = one participant's data missing; e = two participants' data missing; f = MHs intelligence is average (VIQ=106, PIQ=93) as assessed on the WAIS-R.

Figure 4-1: Stimuli used in the 4 Mountains Test



**Legend**: Stimuli used for the 4 Mountains Test. A) Each landscape is comprised of four scattered hills of varying shape and size within a semicircular range of hills. Each stimulus used in the experiment used a unique configuration of hills. Smoothed interpolated 2D noise was also added to the heightfield to produce unique, naturalistic variations between landscapes. The scenes are rendered as through a virtual camera sited at one of seven points (shown by white circles) equidistant from the centre of the heightfield. B) Typical example of a rendered stimulus image based on topography shown in A C) Topography shown in A, rendered under the eight different combinations of non-spatial parameters used in the experiment (see text). These combinations vary cloud cover, lighting (apparent elevation of sun), texture and colour of vegetation: properties that combine to create an overall impression of the distinctive prevailing conditions at a particular time. For each combination, lighting direction (apparent azimuth of sun) could come from either due “north” or “south” relative to camera locations shown in A.

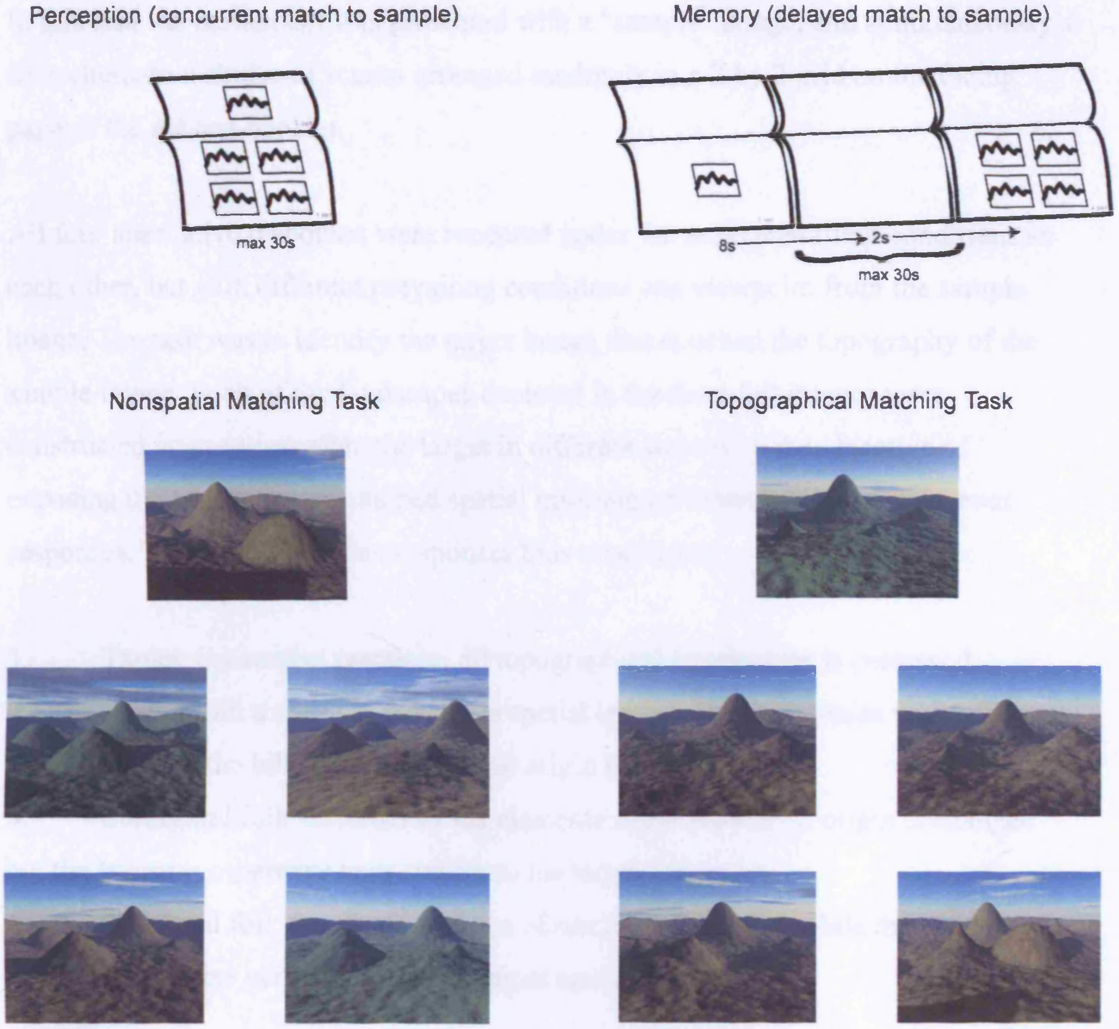
### 4.3.3 Experimental Tasks

The four experimental tasks are summarized in Figure 4-2; a topographical perception task, a topographical memory task, a non-spatial perception task and a non-spatial memory task. All participants completed the tasks in this order - it was not possible to counterbalance task order for the individual patients, and the order was preserved for the control group in order to match the procedure used for the patients.

Participants were seated in a quiet room, and gave informed consent in accordance with UCL or UCLH Ethics Committee requirements. Each task was presented in a separate A4 booklet, with the experimenter turning the pages to control the timing of the stimulus presentation and responses.

Prior to each task, participants read through the instructions. Because the variation in prevailing conditions used in the non-spatial tasks corresponded to environmental features that normally vary over time these tasks were framed in terms of matching the "time of day and time of year" – a description that we found participants readily understood in pilot work. The instructions for tasks involving memory or perception of the topography of the scene were framed in terms of matching the "place". Participants then completed three practice items, with verbal feedback from the experimenter which, where necessary, drew their attention to relevant features of the stimuli. Participants were told to ask for clarification (which reiterated relevant information in the written instructions) if they were unsure of what to do.

**Figure 4-2: Procedure used to administer the 4 Mountains Task**



**Legend**: Top: Timing and layout of test items. Perceptual tests used a concurrent match to sample task. Participants had a maximum of 30s to choose one picture from four alternatives (on the lower page of the test booklet) that matched the sample image (upper page). Memory tests used a delayed match to sample task, interposing a 2s delay (during which a blank page was shown) between sample and test images. Bottom: Examples of non-spatial and topographical items. In non-spatial tests participants had to match images based solely on the non-spatial features in the scene; cloud cover, lighting, texture and colour of vegetation. The target is shown at the bottom left of the four choices. Topographical features were varied between sample and test images. In topographical tasks subjects had to match images based solely on the topographical features; viewpoint, and non-spatial features were varied between sample and test images. The target is shown at the top left of the four choices. The spatial foil is at the top right, the configural foil at the bottom left, and the elemental foil at the bottom right (2 hills changed as in the topographical memory test), see Methods.

#### 4.3.3.1 Topographical Perception

In this task the participant was presented with a "sample" image, and simultaneously a four-alternative choice of scenes arranged randomly in a 2 by 2 grid on the facing page of the A4 test booklet.

All four alternative responses were rendered under the same prevailing conditions as each other, but with different prevailing conditions and viewpoint from the sample image. The task was to identify the target image that matched the topography of the sample image. Each of the landscapes depicted in the three foil images were constructed so as to resemble the target in different ways with the objective of exposing the nature of any retained spatial information in the pattern of erroneous responses. The four alternative responses thus comprised:

1. Target: the correct response, all topographical information is preserved.
2. Spatial foil: a scene in which the spatial layout of the mountains was different, but the order of the hills about the central origin is unchanged.
3. Configural foil: the order of the elements about the central origin is changed but the layout is otherwise very similar to the target scene.
4. Elemental foil: the shape and size of one hill is changed, while the spatial layout is otherwise very similar to the target scene's.

To prevent participants being misled by local matches with small scale features and to ensure that each of the foil landscapes was unambiguously different from any point of view (as any two real landscapes would be) each foil used a unique pattern of 2D noise, and the spatial layout (polar coordinates of hill locations) was also jittered slightly for configural and elemental foils. However, the most obvious differences from the target topology were those resulting from the deliberate manipulation of spatial layout, configuration and elemental shape and size as described above.

#### 4.3.3.2 Topographical Memory

The topographical memory task was essentially the same as the place perception task, except that the sample image was presented in isolation for approximately 8 seconds.

The page of the booklet was turned and participants then saw a blank page for approximately 2 seconds before being presented with the four way choice on the next page.

The four alternative responses were generated for each sample landscape in the same way as the perceptual task, but in order to match difficulty with the perceptual version of the task it was necessary to make the elemental foils more distinctive by changing the shape and size of two of the hills.

#### 4.3.3.3 Non-spatial Perception

In this task participants had to match the prevailing conditions in the sample image to one of the four alternatives presented simultaneously in a 2 by 2 grid on the facing page of the booklet. Each of the four alternative scenes depicted the same place seen from different viewpoints and under a different set of prevailing conditions. Only the combination of texture/colour, lighting and cloud cover was unique to target and sample images – individual elements might also match in foil scenes. Rendered landscapes based on each set are shown in Figure 4-1c.

#### 4.3.3.4 Non-spatial Memory

Items in the non-spatial memory task took the same form of stimuli as the non-spatial perception task, and participants had the same aim, identifying the scene in which prevailing conditions matched those in the sample image, but in this case after a very brief delay. As in the place memory task, participants were given approximately 8 seconds to study the sample image, before the stimulus was obscured and replaced after approximately 2 seconds with the four alternatives arranged in a 2 by 2 grid. As in the non-spatial perception task, the three foil images were generated by randomly rendering the same landscape with a mismatched set of prevailing conditions selected at random.

## 4.4 Results

The mean scores and ranges of scores for both of the control groups on all four tests are shown in Table 4-2 and Figure 4-3, together with the raw scores and percentile scores of all five patients.

To consider first the healthy controls: the performance of the young control group showed no significant effect of task (F(3,21)= 0.75; p>0.05). The performance of the older control group did show an effect of task (F(3,57)= 6.50; p=0.001), with post-hoc tests confirming that performance on the Topographical Memory subtest was significantly poorer than performance on all other subtests. Consistent with this, there was a weak correlation between age and topographical memory performance (r =0.38, p=0.045, n=28; all controls). Similar results have been documented by Inagaki et al., (2002).

To now consider the patients, none were impaired on either non-spatial task. In contrast, all five were significantly impaired on the topographical memory task. The level of impairment was roughly equal in all five patients (scores ranged from 5/15 to 8/15), with scores that would place them all below the 3rd percentile of the normal population (Crawford & Garthwaite, 2002), and all four focal hippocampal cases (RH, JB, Jon, VC) being below the 1st percentile.

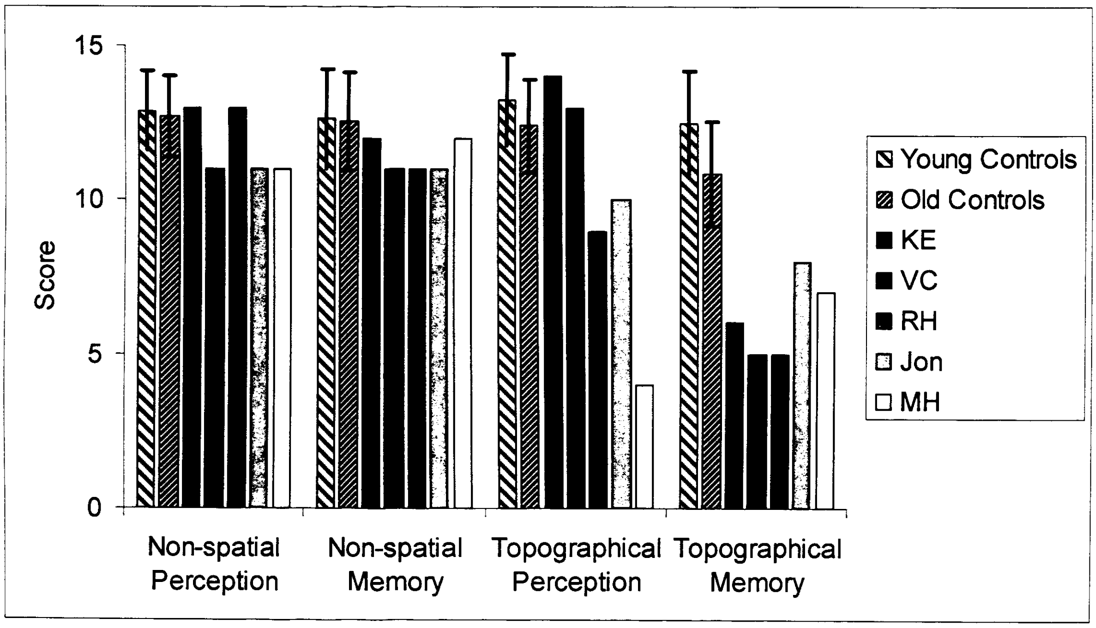
As expected, MH, the patient with a large right MTL lesion including much of the right parahippocampal and right entorhinal cortex as well as right hippocampus, was grossly impaired on the place perception task (well below what would be expected of the 1st percentile of the normal population). Of the focal hippocampal patients, RH and Jon were impaired on place perception. Their impairments were less profound than MH's placing them between the 1st and 5th percentiles, but within the range of the healthy controls (one old control and one young control obtained the same score as RH and Jon respectively). However, the other two focal hippocampal patients, KE and VC, were not only unimpaired, but in fact scored better than the mean of the elderly control group. VC's score on this task is of particular interest because he is densely amnesic, and at age 78 he is one of the oldest participants we tested.

## Table 4-2: Performance on the 4 Mountains task

| Group / subject | Non-spatial perception | | Non-spatial memory | | Topographical perception | | Topographical memory | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile |
| Young Controls | 12.88 (1.5) | 11-15 | 12.63 (1.5) | 11-14 | 13.25 (1.4) | 10-14 | 12.5 (1.1) | 11-14 |
| Jon | 11 | 10-25 % | 11 | 5-10 % | 10 | 1-5 % | 8 | <1 % |
| Old Controls | 12.7 (1.3) | 9-15 | 12.55 (1.6) | 10-15 | 12.4 (1.5) | 9-15 | 10.85 (1.7) | 8-15 |
| KE | 13 | 50-75% | 12 | 25-50 % | 14 | >75 % | 6 | <1 % |
| VC | 11 | 10-25 % | 11 | 10-25 % | 13 | 50-75 % | 5 | <1 % |
| RH | 13 | 50-75 % | 11 | 10-25 % | 9 | 1-5 % | 5 | <1 % |
| MH | 11 | 10-25 % | 12 | 25-50 % | 4 | <1 % | 7 | 1-5 % |

**Legend**: Performance of the two control groups and each patient on each of the four tests (maximum 15). The percentile scores for each patient are calculated according to the procedure of Crawford & Garthwaite (2002) with reference to the appropriate control group. These results are shown graphically in Figure 4-3, below.

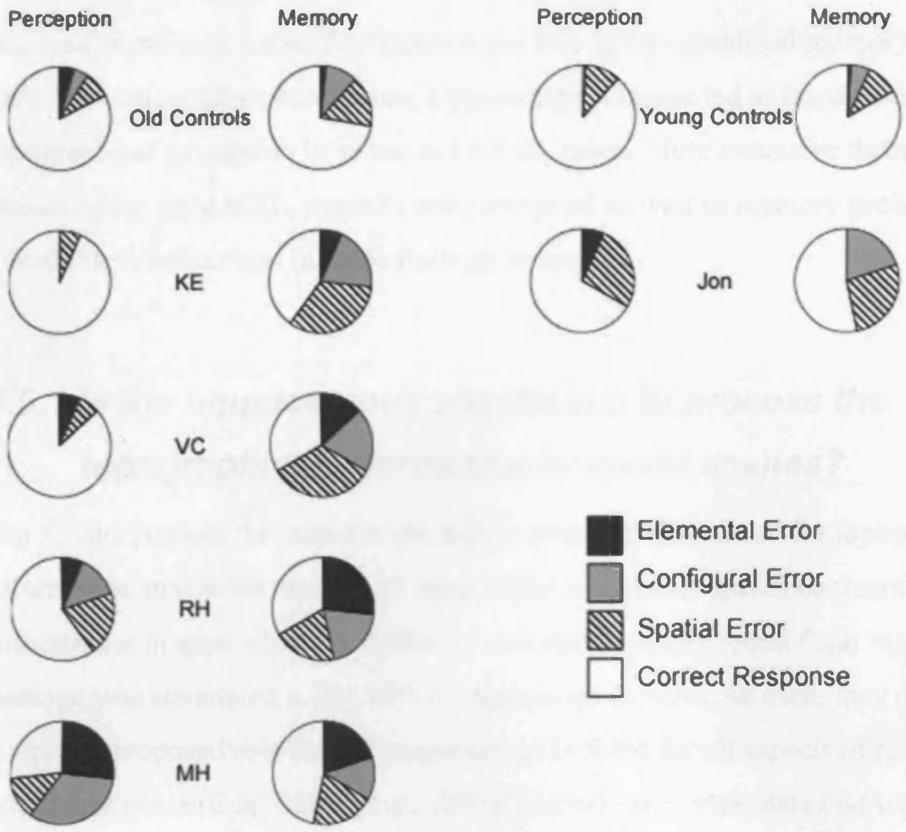
## Figure 4-3: Performance on the 4 Mountains task



**Legend**: Performance of the two control groups and each patient on each of the four tests. For the control groups, the mean score is shown by the bar, error bars indicate the standard deviation.

The 4 possible responses to each topographical question included 3 different types of foil, spatial, configural and elemental, each differing from the target scene in different ways (Figure 4-2). Spatial and configural foils were constructed using the same elements (distinctive hills) as the target scene, but arranged a distinct configuration, whereas elemental foils included elements not present in the target/sample scenes. This was intended to expose the nature of any retained spatial information in the pattern of erroneous responses. The patterns of error made by each patient and the two control groups in the topographical perception and memory tests is shown in Figure 4-4. Although they do not bear formal analysis, some interesting qualitative features are evident. For example, although impaired on both tests, patient Jon appears not to be guessing randomly, making mostly spatial errors in perception and spatial and configural errors in memory. By contrast, RH and MH, also impaired on both tests, make all kinds of errors. Thus Jon's performance may show some preservation of function despite his severe overall deficit, e.g. remembering something of the shapes of individual hills, which would allow him to reject elemental foils.

**Figure 4-4: Pattern of errors on the 4 Mountains Tasks**



**Legend**: Pie charts showing qualitative breakdown of responses to topographical tests. Each response in the topographical tests could take one of four forms: In correct responses (white segments) the selected image shows the same topography as the sample image (albeit from a different viewpoint). In spatial errors (stripes) the selected foil retains the same combination of distinctive hills arranged in the same order around the origin, but with the locations of the hills disrupted. In configural errors (grey) the selected foil retains the same combination of distinctive hills arranged in a different order around the origin. In elemental errors (black) the shape and size of one (perception) or two (memory) hills is changed. The figure shows the breakdown of responses for each patient and for both perception (left column) and memory (right column) tasks. Patient Jon (who is substantially younger than the other patients) is shown on the right of the figure, beneath the overall results for the young control group. The other patients are shown on the left of the figure beneath the overall results for the old control group.

## 4.5 Discussion

Our results indicate a specific hippocampal role in topographical memory, even over very brief delays (2 s). In addition, hippocampal damage led to impairment in topographical perception in some, but not all, cases. More extensive damage, including the right MTL, caused clear perceptual as well as memory problems. We discuss the implications of these findings below.

### *4.5.1 Is the hippocampus specialized to process the topographical information in visual scenes?*

Our results support the idea that the hippocampus is specialized for topographical information in that we tested both topographical and non-spatial conjunctive information in approximately difficulty matched tests and found focal hippocampal damage was associated solely with topographical deficits. As such, they do not support a proposed role for the hippocampus in STM for all aspects of relational or configural processing. Olson et al., (2006) recently presented data that was argued to support this latter, more general theory of hippocampal function. However, the strong spatial component to their task and the lack of detailed behavioural and anatomical data about the patients make comparison with the present study problematic. Although spatial and non-spatial information are inherently qualitatively different we took steps to balance other qualitative differences. So for instance, our non-spatial matching tasks depended on unpredictable conjunctions of multiple global, parametrically varying features, rather than unitary, local or categorical features. Performance may have been aided on some items by use of local/unitary information, but this was also true of the spatial tests, where, for instance, local shape information could generally be used to exclude one of the three foils.

### *4.5.2 What is the hippocampal role in topographical processing for perception and memory?*

Two of the four focal hippocampal patients (RH, Jon) showed deficits in both topographical memory and topographical perception. This is consistent with a recent study documenting spatial perceptual deficits following hippocampal damage (Lee et al., 2005a). However, the preserved performance of the other two focal hippocampal patients (VC and KE) show that an intact hippocampus is not absolutely critical for the topographical tasks until a brief delay is introduced, in which case all of the hippocampal patients are impaired. Importantly, and by contrast to the traditional association of the hippocampus with long-term declarative memory, the delay used in the topographical memory task was only 2 seconds. Consistent with the traditional view, amnesics such as VC are often able to maintain working memory in a range of other tasks involving brief delays such as digit span or Corsi's block span (Cave & Squire, 1992; Milner, 1971). As we argued in the Introduction, many visuo-spatial stimuli can be supported by STM systems in the absence of the hippocampus. The key difference with our task is that the stimuli were explicitly designed to tax flexible allocentric topographical processing (matching the relative location/shapes of the hills despite changes in viewpoint and surface features), and it seems that such processing requires the hippocampus for retention over even very brief delays.

It is possible that the stored hippocampal representation of a spatial scene is allocentric in that the effects of movement of viewpoint can be calculated within it (Burgess, 2002; Gaffan, 1998; King et al., 2002), allowing both topographical memory and perception tasks to be performed. By comparison, the parahippocampal scene representation may be less flexible (Epstein et al., 2003), and so insufficient to support the topographical memory task, but might still be sufficient to support alternative processes which are sufficient for the perceptual task. For example, distinct processes seem to support imagined movement of viewpoint around an array of objects compared to mental rotation of the array relative to the viewer, such that an advantage is observed for movement of viewpoint when the array contains more than one item (Wraga, Creem, & Proffitt, 2000). In our own study all patients were able to successfully complete a simple 2D mental rotation task (Table 4-1), but this is evidently not the same as being able to mentally manipulate a complex 3D scene. A key additional component is the requirement to compute the spatial relationships between features of the scene when the viewpoint changes. We have argued that accurate mental manipulation of viewpoint within a complex scene is only possible within the hippocampal representation (Burgess, 2002; King et al., 2002). However mental rotation based on the parahippocampal representation may be possible when the sample image is present for support (as in the topographical perceptual task), when only a single object location needs be remembered (King et al., 2002), or where 2-D stimuli are used (Cave & Squire, 1992). In addition, parahippocampal representations may be sufficient for processing and short-term memory of scenes that are tested from the same point of view (Ryan et al., 2000; Ryan & Cohen, 2004; Smith & Milner, 1989).

The representation of environmental topography by the hippocampus is consistent with the way in which environmental geometry is encoded by hippocampal place cells in rats (O'Keefe & Burgess, 1996). It is also possible that the hippocampal role in supporting viewpoint independence relates to the ability of the place cell representation of location to perform pattern completion from partial cues (Nakazawa et al., 2002), to accommodate the effects of self-motion (McNaughton et al., 1996) and to generalise across representations of environmental geometry (Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005). All of these properties are thought to result from the presence in hippocampal region CA3 of an extensive and recurrent collateral system that is capable of long-term potentiation (Marr, 1971; McClelland et al., 1995; Nakazawa et al., 2002). It has long been proposed that this distinctive anatomical feature of the hippocampus makes it particularly suited to the rapid acquisition and long-term storage of information. Equally, and as mentioned in the Introduction, the flexible allocentric nature of the spatial representations in the hippocampus are also well suited for LTM – allowing scenes to be recognised from new viewpoints after long delays. Nonetheless, we have shown that for tasks specifically designed to tap this type of representation, the hippocampus is required even over very brief delays. Indeed, our results indicate that hippocampal damage can even lead to perceptual impairments in some cases, although performance is preserved in other cases. We have argued above that the perceptual task may be solvable on the basis of less flexible parahippocampal representations, given the continued availability of the sample.

### *4.5.3 What explains the individual differences in hippocampal patients' topographical perception?*

Before discussing the topographical perception deficit exhibited by RH and Jon, it is worth putting their performance into context. Both patients obtained the same score as the lowest scoring of their respective control groups. Had either patient answered one more item correctly, their score would have been above the 5% cutoff for impairment. Thus, the impairment of both patients is mild. Given the variability inherent in tests that use a forced-choice testing procedure, it is possible that the either or both patients could perform in the normal range on another occasion. However, to take these results at face value does suggest that both patients have difficulties with this subtask.

One potential explanation for the topographical perceptual impairment shown by RH and Jon, but not by VC and KE, would be additional non-specific memory problems in RH and Jon. However, this seems unlikely given VC's generally much denser amnesia than Jon or RH. Another possibility, of additional covert damage to the medial temporal neocortex of RH and Jon (making their performance more similar to that of MH), also seems unlikely given their relatively preserved performance in other tests (e.g. the nonverbal subtest of the RMT, the Doors subtest of the Doors & People Test and in the case of Jon, the Topographical RMT; see Chapter 3) compared to VC. We note that a third possibility, of additional hippocampal damage in RH and Jon, is unlikely given VC's virtually complete hippocampal lesion. A fourth potential explanation is that, for hippocampal patients, successful performance of the perceptual task is possible, but depends on strategy. For instance it might be argued that VC and KE adopted viable non-hippocampal dependent strategies that were somehow unavailable to the other patients. However this would be hard to square with VC's profound amnesia. A more likely, if speculative, explanation is that the patients (RH and Jon) with impaired topographical perception have learned to use compensatory strategies for scene processing which fail in the particular circumstances of our test. For example, patients with poor topographical memory but relatively preserved recognition memory may become reliant on the familiarity of local visual cues to identify places. In everyday life such a strategy would be useful because unique or unusual local features of a scene are often available. However it will fail in our topographical tests since similar local topographical cues are present in all the test images, while the non-spatial cues and viewpoint are explicitly varied between sample and test images. Thus these patients' normally reliable approach may be counterproductive. On the other hand, these counterproductive strategies might not be available to VC due to his more strongly impaired recognition memory (see Table 4-1 and Chapter 3), or to KE who had only recently begun to experience memory problems.

### *4.5.4 Topographical processing beyond the hippocampus*

MH's striking impairment on the topographical perception task is fascinating because it comes in the context of other test results (see Table 4-1 and Chapter 3) which indicate a good degree of preserved function in visuospatial perception and visual memory tasks, including the Topographical RMT. Some of this preserved function may be due to dorsal stream processing, to ventral stream processing involving the spared tissue in the left medial temporal lobe, or else to the more lateral tissue spared bilaterally. In contrast with our topographical tests, the Topographical RMT, on which MH performs very well, depends on recognizing identical images, mostly containing unique local features not shared by the foil items. Our interpretation is that even where there is no delay, strictly topographical processing (i.e., where the task cannot be solved with reference to local features alone) is critically dependent on the right medial temporal cortex. Indeed, given the relative severity of MH's impairment, online processing is probably more dependent on the right parahippocampal/entorhinal cortices than the hippocampus. In this interpretation, MH's impaired topographical memory is likely to result from his impaired ability to perceive the scene's topography, although additional effects of right hippocampal damage cannot be ruled out. The degree of functional lateralization is not clear from the current study (since we have no patients with left-sided lesions). It may be that damage to the left medial temporal lobe would produce a similar deficit, although this seems unlikely in the context of previous studies involving unilateral patients which show a consistent tendency for topographical processing to be somewhat right-lateralized (Burgess et al., 2002).

### 4.5.5 Conclusions

We have presented a new test of perception and memory for topographical and non-spatial aspects of naturalistic landscapes, designed so that topographical information cannot contribute to the non-spatial task and non-spatial visual information cannot contribute to the topographical task. The four conditions show matched performance in healthy young participants, while older participants have slightly worse topographical memory reflecting a weak ageing effect (see also Inagaki et al., 2002).

Hippocampal damage selectively impairs topographical memory at a delay of 2 seconds, while 2 out of 4 hippocampal patients are impaired on the topographical perception task. One patient (MH) with additional MTL and occipital damage, including the right parahippocampal gyrus, showed a very severe impairment in topographical perception. Our results suggest that the hippocampus forms a viewpoint-independent representation of environmental topography which is also insensitive to changes in non-spatial features that are typically transient in the real world. This type of representation would clearly be particularly useful for long-term memory, but may also be useful over shorter timescales when alternative representations or STM systems are not available. The ability to retain allocentric information over short periods may also be necessary to construct a representation of the immediate environment when multiple landmarks are not all visible at the same time (e.g. if standing in the middle of a large square). However, the presence of the sample scene in the perceptual task can allow for successful alternative strategies, possibly based on less flexible parahippocampal representations.

The proposed role of the hippocampus in specifically supporting a flexible or allocentric (viewpoint-independent) topographical representation is consistent with the cognitive map (O'Keefe & Nadel, 1978) and flexible-relational (Eichenbaum & Cohen, 2001) theories of hippocampal function. Nonetheless, our results also indicate a predominantly mnemonic role for the hippocampus, arguing against the most general interpretation of these theories (see also Fortin, Agster, & Eichenbaum, 2002). No deficit was found on the non-spatial tasks, which require perception and memory for conjunctive parametric non-spatial visual features. Our results are consistent with suggestions that a defining characteristic of hippocampal spatial representations is their 'flexibility', in that they can support manipulations of viewpoint (Burgess, 2002; Gaffan, 1998; King et al., 2002). More surprisingly, these results argue against the generality of the long-held dissociation between the neural bases of long-term and short-term memory. Although this dissociation holds for many types of traditionally used memoranda, for which STM systems exist, it appears that the hippocampus, while crucial to long-term memory, is also required for specific forms of spatial processing even over very short timescales.

The following chapter aimed to characterize the performance on the 4 Mountains test in a patient population with pathology associated with medial temporal lobe regions; patients in the early stages of Alzheimer's disease (AD). It was predicted that the performance of the AD patients would be broadly similar to those of the hippocampal patients reported in this Chapter. This would replicate the finding that medial temporal lobe areas involved in LTM are also involved in some aspects of STM and may provide a useful diagnostic marker for the detection of AD in its early stages.

# 5 Chapter 5: Performance on the 4 Mountains Task in a group of patients with Mild Cognitive Impairment or Alzheimer's disease

## 5.1 Background

The data in this chapter were collected in collaboration with Neil Burgess, Dennis Chan and the Dementia Research Centre at the National Hospital (London, UK). This is an ongoing study and therefore the results presented here are only preliminary.

## 5.2 Introduction

In the previous chapter, the 4 Mountains Task was shown to be particularly sensitive to hippocampal pathology. The aim of the investigation reported in this chapter, was to assess its usefulness in detecting cognitive dysfunction in patients with probable Alzheimer's disease (AD).

AD is characterized clinically by a dementia of insidious onset, progressive impairment of memory and other cognitive functions, and pathologically by the presence of large numbers of neuritic plaques and neurofibrillary tangles (e.g. McKhann et al., 1984). There are no motor, sensory, or coordination deficits early in the disease. In terms of behavioural signs, the earliest reported symptoms in patients who go on to develop AD are usually memory problems. The later stages of AD are associated with very severe and global cognitive decline, and concomitant widespread cortical atrophy. However, in the early stages, neural pathology is most commonly associated with the hippocampus and the entorhinal region (e.g. Braak & Braak, 1991; Fox et al., 1996). It is highly plausible that neural changes in these areas underlie the early cognitive changes and therefore, a test that requires the functional integrity of these areas for normal performance should theoretically be useful in the early diagnosis of AD.

Early diagnosis of AD allows the planning of future care for the patient or teaching coping strategies for cognitive impairments which are likely to worsen. Also, pharmacological treatments such as acetylcholinesterase inhibitors have been shown to be effective in slowing the rate of symptomatic progression, and may be particularly useful in the early stages of AD (Scarpini, Scheltens, & Feldman, 2003). Other treatments such as immunotherapy may actually modify the course of the disease (Fox et al., 2005). In both these applications it is critical to differentiate AD from other degenerative conditions such as vascular dementia, dementia with Lewy bodies and frontotemporal lobar degeneration (FTLD), for which certain treatments would not be appropriate. Cognitive tasks are a simple and cost effective way of identifying individuals at risk of AD, and if used in combination with imaging techniques such as serial structural MRI or PET imaging with amyloid tracers, provide powerful tools for the early, differential diagnosis of AD (Klunk et al., 2004). Sensitive cognitive tests also provide a way of monitoring disease progression and any modulation of it, by interventions.

Individuals with memory complaints, but who do not yet match criteria for AD are commonly referred to as having mild cognitive impairment (MCI: Petersen et al., 1999). These people are at high risk of developing a full-blown dementia syndrome in the next few years. Recently, there have been several studies that have aimed to identify which cognitive tests are most efficient at predicting which individuals with MCI will develop AD (see Nestor, Scheltens, & Hodges, 2004). One test that has been reported to be particularly effective in this capacity is the Paired-associates learning (PAL) subtest from the CANTAB battery. This test was shown to differentiate MCI patients who converted to AD from both non-converting MCI patients and individuals with depression (Fowler, Saling, Conway, Semple, & Louis, 2002; Swainson et al., 2001; Blackwell et al., 2004). It was suggested that this is because the PAL requires a high level of "context" memory, but performance is not particularly aided by using a "strategic approach" (Fowler et al., 2002). Moreover, there is evidence from healthy adults that similar brain regions are involved in performing this task to the regions where pathology is implicated early in the course of AD (Owen, Milner, Petrides, & Evans, 1996).

Since the disease process in AD is poorly understood, caution should be taken before asserting that patients with early AD are a good model for the effect of selective MTL damage on cognition. Nevertheless, a very recent study demonstrated a similar pattern of performance on a test of spatial perception as was previously reported in patients with selective hippocampal damage (Lee et al., 2006). Taken together with the data on the PAL, this suggests that tests that are sensitive to the effects of hippocampal and entorhinal damage may be particularly useful in the early detection of AD.

The previous chapter demonstrated the 4 Mountians task to be very sensitive to isolated hippocampal damage and the hippocampal patients showed a consistent pattern of performance on the various subtasks (i.e. very poor performance on the place memory subtask and unimpaired on the non-spatial subtasks). We therefore predicted that AD/MCI patients would show a similar pattern of performance as the patients with hippocampal lesions. Given the results of Lee et al., (2006) it is possible that topographical perception may be more markedly impaired in this population. Finally, if a consistent pattern of performance on the 4 Mountains Task across the AD/MCI patients, then this test may prove useful in the clinical diagnosis of AD in its early stages.

## 5.3 Methods

### *5.3.1 Participants*

The aim of this preliminary study was to investigate the sensitivity of the 4 Mountains Test to cognitive dysfunction in the early stages of AD. We therefore selected a relatively homogenous group of patients who were at a significant risk of developing AD (currently with a diagnosis of MCI) or already suffering from AD. Most of the patients had already participated in research at the Dementia Research Centre at the National Hospital for Neurology and Neurosurgery where they had undergone serial brain imaging as well as serial neuropsychological assessment. Specific selection criteria as well as demographic information and performance on selected cognitive tests are shown in Table 5-1 for each patient.

All patients diagnosed as having AD have been demonstrated to have progressive medial temporal lobe atrophy on serial co-registered MRI scans in addition to progressive decline of memory and other cognitive domains over serial neuropsychological assessments. There were three patients diagnosed with MCI. GOL complains of a worsening of episodic memory and the ability to retrieve names. Her mother has AD and her verbal IQ dropped from 114 to 99 over the period of a year, but otherwise her neuropsychological profile is unremarkable. She is unable to tolerate MRI scanning. ROB complains of a worsening of episodic memory. She has a very unusual memory profile, performing at a very impaired level on most tests of verbal and visual recognition (including very easy recognition memory tests; Clegg & Warrington, 1994), but performs normally on most tests of verbal and visual recall. GEA had evidence of MTL atrophy and complained of a worsening of episodic memory, which was corroborated by neuropsychological assessment.

The same group of healthy older adults that had participated in Chapter 4 served as controls.

### 5.3.2 Materials and Procedures

A selective battery of neuropsychological tests was administered at the same time as the experimental tests. This included the Ravens Advanced Progressive Matrices (set 1), the Flags Test of mental rotation, the Object Decision subtest of the VOSP, the Topographical Recognition Memory Test and the Doors & People Test (DPT).

#### 5.3.2.1 4 Mountains Task

The 4 Mountains Task was administered using exactly the same test materials and procedures as detailed in Chapter 4.

**Table 5-1: Patient details**

| ID | TAY | | GOL | | VAN | | ROB | | KUL | | GEA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Selection crit. | ABC | | AD | | ABCD | | AB | | ABC | | ABC | |
| Diag. | AD | | MCI | | AD | | MCI | | AD | | MCI | |
| Age | 65 | | 63 | | 77 | | 62 | | 72 | | 55 | |
| Sex | M | | F | | F | | F | | M | | M | |
| MMSE (/30) | 23 | | 29 | | 27 | | 29 | | 26 | | 28 | |
| NART | | | | | | | | | | | | |
| Matrices (/12) | 3 | 5-10 % | 9 | >90 % | 9 | >90 % | 11 | >90 % | 6 | 50-75 % | 11 | >90 % |
| Flags (/10) | 9 | wnl | 10 | wnl | 9 | wnl | 9 | wnl | 9 | wnl | 8 | bord |
| Obj Dec (/20) | 15 | wnl | 19 | wnl | 16 | wnl | 20 | wnl | 16 | wnl | 19 | wnl |
| TRMT (/30) | 17 | 5-10 % | 27 | >75 % | 26 | >75 % | 15 | <5 % | 15 | 5-10 % | 28/30 | >75 % |
| DPT | | | | | | | | | | | | |
| Verbal Recall (/36) | 3 | <5 % | 24 | >75 % | 10 | <10 % | 29 | 50-75% | 13 | <10 % | 18 | 5-10 % |
| Verbal Recog (/24) | 9 | <5 % | 20 | >75 % | 15 | 25 % | 12 | 1-5 % | 11 | 5 % | 17 | 50 % |
| Visual Recall (/36) | 5 | <5 % | 31 | >75 % | 21 | 10-25 % | 36 | 90 % | 11 | <5 % | 14 | <1 % |
| Visual Recog (/24) | 11 | <5 % | 22 | >75 % | 14 | 25 % | 9 | <1 % | 14 | 10-25 % | 16 | 10-25 % |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**Legend**: Selection crit. = selection criteria; (A) subjective deterioration of episodic memory (B) impairment of one or more cognitive domains including memory; (C) evidence of progressive medial temporal lobe atrophy; (D) family history of AD. Diag. = diagnosis; Obj Dec = Object decision subtest of the VOSP, TRMT = Topographical Recognition Memory Test; DPT = Doors & People Test; % = percentile score, wnl = within normal limits, bord = borderline impaired

## 5.4 Results

### 5.4.1 Cognitive Assessment

The results of the cognitive assessment are shown in Table 5-1. A wide range of performance was obtained, although it is clear that the general level of ability was relatively high. Thus, performance on a stringent test of abstract problem solving (Matrices) is generally high in all but one patient (TAY). No patient was impaired on the test of object perception. Similarly, no patient was impaired on the Flag's test of mental rotation although GEA's score was weak and GOL performed the test very slowly. In fact, GOL's performance on another test of spatial perception (the Cube Analysis subtest of the VOSP), was also very slow. All patients except for one (GOL) was impaired on one or more test of memory. In general, performance on the recall subtests of the DPT was poorest. However, one patient (ROB) consistently passed tests of recall but failed tests of recognition (although delayed recall was poor). It is unclear what underpinned this extremely unusual pattern of performance, which is certainly atypical in the context of AD.

### 5.4.2 Experimental tasks

The results for the MCI/AD group and the healthy adults on the 4 Mountains task are shown in Table 5-2 and Figure 5-1.

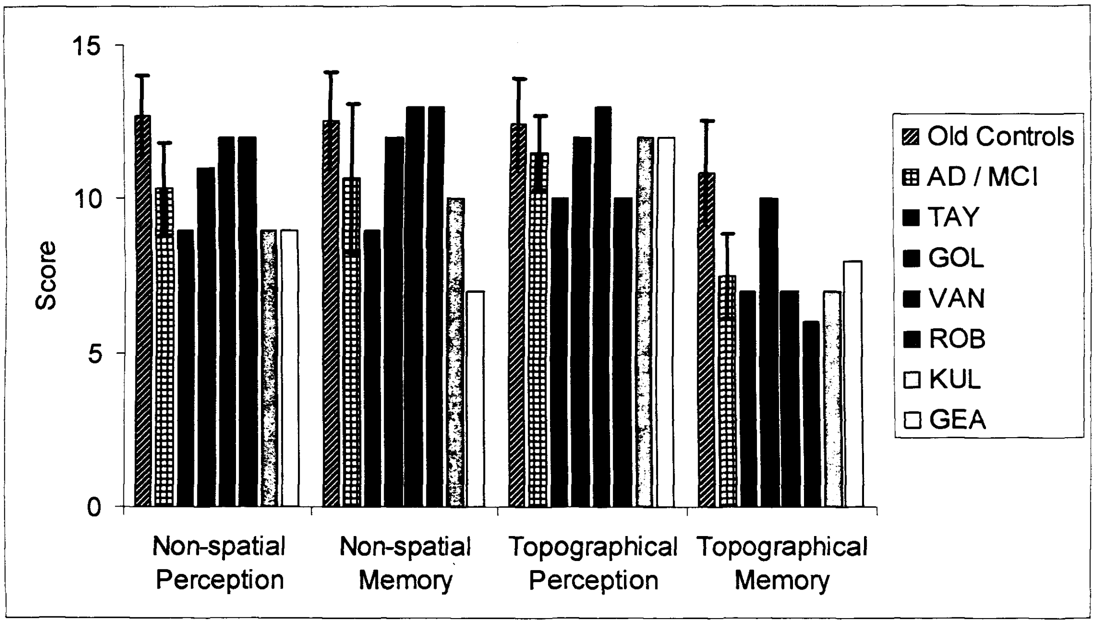
In the first instance, the data were analysed using a repeated measure ANOVA, with "Health" (MCI/AD versus controls) being the between subjects factor and "Task" being the within subjects factor. There was both a significant effect of Health (F (1,24) = 27.3, P<0.001) and of Task (F(3,72) = 13.9, P<0.001), reflecting poorer performance of the MCI/AD group compared with the controls, and poorer performance of the Topographical Memory task compared with the others. The interaction between Health and Task was marginally significant (F(3, 72) = 2.3, P = 0.08).

**Table 5-2: Performance on the 4 Mountains task**

| Group / subject | Non-spatial perception | | Non-spatial memory | | Topographical perception | | Topographical memory | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile | Mean (SD) | Range / %ile |
| Old Controls | 12.7 (1.3) | 9-15 | 12.55 (1.6) | 10-15 | 12.4 (1.5) | 9-15 | 10.85 (1.7) | 8-15 |
| AD/MCI group | 10.3 (1.5) | 9-12 | 10.7 (2.4) | 7-13 | 11.5 (1.2) | 10-13 | 7.5 (1.4) | 6-10 |
| TAY | 9 | <1 % | 9 | 5-10 % | 10 | 5-10 % | 7 | 1-5 % |
| GOL | 11 | 10-25 % | 12 | 25-50 % | 12 | 25-50 % | 10 | 25-50 % |
| VAN | 12 | 25-50 % | 13 | 50-75 % | 13 | 50-75 % | 7 | 1-5 % |
| ROB | 12 | 25-50 % | 13 | 50-75 % | 10 | 5-10 % | 6 | <1 % |
| KUL | 9 | <1 % | 10 | 1-5 % | 12 | 25-50 % | 7 | 1-5 % |
| GEA | 9 | <1 % | 7 | <1 % | 12 | 25-50 % | 8 | 5-10 % |

**Legend**: Performance of the control group, AD / MCI group and individual patients on each of the four tests (maximum 15). The percentile scores for each patient are calculated according to the procedure of Crawford & Garthwaite (2002) with reference to the control group. Results are summarised in Figure 5-1, below.

**Figure 5-1: Performance on the 4 Mountains task**



**Legend**: Performance of the control group, the AD / MCI group and each patient on each of the four tests. For the group data, the mean score is shown by the bar, error bars indicate the standard deviation.

Despite the lack of a significant interaction, inspection of Figure 5-1 suggested a greater impairment in the MCI/AD group on the Place Memory task, for at least some patients. To investigate this, the performance of both groups on all tasks was compared with an Oneway ANOVA, which showed a significant difference in the mean scores (F(7, 96) = 10.8, P<0.001). A scheffe post-hoc test confirmed that the only significant difference between the patients and the controls on a task was on the Topographical Memory subtest (P<0.01). In addition, we compared each patient's performance on the 4 Mountains Task with the control group on a case by case basis, using the procedure of Crawford & Garthwaite (2002). The results of this analysis, in terms of percentile scores, are shown in Table 5-1. None of the patients were impaired on the Topographical Perception subtask, but four of the six patients were impaired on the Topographical Memory Task (and the performance of a fifth was markedly weak). Three of the patients were also impaired on the Visual Perception task and two of whom were also impaired on the Visual Memory Task (whilst the third obtained a weak score).

## 5.5 Discussion

We aimed to assess whether the 4 Mountains Task is sensitive to cognitive dysfunction in patients that may have Alzheimer's disease. The preliminary data is encouraging. Overall, the performance of the patients was somewhat similar to, but poorer than, the healthy adults. Nevertheless, pairwise comparisons between the scores of the patients and controls on each subtest suggested group differences only on the Topographical Memory subtest. Additional casewise analyses revealed that 60% of the patients were significantly impaired on this subtest, whilst none were impaired at Topographical Perception. Although performance on the Visual Memory subtask was also impaired in two patients, both of these (and a third) were additionally impaired on the Visual Perception subtasks. This suggests that maintenance of the non-spatial visual aspects of the scene is not necessarily impaired in this group, provided that the information is accurately perceived in the first case. These findings will be discussed in more detail below.

An important question is whether the performance of the MCI/AD group was simply (non-specifically) poorer than the control group. This is difficult to answer, since the Topographical Memory subtest – which was predicted to be sensitive to AD - taps allocentric spatial processing, which has been shown to be susceptible to aging (Inagaki et al., 2002). Similarly, allocentric spatial processing has been linking with "recollection", which is also known to deteriorate with age (Bastin & Van der Linden, 2003; King et al., 2004; Jennings & Jacoby, 1997; Parkin & Walter, 1992). Thus, the finding of similar, but exaggerated pattern of performance in the MCI/AD group compared with the controls is consistent with our predictions. Critically however, performance of the patients was significantly lower that the controls only on the Topographical Memory subtest, and 4/6 patients performed below the 5th percentile, with a fifth also performing poorly. Thus, the MCI/AD group may have a *disproportionate* impairment in retaining allocentric spatial representations across short delays. It should be noted that the formal test of this – the ANOVA interaction between task and group – was only marginally significant. This probably reflects the small group sizes, but further data is needed to clarify this issue. If further research corroborates these preliminary findings, this would be consistent with the view that impairment of allocentric spatial memory may underpin the topographical disorientation that is associated with the early stages of AD (Burgess, 2006).

The finding of intact topographical perception in the patients is inconsistent with recent findings by Lee et al., (2006). The AD patients included in Lee et al.'s study had a mean MMSE of 23.6, which is lower than the patients included in our study. It is therefore possible that these patients had more widespread atrophy which could have impacted on performance. It should be noted that others have failed to find impaired topographical perception even in the context of very large bilateral MTL lesions (Shrager, Gold, Hopkins, & Squire, 2006).

One of the patients (GOL) performed normally on all subtests of the 4 Mountains Test. However, GOL's cognitive profile was uncharacteristic of the group as a whole for a number of reasons. She performed very well of the Topographical RMT and all subtests of the Doors & People Test although it was noted that her performance was very slow on the Flags Test and the Cube Analysis subtest of the VOSP. This was uncharacteristic of the other patients. Thus there is considerable evidence to suggest that her putative cognitive impairment is qualitatively different from the other patients and it is uncertain whether she will develop AD (or at least, the "typical" MTL variant of AD).

Three of the patients were impaired on both the Visual Perception and Visual Memory subtests. No visual perceptual deficits had been detected through background neuropsychological testing using subtests of the VOSP and none of the patients were colour blind. Perhaps the most plausible reason for their impairment on the visual perception and memory tasks may be that they did not adequately understand the tasks. Thus, GEA, who showed little evidence for general cognitive impairment, reported matching the target on the basis of the length of the shadows in the pictures, despite having been explicitly instructed to attend to multiple aspects of the scenes during the practice trials (such as the colour of the vegetation and the weather conditions as well as the lighting). Focusing on only one aspect of the scene, would result in impaired but above chance performance. Nevertheless, the presence of subtle visual perceptual deficits in these patients cannot be excluded.

## 5.6 Summary

These very preliminary results suggest that the 4 Mountains Task may be a useful diagnostic test for the detection of cognitive impairment in the early stages of AD. Four out of six patients with early AD or MCI were impaired in the ability to retain allocentric spatial information over very short periods. Interestingly, all patients were able to perceive topographical information. The poor performance of some of the patients on the visual perception subtests may be due to poor comprehension of the task requirements.

The previous two chapters have focussed on the MTL involvement in the short-term retention of information. In the following two chapters I will investigate its role in long-term retention of information. Although it is widely accepted that the MTL plays a critical role in LTM, several issues are still highly contentious. For example, some studies have reported category specific LTM impairments following MTL damage, although these remain poorly understood (e.g. Carlesimo, Fadda, Turriziani, Tomaiuolo, & Caltagirone, 2001). There is also debate as to which MTL areas subserve two putative memory processes; recollection and familiarity. These issues will be explored through detailed investigation of the memory profiles of four memory impaired patients; VC, RH, JC and Jon (see Chapter 3).

# 6 Chapter 6: Recollection and familiarity for different materials following medial temporal lobe lesions

## 6.1 Background

This chapter reports a detailed investigation of the anterograde memory abilities of three neurological patients (RH, VC and JC), on three new experimental tasks. VC's data has been published in a manuscript by Cipolotti et al., (2006). This study also included a detailed anatomical investigation, which is referred to in Chapter 3. In a subsequent investigation, the same tasks were administered to RH and JC, and have been submitted for publication in a manuscript by Bird, Shallice and Cipolotti. The results were also presented at the Autumn Meeting of the British Neuropsychological Society in 2005. Two related issues are addressed in this chapter: (1) category-specific memory impairments, with particular reference to the medial temporal lobes, and (2) the role of the hippocampus in recollection- and familiarity-based memory processes. These issues will both be addressed concurrently, using ROC analyses of memory performance on tests using different categories of stimuli.

## 6.2 Introduction

### *6.2.1 Category-specific memory impairments*

Studies of neurological patients with selective episodic memory deficits provide invaluable information regarding the organization of memory functions in the brain. Such studies have indicated that selective verbal memory deficits can follow left medial temporal lobe (MTL) lesions whereas right MTL lesions have been associated with selective deficits in non-verbal memory (Frisk & Milner, 1990; Smith & Milner, 1981). Interestingly, striking dissociations have been reported within the domain of non-verbal memory functions. It has been shown that memory for human faces and memory for topographical materials can dissociate. For example, there are on record patients with neurodevelopmental impairments that presented with selective preservation of topographical memory (recognition of unfamiliar scenes), despite impairment of memory for human faces (see Blair, Frith, Smith, Abell, & Cipolotti, 2002, for a group study of individuals with autism, and; Cipolotti, Robinson, Blair, & Frith, 1999, for a single case study of an individual with Gilles de la Tourette syndrome and autism). Furthermore, dissociations between topographical and human face memory have been described also in adults with acquired brain lesions.

Several patients have been reported with either selective impairment of, or selective sparing of, memory for topographical materials (such as pictures of outdoor scenes, buildings or landscapes). Two patients reported by Warrington and colleagues fall within the former class of patients (Incisa della Rocchetta, Cipolotti, & Warrington, 1996; Whiteley & Warrington, 1978). Both of these patients had a selective impairment in recognizing topographical material, whilst memory for other material, including human faces, was normal. In contrast, two patients with selective sparing of topographical recognition memory, despite severe memory impairment for human faces and verbal material have been described (Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998). These patients both had semantic dementia, a disease process associated with atrophy in the anterior temporal lobes, but with relative sparing of the hippocampus in the early stages. A subsequent group study also documented an impairment of face recognition memory but intact scene recognition memory in semantic dementia patients (Lee et al., 2006). Interestingly, the same study showed the reverse dissociation with respect to memory for these materials in patients with Alzheimer's disease.

Similar dissociations have been reported for face recognition memory. Thus, Tippett et al., (2000) reported a patient who suffered a traumatic brain injury and subsequently was unable to recognize new faces, despite spared memory for verbal material and abstract designs. Unfortunately, the authors did not investigate the patient's topographical memory functions. The opposite pattern of impairment has been described by Carlesimo and colleagues (2001). They reported a patient with a selective sparing of recognition memory for faces in the context of an otherwise global amnesia encompassing a wide variety of verbal and non-verbal materials including topography.

Since memory processes for these types of materials have been demonstrated to be functionally dissociable, it is of interest to ascertain which anatomical areas are necessary to subserve them. To date, the case reports have been largely uninformative in this respect. With the exception of the patient reported by Carlesimo and colleagues (2001), the patients have had non-focal brain lesions, which have implicated widespread cortical areas.

#### 6.2.1.1 Summary

Despite the rather limited number of detailed case reports, it is clear that memory can fractionate beyond the well established verbal versus non-verbal split. However, the anatomical lesions responsible for causing these memory impairments are unknown. Studies that average performance over patients and across tests may mask any material specific effects. Therefore, to investigate these issues, detailed characterization of the memory profiles of patients with focal brain lesions using suitable experimental materials are necessary.

### *6.2.2 Recollection and Familiarity*

Several researchers have proposed that memory is subserved by two separate processes – the "Dual Process Theory" (Jacoby & Dallas, 1981; Mandler, 1980; Tulving, 1985). These processes are commonly termed recollection and familiarity. Recollection is the conscious retrieval of information from the past. Familiarity is the ability to judge whether something has been experienced before, without retrieving additional information about the initial experience. In recent years there has been considerable debate concerning the anatomical underpinnings of these two putative processes.

The strongest version of the dual process theory proposes that the two processes are independent, and have distinct neural underpinnings (Aggleton & Brown, 1999; Rugg & Yonelinas, 2003). I will refer to this as theory 1. Recollection is subserved by the hippocampus; whilst the perirhinal cortex is sufficient to subserve familiarity. According to this theory, it would theoretically be possible to find double dissociations where recollection or familiarity could be independently spared or impaired. In contrast, a second prominent theory (theory 2) posits that both processes are part of a fairly general "declarative" memory system that is subserved by several structures in the medial temporal lobe (MTL), particularly the hippocampus and perirhinal cortices (e.g. Squire et al., 2004). A third position, where familiarity and recollection are seen as separate but non-independent processes is possible. This position, referred to as a "redundancy" account, proposes that recollection and familiarity depend on some common processes and neural mechanisms (Knowlton, 1998). Accordingly, familiarity may or may not trigger further recollection-specific processes that lead to recollection. Thus, according to this position, some level of familiarity must always accompany recollection. Importantly, this position does allow for situations whereby recollection may be impaired whilst familiarity is intact, but not the opposite dissociation. Since the bulk of the experimental data has explicitly contrasted evidence for and against the first two theories, I shall focus on these. However, I will return to discuss the MTL redundancy view in the discussion.

It is, of course, possible to directly test the two dominant theories since they make different predictions about the type of memory impairments that should be observed in patients with hippocampal damage. Theory 1 predicts selective deficits in recollection, whilst familiarity based processes should remain intact. In contrast, theory 2 predicts equal impairments of both recollection and familiarity. It should be noted that the contribution of recollection and familiarity to performance on memory tests can be estimated directly or indirectly. Direct estimates aim to quantify both parameters according to dual process models of memory (e.g. Remember/Know paradigms or ROC analyses, Tulving, 1985; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). Indirect estimates contrast performance on recall memory tests with recognition memory tests, assuming that performance on recall tests is almost entirely driven by recollective processes, whilst performance on recognition tests may be driven by familiarity, if recollection fails. Following this, according to theory 1, a selective deficit in recollection will impact on recall, but to a lesser extent on recognition memory. For theory 2, recall and recognition should be equally impaired. Lastly, some studies use "process dissociation" techniques to isolate the two processes. In the following sections I shall review the contrasting evidence for both theories.

#### 6.2.2.1 Support for Theory 1

A number of studies have concluded that the hippocampus does not play a role in recognition memory. For example, Baxendale (1997) reported normal or near normal performance on the Recognition Memory Test (Warrington, 1984) in a group of patients with longstanding epilepsy and unilateral hippocampal sclerosis. However, longstanding epilepsy may be associated with atypical cerebral organization of cognitive functions. More recently, Turriziani et al. (2004) reported a relative sparing of single item recognition in a subgroup of amnesic patients. Unfortunately, quantitative neuroradiological data demonstrating the selective nature of their hippocampal damage was not provided. In addition, their experimental tasks used only unfamiliar faces. I shall argue in the Discussion that areas outside the hippocampus may subserve memory for this type of material.

Yonelinas and colleagues carried out a series of interesting studies investigating recall and recognition memory in a group of patients with mild hypoxia who were assumed to have hippocampal lesions on the basis of a relatively short coma duration (Quamme, Yonelinas, Widaman, Kroll, & Sauve, 2004; Yonelinas et al., 2004). Recall deficits were reported as being significantly greater than recognition deficits. This difference was thought to be due to a deficit in recollection but not familiarity. Using structural covariance modeling recollection estimates were shown to correlate with the coma duration (a proxy measure of presumed hippocampal damage) whilst familiarity estimates did not. Furthermore, structural equation modeling found that the dual process theory fitted the recall and recognition data better than a number of alternatives, including a single process theory (Quamme et al., 2004). However, Wixted and Squire (2004a) have argued that, after excluding an outlier from the Yonelinas et al., (2002) control group, these data indicated that hippocampal damage affects to a similar extent recognition and recall. Yonelinas and colleagues (2004) did consider this artifact explanation and argued that it does not provide an adequate account for their results. In a small number of patients, extra tasks were administered to directly quantify the contribution of recollection and familiarity to performance, using the Remember/Know and ROC paradigms. Data from the hypoxia patients were compared with those of patients with more extensive MTL lesions. Specific deficits in recollection but not familiarity were documented using the Remember/Know task, but the results of the ROC analysis were less clear cut. However, the lack of any neuroanatomical data in these studies makes inferences concerning the critical role of the hippocampus at best, problematic (see also Wixted & Squire, 2004b, for a similar view).

Since it is usually impractical to carry out detailed anatomical investigations in the context of group studies, much of the evidence in this debate is from single case studies. One of the most intensively studied patients supporting Theory 1 is YR, a woman whose hippocampi are approximately 50% smaller than those of age matched controls (Holdstock et al., 2002; Mayes et al., 2001; Mayes et al., 2002). Despite being impaired on tests of recall, she performed in the normal range on almost all recognition memory tests. For example, YR was impaired on the recall subtests of the Doors and People Test but was unimpaired on the recognition subtests (DPT: Baddeley et al., 1994). On recent investigation she was shown to be impaired in recall/recollection and recognition of associations between different kinds of information while showing preserved recognition for single items, intra-item associations and associations between items of the same kind. Additionally, her performance on remember/know tasks indicated a severe deficit in recollection whilst familiarity was spared, although the authors noted that she had difficulty grasping the concept of "recollection" (Holdstock et al., 2002; Mayes et al., 2004). The authors argued that YR's hippocampal lesion had selectively affected her recollective memory. Her spared familiarity-based recognition abilities were thought to be mediated by her intact medial temporal lobe cortices (Holdstock et al., 2002; Mayes et al., 2004).

A pattern of memory profile similar to YR has been described in the context of developmental amnesia (Vargha-Khadem et al., 1997). In the first study, three patients with bilateral reductions in the hippocampus were demonstrated to perform well on tests of item recognition, despite severe amnesia for everyday events and poor performance on tests of free recall. Of these three patients, one (patient Jon) has been the most extensively studied. Jon had a long-standing reduction of 50% of hippocampal volume incurred perinatally which is equivalent to that of YR (Vargha-Khadem et al., 1997). Interestingly an fMRI study revealed that Jon's residual hippocampal tissue was active during memory retrieval (Maguire et al., 2001).

Similarly to YR, Jon performed well on the recognition subtests of the DPT and poorly on the recall subtests. Jon's intact recognition memory performance was interpreted as mediated by unimpaired familiarity-based recognition judgements. Vargha-Khadem and colleagues (1997) suggested that perirhinal and entorhinal cortices are critical structures for such processes. However, it may well be that the effects of damage in the immature brain are quite different from those in the mature brain. Therefore, such conclusions may not be easily generalizable (for further discussion, see also Maguire et al., 2005).

Two further single case studies describe adult patients with hippocampal damage who show preserved familiarity and impaired recollection (Aggleton et al., 2005; Bastin et al., 2004). Bastin et al (2004)'s patient (MR) performed well on several recognition memory tests despite being impaired in recall memory tests. Additionally, process dissociation procedures revealed impaired recollection for verbal material whilst familiarity was intact. It should be noted however, that he showed fluctuations in his scores on a standard memory test such as the Doors and the Shapes subtests of the DPT as well as on the verbal subtests of the WAIS-R. Second, the case description raised the possibility that he may have had some degree of psychiatric problems. Therefore his recall memory impairment must be interpreted with caution. Third, the patient produced a rather high number of false alarm rates in the task used to evaluate the contribution of familiarity and recollection to his memory performance (see Wixted & Squire, 2004b for discussion of the problems that false alarms create for the evaluation of familiarity and recollection). The patient (KN) described by Aggleton et al. (2005) showed deficits on standard tests of recall memory and selective sparing of familiarity in tests using Remember/Know and ROC procedures. Nevertheless, the patient's recollection, as estimated by the ROC procedure was only borderline impaired. These data represent an improvement from his initial assessment where he performed poorly on several item recognition tests (involving words, scenes and faces, McKenna & Gerhand, 2002). KN also had significant damage in extrahippocampal areas, including the occipital lobes (particularly on the right), the amygdala and possibly the thalamus. Furthermore, on a previous volumetric analysis his hippocampi were reported being in the normal range, albeit somewhat small (McKenna & Gerhand, 2002).

Two other studies reported patients with bilateral hippocampal damage, but with evidence for extrahippocampal damage in the left hemisphere (Barbeau et al., 2005; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005). Barbeau et al.'s (2005) patient (FRG) was reported to have bilateral hippocampus damage, as well as extensive damage to the parahippocampal gyrus on the left following herpes simplex encephalitis. By contrast, the right parahippocampal gyrus was relatively spared. Despite severely impaired verbal and visual recall memory, and verbal recognition memory, the patient performed within the normal range on several visual recognition tests. The dissociation between impaired verbal recognition and intact visual recognition was hypothesized to be due to greater damage to the left parahippocampal gyrus. Of note, FRG failed four visual memory tests consisting of items belonging to specific semantic categories, including faces. The authors suggest that the patient may have a mild agnosia for biological entities. The second patient, BE, was reported to have damage outside of the hippocampus in the left hemisphere according to the results of a SPECT scan (Holdstock et al., 2005). By contrast, extrahippocampal areas on the right appeared intact. The patient showed a relative sparing of item recognition over recall for nonverbal materials and a global anterograde amnesia for verbal materials. On a Remember/Know task, BE tended to make a greater proportion of "know" responses than "remember" responses, which was the opposite pattern to the controls, although it should be noted that his overall performance on this task was impaired. The authors interpreted this as suggesting that BE relied more on familiarity to perform the test than in the controls. Similarly to the patient reported by Aggleton et al., (2005), these scores reflect an improvement in recognition memory from those obtained sooner after brain injury (Kapur & Brooks, 1999).

In sum: there are a large number of patients on record who show relative sparing on tests of recognition over recall, for at least some kinds of materials. When recognition was shown to be relatively spared, this appeared to be underpinned more by familiarity than recollection based processes. Although these results support theory 1, it should be noted that the reverse dissociation, namely intact recollection in the context of impaired familiarity has never been documented, at least in the context of MTL amnesia. The results are therefore also compatible with a MTL redundancy view, whereby recollection always follows a feeling of familiarity, but that recollection can be selectively impaired (see also Montaldi, Spencer, Roberts, & Mayes, 2006).

### 6.2.2.2 Support for Theory 2

There is also evidence suggesting that the hippocampus plays a role in both recollection and familiarity. Chan, Revesz & Rudge (2002) have reported neuropathological findings on patient NT, who became densely amnesic following a unilateral right temporal lobectomy for epilepsy which included the hippocampus and the amygdala (Warrington & Duchen, 1992). The patient presented with severe global impairment both in recognition and recall memory tests. Her postmortem pathological re-examination revealed sclerosis of the unresected left hippocampus but no significant pathology extended beyond the hippocampus. The appearance of the resected right temporal lobe was unremarkable. Thus, it is possible that NT's recognition memory deficit was caused by the bilateral hippocampal damage. However, as Squire and Bayley (2006) point out, NT's right temporal lobe resection means that the damage extends well outside of the hippocampus, and therefore interpretation of these results is problematic.

A large body of evidence supporting Theory 2 comes from a series of studies by Squire and colleagues (Manns & Squire, 1999; Manns et al., 2003; Reed & Squire, 1997; Wais, Wixted, Hopkins, & Squire, 2006). They have described at least 12 patients with relatively selective hippocampal damage who were impaired on a range of recognition memory tests. More recent studies have included relatively large groups of patients with selective hippocampal damage and directly estimated recollection and familiarity using the Remember/Know technique and ROC analyses of confidence rating data (Manns et al., 2003; Wais et al., 2006). Both of these studies documented impairments in both recollection and familiarity. However, some patients had damage extending outside the hippocampal formation (GD, LM and WH: Rempel-Clower et al., 1996) and MRI data has not been available for one case (e.g. Manns et al., 2003). Moreover, in the studies reporting quantitative volumetric MRI data, hippocampal volume loss was minimal in one case (10% for patient MJ: Manns et al., 2003), and individual data was either missing (KE: Wais et al., 2006), or inconsistent across studies (e.g. LJ's hippocampal volume reduction has been reported as 34% and 28%: Manns & Squire, 1999; Manns et al., 2003; and RS's as 40% and approximately 30%: Manns et al., 2003; Gold & Squire, 2005). Thus, whilst these data appear compelling, it is questionable whether all these reported cases would stand up to the rigorous anatomical scrutiny that is commonly applied to single cases.

#### 6.2.2.3 Summary

This review of the lesion studies, focusing on the anatomical structures concerning the anatomical underpinnings of recollection and familiarity processes in anterograde memory indicate that the available evidence is inconclusive. It has been suggested that "...more patients with apparently selective hippocampal lesions urgently need to be identified and given extensive hypothesis-driven neuropsychological assessments..." (page 339, Mayes et al., 2002).

### *6.2.3 Aims*

The present study had two main aims. First, to investigate material specific memory effects following focal medial temporal lobe damage, focusing on verbal materials and two classes of non-verbal materials (scenes and faces). The second was to investigate the role of the hippocampus in recollection- and familiarity-based memory processes for these materials. Data will be presented from three patients with adult acquired brain lesions, VC, RH and JC. VC and JC had bilateral hippocampal damage, and JC had neuropsychological evidence for pathology that probably extended to other temporal and possibly frontal areas. RH had unilateral right hippocampal damage. All patients carried out a comprehensive battery of standard neuropsychological tests, including a detailed investigation of anterograde memory abilities (see Chapter 3). In addition, three performance-matched experimental tests, designed to estimate the contribution of recollection and familiarity to memory performance employing three different types of memoranda (words, unfamiliar scenes and unfamiliar faces) were administered.

## 6.3 Summary of the neuropsychological profiles of the three patients

The results of detailed neuropsychological investigations of the three patients are presented in Chapter 3. However, it is useful to summarize the relevant points here.

### *6.3.1 Patient VC*

VC performs adequately on all tests of intellectual, naming, perceptual and executive abilities that he has been administered. His performance on a comprehensive battery of semantic memory tests is also perfectly adequate. The results of the previous chapter also indicate that his topographical perception is also well preserved. However, VC has a very severe global amnesia. He performs close to floor on both verbal and non-verbal memory tests. He is also very impaired on almost all tests of verbal and non-verbal recognition. On the Doors & People Test, his performance is impaired on all subtests. Within the context of his global amnesia, it is interesting to note that his face recognition memory, as assessed by the RMT, appears to be somewhat preserved, at least over more recent assessments (from 7 years previous to the current investigation).

### *6.3.2 Patient RH*

Similar to VC, RH performs well on tests of intellectual, naming, perceptual and executive abilities. Her performance on an extensive semantic memory battery was also normal. The results of the previous chapter suggested that RH's topographical perception may be mildly impaired. Assessment of her memory skills revealed a mixed pattern of performance. In general, she performs well on most tests of verbal memory, although noticeably less well on tests of story recall. Her overall performance on non-verbal memory tests is much poorer. Thus, her performance on tests of figure recall and scene recognition falls below the 10th percentile and she is impaired on the visual recall subtest of the Doors & People Test. However, she scored in the normal range on the visual recognition subtest of the Doors & People Test. Her face recognition is intact.

### *6.3.3 Patient JC*

In contrast with VC and RH, JC has clear impairment in cognitive modules other than long-term memory. His performance IQ was below that predicted on the basis of his NART IQ and educational level. His nominal skills were profoundly impaired and his performance on executive tests was inefficient. However, he performed adequately on tests of visual perception and he remained alert and cooperative throughout testing sessions. On tests of anterograde memory, his performance was consistently impaired, irrespective of test materials or format.

## 6.4 Experimental Methods and Procedures

### *6.4.1 Participants*

All three amnesic patients took part in the experimental study (VC, RH and JC).

#### 6.4.1.1 Controls

There were two groups of controls; an older adult group matched in terms of age to VC, and a younger adult group matched in terms of age to RH and JC. The older group comprised 23 adults (19 males, 4 females). Their mean age was 76.3 years old (SD = 2.7, range = 70-80). Their NART estimated IQ was 110.6 (SD = 9.8, range = 96-129). The younger group comprised 16 adults (4 males, 12 females). Their mean age was 63.1 years old (SD = 5.6, range = 55-73) and their NART estimated IQ was 101.2 (SD = 7.7, range = 95-113). All controls were neurologically intact. Not all controls were administered all three of the memory tests. However, it was ensured that the subsample that served as controls for each test were representative of the larger "pool". The number of controls for each test is presented together with the results.

### *6.4.2 Three new verbal and non-verbal recognition memory tests*

#### 6.4.2.1 Materials

There were three new experimental tests. For the verbal test, 160 words from the Toronto word pool were used, comprising both concrete and abstract words. For the scenes test, 160 black and white photographs of outdoor scenes, containing buildings with no obvious distinguishing local features, were used. The scenes did not contain people. Verbal cues (e.g. house numbers, street names) were digitally removed. For the faces test, 160 black and white photographs of male Caucasian faces with no obvious distinguishing features were used. For each test the 160 stimulus items were split to form a set of 80 study items and 80 unstudied "lure" items.

#### 6.4.2.2 Procedure

For each test there was a Study phase and a Test phase. The Study phase required the subjects to decide whether (1) the word was "concrete" or "abstract" (Words test); (2) the architecture was "pleasant" or "unpleasant" (Scenes test), or; (3) the face was "pleasant" or "unpleasant" (Faces test). Study items were presented individually for approximately 3 seconds each.

In the test phase the study items and lure items were randomly intermixed and presented sequentially. Subjects made recognition judgements after each item. Judgements were made according to a 6-point confidence scale. "1" corresponded to the most confident judgement that the item was "new" (previously unstudied) and "6" corresponded to the most confident judgement that the stimulus was "old" (previously studied). It was stressed that participants had to make full use of the 6-point scale by spreading their responses across all the possible confidence ratings.

#### 6.4.2.3 Design

For the words test, the 80 study items were presented in one block, immediately followed by the 160 items used in the tests phase (80 studied and 80 unstudied lure items). In order to equate the non-verbal tests with the verbal tests for difficulty, the 80 study items and 160 test items in the visual tests, were presented in 2 blocks separated by a short break (no less than 10 minutes). In each block we presented 40 study items and 80 test items. In our subsequent analyses we sum across the results obtained in the two blocks for each non-verbal memory test. Despite the relatively large number of study items, there was no indication that any of the patients or controls suffered from a lack of attention or motivation during the tasks.

#### 6.4.2.4 Analyses

##### *Analysis 1*

The main aim of the first analysis was to compare the overall level of performance of the three patients with their age-matched controls. Z-transformed ROC curves were plotted from the confidence ratings for the recognition responses for all tests. From these zROC plots, an unbiased measure of sensitivity can be calculated (da). According to signal detection theory, the slopes of the zROCs provide a measure of the variance ratio between the strength of "old" items and "new" items (Macmillan & Creelman, 2003). This corresponds to the asymmetry of the ROC function, which may be affected by recollection (Aggleton et al., 2005). Therefore the slopes of the zROCs of patients were also compared to those of the controls. Full details of this analysis are in the Appendix at the end of this chapter.

##### *Analysis 2*

The aim of the second analysis was to estimate the contribution of recollection and familiarity to the patients' performance on the tasks. The dual process theory assumes that performance on recognition memory tasks is underpinned by two independent processes (recollection and familiarity). Recollection is held to be a high-threshold retrieval process whilst familiarity may be described by a standard equal-variance signal detection model. The procedure used by Yonelinas and colleagues (e.g. Yonelinas et al., 1998) fits the points of the ROC to a quadratic curve, but allows the intersect with the y-axis to vary. The intersect is taken as an estimate of the probability that an item is recollected whilst the degree of curvature is taken as an estimate of familiarity. Curve fitting can be carried out by the Solver in Excel.

This procedure typically gives very good fits to group averaged data, but we have found that it is unsuitable for estimating recollection and familiarity on a case-by-case basis. There were three main reasons for this. First, in both patients and healthy controls, the model would occasionally generate fits to the data where the estimate of recollection was negative. This even happened in cases where the overall performance was high and the testee justified their responses with answers the demonstrated that the item was recollected. It was further noted that when the estimates of recollection were negative, very high estimates of familiarity were also obtained. Second, in some cases the Solver gave inconsistent fits to the same ROC if rerun several times. This could cause the estimate of the probability that an item was recollected to change by as much as 0.6 (out of 1). Third, as a consequence of these issues, the variability in recollection estimates in the controls was very large indeed, which greatly limited the power of this procedure to detect an impairment in recollection (and to a lesser extent, familiarity).

Our heuristic solution to these problems preserved the assumptions of the dual-process model, avoided the above problems and gives sensible estimates of recollection (see Appendix for full details). Briefly, recollection was estimated using the hit and false alarm rates for the most conservative criterion adopted by a subject ("most confident that the item was previously seen"). This adopted estimate (hits - false alarms) effectively assumes that all highly confident responses reflect recollection, after correcting for guessing (see Appendix for a full discussion of whether this assumption is justified). Familiarity estimates were then obtained by constraining the intercept with the y-axis according to the probability that an item was "recollected" and then fitting the points of the ROC curve using a standard equal variance model using the Solver in excel.

## 6.5 Results

### *6.5.1 Results of analysis 1*

The results of analysis 1 are shown in Table 5-1. The results are also summarized in Figure 6-1, where poorer overall performance results in flatter ROCs and zROCs which lie closer to the diagonal (which represents chance performance).

Striking differential results were found according to the types of material used for two of the three patients (VC and RH). VC was significantly impaired on the verbal and topographical memory tests. In contrast, his performance on the faces test was preserved. RH showed material specific effects, although these were somewhat different than those found for patient VC. Her performance was unimpaired for verbal and faces material. However, her memory for topographical material was impaired. Unlike VC or RH, no material specific effects were observed in JC's performance on the three tests. In fact, he was clearly impaired for all types of material.

The slopes of the patients' zROCs were generally close to 1, whereas the slopes of the controls' zROCs were generally less than 1. However, this was not always the case and there was only one instance where there was a *significant* difference in slopes between a patient's zROC slope and the controls (VC's performance on the scenes test). Therefore, there is little evidence that the asymmetries of the patients ROC curves are qualitatively or quantitatively different from that of the controls (Figure 6-1).

Overall, this first analysis indicated that VC and RH, with clear cut hippocampal damage, showed impaired performance on the memory test using topographical materials, but preserved performance on the test using human faces. In contrast, JC showed memory impairment for both types of non-verbal materials. VC and RH differ markedly on their performance on a test of verbal memory; VC was very impaired, whilst RH obtained a normal score. JC obtained very impaired scores on the verbal memory test. In the second analysis we wished to extend these findings by analyzing separately the contribution of recollection and familiarity to the patients' performance on these tests.

### Table 6-1: Analysis 1 – Overall performance on the three experimental tasks

| | | VC | | | RH | | | JC | | | Old controls | | | Young controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | value | t | P | value | t | P | value | T | P | N | Mean | SD | N | Mean | SD |
| Accuracy (*da*) | Words | 0.57 | -3.80 | <0.00 | 2.26 | 1.57 | 0.08 | -0.01 | -5.93 | <0.00 | 15 | 1.61 | 0.26 | 8 | 1.75 | 0.31 |
| | Scenes | 0.48 | -2.80 | 0.01 | 0.95 | -2.57 | 0.02 | 0.35 | -3.13 | <0.00 | 12 | 1.61 | 0.39 | 8 | 1.76 | 0.30 |
| | Faces | 1.25 | -0.93 | 0.19 | 1.58 | -0.09 | 0.47 | 0.61 | -2.67 | 0.01 | 9 | 1.58 | 0.35 | 8 | 1.61 | 0.38 |
| Slopes | Words | 1.28 | 1.60 | 0.07 | 0.89 | 0.66 | 0.26 | 1.12 | 0.95 | 0.18 | 15 | 0.88 | 0.24 | 8 | 0.73 | 0.22 |
| | Scenes | 1.24 | 1.94 | 0.04 | 0.85 | 0.06 | 0.48 | 1.08 | 1.25 | 0.12 | 12 | 0.80 | 0.22 | 8 | 0.84 | 0.19 |
| | Faces | 0.70 | -1.03 | 0.17 | 0.70 | -0.27 | 0.40 | 0.97 | 0.44 | 0.33 | 9 | 0.89 | 0.18 | 8 | 0.77 | 0.22 |

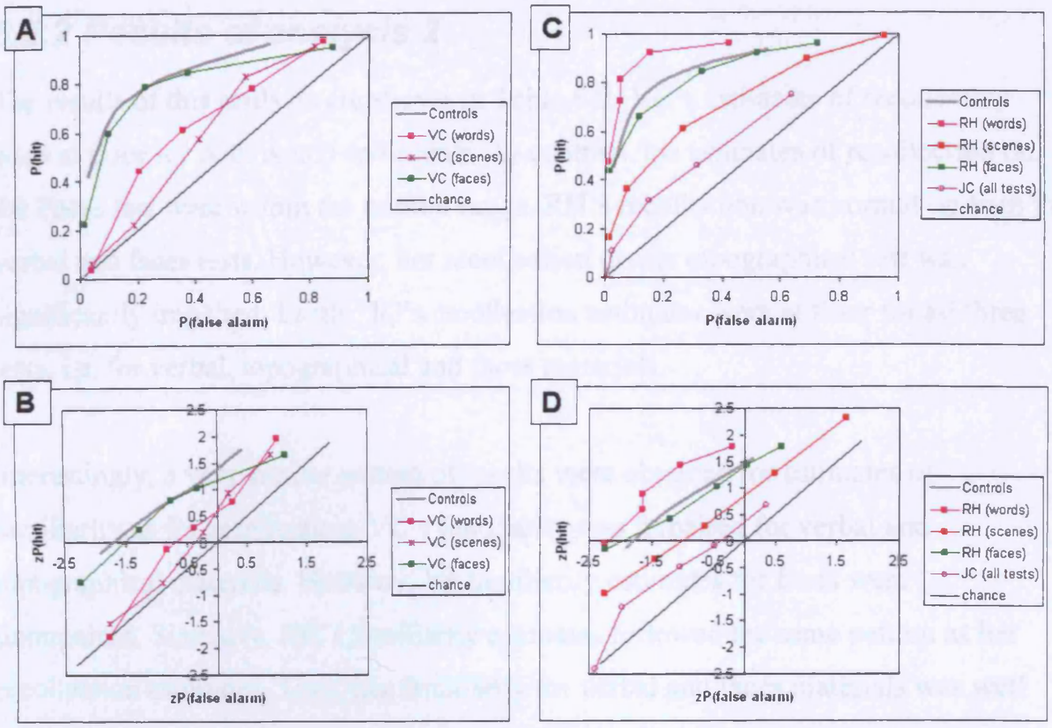
**Legend**: Accuracy (*da*) and the slope of the zROCs for each patient and controls (see text for details). Comparisons were made based on the procedure of Crawford & Garthwaite (2002).

### Table 6-2: Analysis 2 - Estimates of recollection and familiarity

| | | VC | | | RH | | | JC | | | Old controls | | Young controls | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | value | t | P | value | t | P | value | t | P | Mean | SD | Mean | SD |
| Recollection | Words | 0.00 | -2.63 | 0.01 | 0.46 | -0.22 | 0.42 | 0.00 | -4.59 | 0.00 | 0.38 | 0.14 | 0.49 | 0.10 |
| | Scenes | 0.03 | -4.43 | <0.00 | 0.15 | -3.02 | 0.01 | 0.00 | -4.51 | 0.00 | 0.44 | 0.09 | 0.45 | 0.10 |
| | Faces | 0.21 | -0.79 | 0.23 | 0.43 | +0.64 | 0.27 | 0.03 | -2.49 | 0.02 | 0.36 | 0.18 | 0.34 | 0.12 |
| Familiarity | Words | 0.63 | -1.85 | 0.04 | 1.60 | +1.16 | 0.14 | 0.31 | -2.73 | 0.01 | 1.24 | 0.32 | 1.21 | 0.31 |
| | Scenes | 0.45 | -1.87 | 0.04 | 0.74 | -1.68 | 0.07 | 0.31 | -3.52 | 0.00 | 1.19 | 0.38 | 1.36 | 0.28 |
| | Faces | 1.28 | +0.03 | 0.49 | 1.05 | -0.69 | 0.26 | 0.61 | -1.74 | 0.06 | 1.27 | 0.36 | 1.34 | 0.39 |

**Legend**: Estimates of recollection and familiarity for each patient and controls (see text for details). Comparisons were made based on the procedure of Crawford & Garthwaite (2002).

**Figure 6-1: Performance on the three experimental tasks**



**Legend**: A. Recognition memory ROCs for VC and age-matched controls on the tasks. Control data across all tasks are combined. Note that VC's faces ROC is similar to the controls, whilst his words and scenes ROCs are much flatter and closer to chance. B. Recognition memory zROCs for the same tasks. Note that the distance between the zROC and the line representing chance performance provides a measure of sensitivity, whilst the gradient of the straight line is a measure of the asymmetry of the ROC function, which some have argued may be related to recollection (Aggleton et al., 2005). C. Recognition memory ROCs for RH, JC and age-matched controls on the tasks. Control data across all tasks are combined. RH's data from all tasks is shown separately. JC's data across all tasks are combined. Note RH's superior performance on the words test and that her face ROC is similar to the controls whilst her scenes ROC and JC's words/scenes/faces ROC is flatter. D. Recognition memory zROCs for the same tasks.

### 6.5.2 Results of analysis 2

The results of this analysis are shown in Table 6-2. VC's estimates of recollection were at floor for both words and scenes. In contrast, his estimates of recollection on the Faces test were within the normal range. RH's recollection was normal on both the verbal and faces tests. However, her recollection on the topographical test was significantly impaired. Lastly, JC's recollection estimates were at floor for all three tests, i.e. for verbal, topographical and faces materials.

Interestingly, a very similar pattern of results were obtained for estimates of familiarity as for recollection. VC's familiarity was impaired for verbal and topographical materials. However, his familiarity estimates for faces were unimpaired. Similarly, RH's familiarity estimates followed the same pattern as her recollection estimates. Thus, her familiarity for verbal and faces materials was well within the normal range. In contrast, her familiarity for topographical materials was weak, with the difference between RH and the controls being marginally significant ($P = 0.07$). JC continued to show no clear evidence of spared memory processes for any material. His familiarity estimates were markedly low on all three tests; they were impaired on the verbal and topographical memory tests and borderline impaired for the faces memory test ($P = 0.06$).

Overall, the second analysis produced a number of interesting results. First, the material specific effects found for both patients with hippocampal lesions (VC and RH), were in evidence both for recollection and familiarity estimates. Patient JC, with neuropsychological evidence of more extensive cortical damage showed no clear evidence of sparing of either recollection or familiarity for both visual materials. The contrast between VC and RH's verbal memory processes is also striking; VC was grossly impaired both in terms of recollection and familiarity, whilst RH's estimates of recollection were similar, and in the case of familiarity, better, than the controls'. JC's estimates of recollection and familiarity for verbal materials were grossly impaired.

## 6.6 Discussion

The present study had two related aims: first, to investigate the role of the MTL, particularly the hippocampus, in memory for different categories of materials; second, to investigate the contribution of recollection- and familiarity-based processes to the recognition judgments made by these MTL amnesics. We were particularly interested in contrasting recognition memory for two categories of non-verbal materials; human faces and outdoor scenes. All three patients were administered three new experimental tasks (using words, scenes and faces memoranda). The results were analyzed using two separate ROC analyses to assess overall level of performance and to estimate the contribution of recollection and familiarity to recognition judgments. The results are summarized in Table 6-3 and these findings will de discussed in detail below.

**Table 6-3: Summary of the results on the 3 new memory tests**

| | VC | RH | JC |
|---|---|---|---|
| Words | × | ✓ | × |
| Scenes | × | × | × |
| Faces | ✓ | ✓ | × |

Legend: × = poor performance, ✓ = normal performance

### *6.6.1 Category specific memory impairments*

#### 6.6.1.1 Is the right hippocampus necessary for scene recognition?

All three of the patients were impaired on the topographical memory test, including RH with unilateral right-sided hippocampal damage. The items of this test were pictures of outdoor scenes, all showing buildings in the context of a large-scale space. Impaired scene recognition has also been reported in another patient with selective hippocampal damage and in patients with mild AD, with damage that consistently included the whole of the hippocampus (Carlesimo et al., 2001; Lee et al., 2006). It is possible that such items are normally encoded as stimuli potentially relevant for navigation. Therefore, one can speculate that performance on these tasks may be underpinned by the same areas known to subserve navigation in healthy adults (see Henson, 2005 and; Maguire & Cipolotti, 1998 for a similar proposal). There is a considerable body of evidence that the right hippocampus plays a critical role in navigation and spatial memory (reviewed in Chapters 1 and 4).

There are patients with selective hippocampal damage who nevertheless have been reported to show intact performance on tests of scene recognition, at least when seen from the same view at test and retest. Data from one of these patients, Jon, will be presented in the next chapter. Another, YR, is discussed in detail below.

#### 6.6.1.2 Is the hippocampus necessary for face recognition?

Both VC and RH had spared memory for unfamiliar faces. We noted that this is not an uncommon finding in patients with hippocampal lesions. A number of patients have been reported who, despite being very amnesic, show somewhat preserved performance on the faces subtest of the RMT (patients LM, PH, LJ, AB and WH, Reed & Squire, 1997; patinet BE, Kapur et al., 1999). In keeping with this, patients with hippocampal damage recently reported by Lee et al., (2005b; 2005a) performed well on the faces subtest of the RMT (the mean for the group was 93%).

VC and RH share similarities with a patient reported by Carlesimo and colleagues (2001) who had shrunken hippocampi bilaterally. In the context of an intact cognitive profile, the patient presented with a severe and global anterograde amnesia but preserved face recognition memory. The authors speculated that in their patient neural circuits *within* the hippocampal formation underlying the "storage and consolidation of visuoperceptual information relative to human faces were selectively preserved" (Carlesimo et al., 2001: p345-6). Our findings of preserved recognition memory for faces in the context of selective hippocampal damage in patients VC and RH support the view that this type of memory is not critically dependent on the hippocampus, and may depend on other structures.

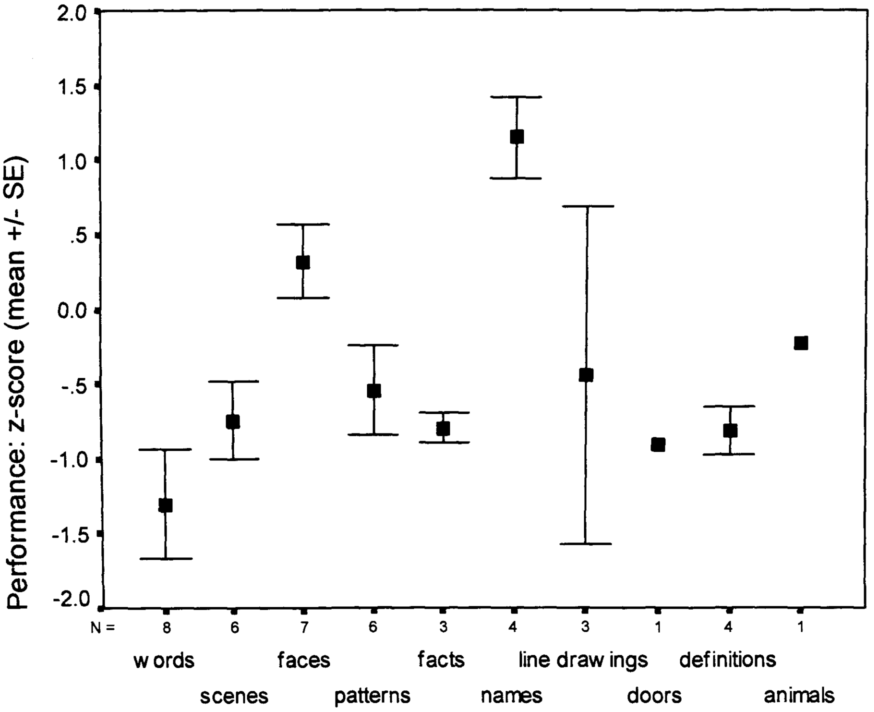
I am aware of at least two patients on record with impaired face recognition in the context of selective hippocampal damage (patient GD, Reed & Squire, 1997; patient PS, Verfaellie, Koseff, & Alexander, 2000). However, interpretation of these cases is problematic. GD was described as being "uncooperative, depressed, and uninterested in testing" and "his frequent low motivation during testing sessions made it difficult to interpret low scores" (Rempel-Clower et al., 1996: p5293). The pathology in patient PS may extend beyond the hippocampus as her MRI scan is reported to show "mild generalized cortical atrophy" and "ventricular enlargement for her age may be present" (Verfaellie et al., 2000: p487). A third patient, KN, also performs poorly on tasks of face recognition, in the context of rather selective hippocampal lesions (Aggleton et al., 2005). However, this patient is also reported to have bilateral ischaemic damage to the occipital lobes (greater on the left than the right) and the authors also raise the possibility that his poor performance on face recognition memory tasks may be related to additional amygdala damage.

#### 6.6.1.3 Patient YR – a special case?

Together with VC and Jon, YR is one of the most extensively studied hippocampal amnesic patients in the literature. YR's hippocampus is reduced in size by approximately the same amount as VC and Jon, and there is no evidence for any extrahippocampal damage. YR's performance on memory tests is one of the most compelling demonstrations that recognition can be intact whilst recall is impaired. Further studies have suggested that her memory performance on recognition tests is mediated by familiarity processes (Holdstock et al., 2002; Mayes et al., 2004). There are therefore, clear differences between her memory profile and VC's, which would not be predicted on the basis of anatomy. It may therefore be fruitful to ascertain whether there are any similarities between the patients.

In 2002, Mayes and colleagues documented YR's performance on a large range of tests of recall and recognition. The tests involved a range of materials, including words, faces, and scenes. Her performance on all tests, collapsed across test format and delay interval is summarized in Figure 6-2.

**Figure 6-2: Performance of YR on item recognition tests**



On the basis of our study, YR, with selective bilateral hippocampal damage, would be predicted to perform better on recognition tests involving faces than either words or scenes. An oneway ANOVA comparing her performance on these three materials was significant (F=7.6, d.f.=2, 18, P<0.01). Post-hoc comparisons revealed the difference between her performance on words and faces tests was significant (P<0.01), with the comparison between scenes and faces failing to reach significance (P<0.1). Interestingly, there was a very large difference on YR's performance on tests using names and words as stimuli, hinting at an intriguing material specific memory effect not addressed by our data (Figure 6-2). In sum: although there are still clear differences between YR and VC, this brief analysis suggests that correspondences can be observed.

### 6.6.1.4 Which brain areas are necessary for face recognition memory?

In contrast to VC and RH, JC was impaired on tests of face recognition. This demonstrates that non-verbal memory impairments are not always associated with spared recognition memory for unfamiliar faces. Unfortunately, the extent of JC's pathology is unclear. There has only been one case in the literature which has convincingly shown a selective deficit in face learning (with normal face perception) in the context of an adult acquired lesion, but this patient had diffuse brain damage following a head injury (Tippett, Miller, & Farah, 2000). Consequently, it is unclear which brain regions are necessary to subserve face recognition memory. This issue is discussed in the General Discussion of this thesis, where it is speculated that the interaction between face processing areas in the fusiform gyrus and anterior temporal lobe regions in the right hemisphere may be critical.

### *6.6.2 Recollection and familiarity*

The issue of whether the hippocampus plays a critical role in both recollection and familiarity based recognition processes is highly contentious (for reviews, see (Aggleton & Brown, 1999; Rugg & Yonelinas, 2003; Squire et al., 2004). Some researchers have proposed that extrahippocampal areas such as the perirhinal cortex may be sufficient to subserve familiarity-based recognition processes (Theory 1), whilst others have argued that MTL regions support a more general declarative memory system underpinning both processes (Theory 2). It should be noted that any conclusions made about the contribution of recollection and familiarity to memory performance are necessarily constrained by the methods used to estimate these putative processes. However, we have attempted to use the same methodology as other recent studies in order to permit direct comparisons between our results and those from other amnesic patients. Our experimental tasks revealed that deficits in recollection were always associated with deficits in familiarity. This is of particular interest in the context of patients VC and RH, who have relatively selective hippocampal damage. The ROC data revealed that whilst recollection was at floor in several instances, familiarity was somewhat preserved. It is proposed that the patients' above chance performance on the tests was underpinned by familiarity based processes. Nevertheless, these residual familiarity processes could not support adequate recognition memory. These results are difficult to reconcile with Theory 1, and are more consistent with Theory 2. However, these data could be seen to be most compatible with a MTL redundancy theory (Montaldi et al., 2006). This proposal is explored further in the general discussion of this thesis (Chapter 8). With respect to memory for faces, it is important to note that there was no evidence that either VC's or RH's spared face recognition was underpinned by familiarity processes alone.

These conclusions are consistent with the results of the anterograde memory assessment in the case of VC. VC was clearly impaired on tests of recall and recognition for virtually all types of memoranda, although his performance was usually above chance on recognition tests. These data provide a degree of cross validation with the experimental studies reported here. However, RH's memory profile was less clear cut. Despite performing well on most verbal recall tests, her performance was noticeably poorer on story recall. These tests were taken from the Adult Memory and Information Processing battery (Coughlan & Hollows, 1985). It is possible that performance on these tasks is in part supported by spatial memory, since the narrative contains involves characters moving through an environment. We hope to investigate this issue in the future. RH's performance on the Doors recognition subtest of the DPT was within the normal range. This could reflect an impairment of recollection but not familiarity for these materials (as is argued to be the case for YR and Jon: Mayes et al., 2001; Baddeley et al., 2001). However, it is also possible that RH may have relied in part upon verbal strategies to perform the task, or that both her recollection and familiarity for this type of material was intact (as appeared to be the case for unfamiliar faces). The performance of hippocampal amnesics on the DPT is further discussed in the General Discussion.

Our conclusions may be considered not easily reconcilable with fMRI studies of human memory in normal subjects reporting greater activity in the hippocampus during recollective recognition than in tasks more likely to depend on familiarity (Davachi, Mitchell, & Wagner, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Ranganath et al., 2004; Montaldi et al., 2006). However, it should be noted that the hippocampal damage in VC and RH almost completely abolished recollection while it led to impaired, but above chance, familiarity. This suggests that the hippocampus is completely critical for recollection and also that it contributes, at least in part, to familiarity. Thus, our findings are compatible with the fMRI findings of greater activation of the hippocampus during a recollection response than a familiarity one.

A recent review of functional imaging studies of recognition memory found little clear evidence for divisions of labour between hippocampal and extrahippocampal regions (Henson, 2005). Nevertheless, there does seem to be a general trend that familiarity effects can be observed in regions of the anterior temporal lobe which typically have taken the form of decreases in the fMRI signal (e.g. (Henson, 2005; Montaldi et al., 2006). One possible interpretation of these findings is that they reflect decreases in neuronal activity to repeated items, as has been observed in the perirhinal cortex (Brown & Xiang, 1998). If this is the case, these data are not necessarily in opposition to our results, if the areas are necessary but not sufficient to underpin normal recognition memory. This is rather hard to ascertain using functional imaging techniques. It should also be noted that another plausible interpretation of these effects is that they reflect activation due to encoding of new items. In sum: it is unclear at the moment whether the functional imaging data is consistent with the neuropsychological data presented in this thesis. It may be that functional imaging of patients with focal lesions could be useful in resolving these issues.

## 6.7 Conclusions

In summary, we have documented a detailed cognitive investigation of three patients with memory impairments. Two of the patients had relatively selective hippocampal damage; one bilaterally (VC) and one with unilateral right-sided damage (RH). Both of these patients performed poorly on tests of memory involving pictures of outdoor scenes, highlighting a critical role for the right hippocampus in memory for these types of visual memoranda. VC was additionally impaired on a test of verbal recognition memory (using words), suggesting that the left hippocampus is sufficient to subserve performance on this test. Importantly, both patients were unimpaired on a test of visual memory involving pictures of faces, which indicates that the hippocampus is not necessary for face learning and recognition processes – at least over the durations employed in these tasks. Results from a further severely amnesic patient (JC) demonstrated that spared recognition memory for faces is not invariably found in the context of global memory impairment. Analyses of the patients' ROCs suggested that their above chance memory processes may be underpinned by residual, but compromised, familiarity processes.

In the next chapter I aimed to replicate the findings of this chapter with respect to memory for scenes versus faces in a third hippocampal amnesic; patient Jon.

## 6.8 Appendix – Details of analysis 1 and analysis 2

### *6.8.1 Analysis 1*

The receiver operating characteristic (ROC) is a function that relates the proportion of correct recognitions (i.e. the hit rate) to the proportion of incorrect recognitions (i.e. the false alarm rate). The ROC can be plotted as a function of confidence, such that the leftmost point includes only the most confidently recognized items and subsequent points include less and less confident responses. ROCs plotted from recognition memory experiments are typically curvilinear and the precise shape of the ROC can offer some insight as to how recognition judgements are made. It is also often useful to z-transform the ROC (zROC) as the shape of this is also informative.

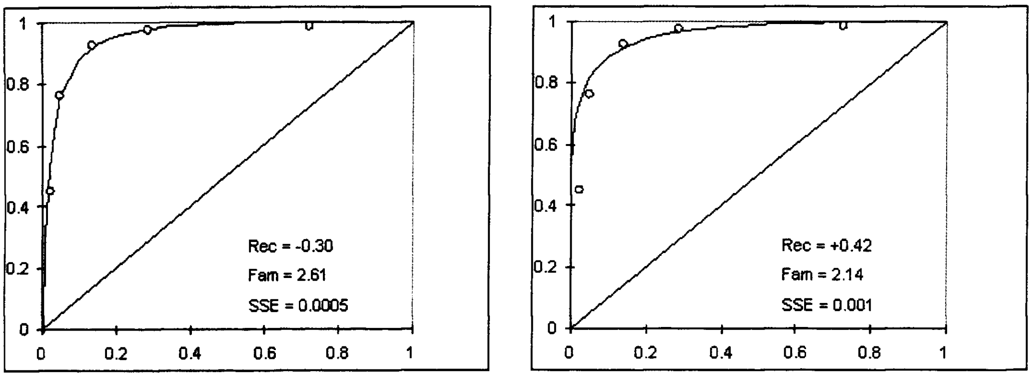
A simple measure of overall performance accuracy (or sensitivity) is d-prime (*d'*), which assumes that the ROC curve is symmetrical about the diagonal, and that the slope of the zROC has a gradient of 1. However, it is well established that ROCs plotted from memory experiments are often asymmetrical and that zROCs are approximately linear with a gradient less than 1. Since, neither the degree of asymmetry of the ROC nor the slope of the zROC necessarily vary systematically with recognition accuracy, at least two parameters are needed to fully characterize individuals' performance on the test (see (Macmillan & Creelman, 2003; Yonelinas, 2001). Provided the zROC is linear, it is possible to use an unequal variance signal detection methodology (Macmillan & Creelman, 2003). Importantly, this method does not make any assumptions about the contribution of recollection and familiarity to recognition performance and has been shown to provide good fits to ROC data acquired using similar procedures to ours (Heathcote, 2003; Glanzer, Kim, Hilford, & Adams, 1999; Yonelinas et al., 1998; Aggleton et al., 2005). The two parameters needed to characterize performance are a measure of the degree of asymmetry of the ROC and a measure of sensitivity. The asymmetry of the ROC was measured as the slope of the z-ROC (which corresponds to the variance ratio of the noise distributions of studied and unstudied items). Sensitivity (da) is calculated from the slope of the z-ROC and its intercept with the y-axis (Macmillan & Creelman, 2003).

We plotted separate z-transformed ROC (zROC) curves for each subject based on their confidence rating judgements. In a small number of cases, the hit rate or false alarm rate was 0 or 1; i.e. values which cannot be z-transformed. In these cases the value was taken to lie between midway between 0 items and 1 item. Thus, a rate of 0/80 was converted to a rate of 0.5/80 and a rate of 80/80 was converted to a rate of 79.5/80. All participants' zROCs were approximately linear.

### 6.8.2 Analysis 2

As mentioned in the main text, we found that the procedure used by Yonelinas and colleagues was unsuitable for assessing whether recollection and familiarity were significantly impaired at the level of a single case. In fact, similar studies to ours failed to find significant deficits in recollection using this technique, although the patients studied were reported to have recollection impairment on the basis of other tests (Aggleton et al., 2005; Yonelinas et al., 2002). The main concern was that the procedure would sometimes generate negative estimates of recollection (see Figure 6-3). Our solution to this problem was to assume that responses using the most conservative confidence level (most confident that the item was seen previously), were made on the basis of recollection. Since a small number of false alarms were made using this criterion, we subtracted the false alarm rate from the hit rate, to obtained am estimate of recollection that was corrected for these false alarms (which may represent guesses, lapses in attention or false memories). The fits made by the two procedures are shown in Figure 6-3.

**Figure 6-3: Example of the curve fitting procedure used to estimate recollection and familiarity**



**Legend**: Left; an individual's performance on the scenes test fitted to the dual-process model. Although the curve provides a good fit to the data, the value for recollection is impossibly low. Right; the same data fitted with the modified procedure used in this study. Recollection (Rec) is estimated as hits-false alarms when using the most conservative criterion. Familiarity (Fam) is calculated as the best fitting curve to the points given this constraint. Note that the data is still well fitted by this procedure and there is little change in the sum of squared errors (SSE) between the predicted and the obtained data.

The main potential problem with our procedure is that highly confident responses may not reflect only recollection (Yonelinas, 2001). Participants were strongly encouraged to make use of the full confidence scale, and only use the extreme confidence responses when they were most sure that an item was new or old. Thus our assumption is not unreasonable. However, if highly confident responses were made on the basis of familiarity, these will contribute to the estimate of *recollection*, and will not be included in the estimate of familiarity. It may therefore be that our procedure slightly increased the estimates of recollection and reduced the estimates of familiarity. However, when the patients were performing poorly on the tasks, they tended to use the extreme confidence responses only rarely, and therefore recollection estimates were close to floor and considerably lower than the controls. I therefore consider it unlikely that the recollection impairments were unreliable. In the cases where recollection was close to floor, the patients' performance was driven almost entirely by familiarity based processes. If our analysis did underestimate familiarity for the reasons given above then the controls' estimates of familiarity would be more affected than those of the patients. Thus, any differences between the patients and the controls might be an underestimation of the “true” differences. In fact, additional analyses showed that, with respect to familiarity, the differences between the results obtained using Yonelinas’s original procedure and our modified procedure were trivial.

# 7 Chapter 7: Non-verbal recognition memory in developmental hippocampal amnesia

## 7.1 Introduction

The previous chapter demonstrated striking material specific memory deficits in two patients with relatively selective hippocampal damage. The aim of this chapter was to investigate whether such deficits would be apparent in another patient with hippocampal damage – Patient Jon. Jon has taken part in several investigations of his residual memory skills (see Chapter 3). These have demonstrated a marked dissociation between his performance on tests of recall (which he generally performs poorly) and tests of recognition (which he generally performs well). He is therefore one of the patients who has been taken as supportive of the position that recollective processes can be selectively impaired in the context of preserved familiarity.

There are several reasons why it is of interest to investigate Jon's performance on the tests for scenes and faces from the previous chapter. Face recognition has never been directly contrasted with scene recognition in Jon. Given the evidence for dissociations between memory (and perception) for these types of materials in the context of hippocampal damage, this is clearly of interest. Jon is documented as having preserved visual recognition, hypothesized to be supported by residual familiarity-based processes. However, Jon has never been administered memory tests where he has been required to make confidence judgements in order that the results can be analysed using ROC procedures to assess the contribution of recollection and familiarity. If Jon cannot use recollective-based memory processes to guide his responses, then this will impact upon the shape of the ROC of his performance.

## 7.2 Methods

### *7.2.1 Participants*

Patient Jon (see Chapter 3 for case report) took part in the investigation as well as 4 adult males who served as controls. The controls were 27.5 years old (individual ages;

25, 25, 28 & 32 years old) and had a Ravens Matrices Score of 11.5/12 (individual scores; 11, 11, 12 & 12 correct).

### 7.2.2 Procedures

The same Buildings test and Faces test that were used in the previous Chapter were used, with one important modification. To avoid ceiling effects in the young adult controls, all 80 target items were shown consecutively in the study phase and all 160 test items (80 targets plus 80 lures) were shown consecutively in the test phase. The words test was not administered since pilot studies had already shown that young adults performed close to ceiling and that the test was not matched for difficulty with the Buildings and Faces tests.

### 7.2.3 Results

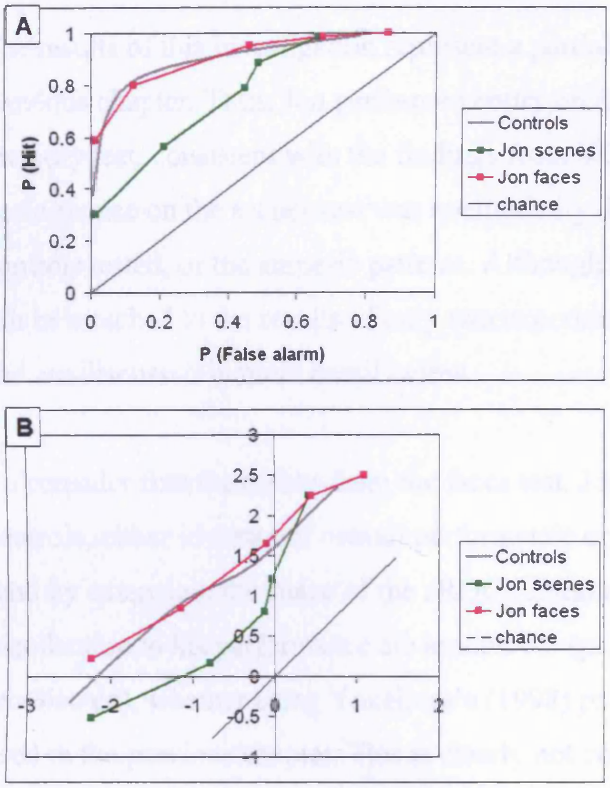
Importantly, the Scenes Test and the Faces Test were matched for overall level of difficulty in the 4 controls. Jon's performance and that of the healthy adults is shown in Table 7-1 and Figure 7-1.

**Table 7-1: Performance of Jon and the controls**

| | Test | Items | Number of responses | | | | | | Sensitivity (Da) |
|---|---|---|---|---|---|---|---|---|---|
| | | | Confidence level | | | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | |
| Controls | Scenes | Old | 1 | 3.5 | 5.8 | 12.2 | 23 | 34 | 2.1 (0.31) |
| | | New | 21.5 | 29.2 | 19.5 | 6.8 | 2.2 | 0.8 | |
| | Faces | Old | 0.5 | 7.8 | 9 | 14.8 | 22.2 | 25.8 | 1.8 (0.45) |
| | | New | 13.8 | 30.5 | 23.5 | 8.5 | 3.5 | 0.2 | |
| Jon | Scenes | Old | 1 | 8 | 8 | 18 | 21 | 24 | 1.3 |
| | | New | 27 | 14 | 3 | 19 | 16 | 1 | |
| | Faces | Old | 0 | 1 | 3 | 12 | 17 | 47 | 2.0 |
| | | New | 11 | 15 | 17 | 27 | 9 | 1 | |

**Legend**: Confidence levels – 1 = most confident that an item <u>was not</u> seen previously, 2 = most confident that an item <u>was</u> seen previously. Mean number of responses are shown for the controls.

**Figure 7-1: Performance of Jon and the controls**



**Legend**: A. Recognition memory ROCs for Jon and age-matched controls on the tasks. Control data for both tasks are combined. Note that Jon's faces ROC is similar to the controls (curved and asymmetrical about the diagonal), whilst his scenes ROC is virtually linear. B. Recognition memory zROCs for the same tasks. Note that Jon's faces zROC and the controls' zROCs are linear, whilst Jon's scenes zROC is u-shaped.

The first important point to be made about Jon's performance on the Scenes test is that his data were not well fitted by either the dual-process model of Yonelinas (e.g. (Yonelinas et al., 1998) or a standard unequal variance signal detection model. Both of these models predict curvilinear ROCs and virtually linear zROCs (if performance is above chance). In fact, Jon's scenes ROC resembled a straight line, whilst his scenes zROC was U-shaped. In terms of overall performance, Jon was impaired (t=-4.4, d.f.=3, P<0.05). However, given the very small size of the control group, this result should be interpreted with caution.

In contrast, Jon's faces ROC and zROC were well fitted by a dual-process model and an unequal variance signal detection model. Moreover, his pattern of performance was indistinguishable from the controls.

## 7.3 Discussion

The results of this investigation represent a partial replication of the findings of the previous chapter. Thus, Jon performed better on the faces memory test than the scenes memory test, consistent with the findings from VC and RH. However, Jon's performance on the scenes test was qualitatively different than that of any of the controls tested, or the amnesic patients. Although there is a limit to how much weight can be attached to the results of only two experimental tests, the results are intriguing and are discussed in more detail below.

To consider first the results from the faces test. Jon performed no differently from controls, either in terms of overall performance or in terms of the shape of the ROC (and by extension, the shape of the zROC). Estimates of the contribution of recollection to his performance are around 0.5 (probability of an item being recollected), whether using Yonelinas's (1998) procedure, or the modified procedure used in the previous chapter. This is clearly not consistent with the view that Jon's residual recognition memory abilities are subserved by familiarity processes alone. In fact, these data are more consistent with the conclusions of the previous chapter; that "recollection-like" and "familiarity-like" recognition processes for unknown faces are not hippocampal dependent.

Jon's pattern of performance on the scenes test was quite different. Jon appeared to be able to confidently accept old items (hits) and confidently reject new items (false alarms) whilst making few errors. In fact, his accuracy was comparably to the controls, if one only includes the extreme confidence levels. This was quite unlike the three amnesic patients in the previous chapter and other amnesic patients in the literature, who are generally (and unsurprisingly) reluctant to use the extreme confident levels if their overall memory for the stimuli is weak. However, Jon was much poorer at distinguishing old and new items when using the middle confidence levels. In fact, during the scenes test, Jon commented that he was either quite sure about the items (in which case he gave 1 or 6 responses) or he felt he was just guessing (in which case he spread his responses almost randomly). Such a pattern of performance is perhaps unsurprising in an individual who has spent his whole life coping with severe memory problems. It appears that his strategy is to attribute a highly confident response to any item that he feels is familiar, and his ability to judge varying degrees of familiarity is compromised – or at least, not expressed in his performance of the scenes test. However, it remains a possibility that Jon has some insight into his ability to judge the strength of his ability to *reject* items (the portion of Jon's ROC corresponding to previously unseen items – the rightmost section – may be somewhat curved, rather than linear; Figure 7-1A).

These findings are somewhat at odds with previous investigations that have documented Jon's intact performance on same-view recognition memory tasks (e.g. (Spiers et al., 2001a; King et al., 2002; King et al., 2004). There are a number of reasons for this. First, and perhaps most important, is that the list lengths of the tests were very much longer than is normally used in recognition memory tests. Jon's performance on a same view task was shown to be affected by increasing the list length (King et al., 2002). Second, it is possible that subtle differences in the stimuli contributed to performance. For example, both the Topographical RMT and the scene recognition task used by Spiers et al., (2001a) contain distinctive objects or people of the sort that were purposely omitted from the stimuli used in the scenes test in this study. Third, our tests used a yes-no procedure, rather than a forced-choice testing procedure, which has been generally used before. This has been reported to affect hippocampal amnesics' performance, especially when the targets and foils are highly similar, as could be argued to be the case in our study (Holdstock et al., 2002; Mayes et al., 2004).

It has been argued that Jon's residual memory processes may reflect functional reorganisation, since his hippocampal damage occurred very early in life (e.g. Manns et al., 2003). It is also plausible, that these processes may be mediated in part by functionally intact portions of his hippocampus, which were demonstrated in a neuroimaging study (Maguire et al., 2001). However, these proposals cannot explain the pattern of results presented here, without first postulating a fundamentally different role of the hippocampus in recognition memory for faces and scenes.

### 7.3.1 Summary

This study has demonstrated, using difficulty-matched tasks, a dissociation between scene recognition and face recognition memory in Jon, a developmental amnesic with selective bilateral hippocampal lesions. Whilst the dissociation in terms of overall performance is interesting, perhaps more informative are the qualitative differences between Jon's performance on the two tasks. On the scenes test, Jon was able to confidently accept old items and confidently reject new items at comparable levels to the controls. However, he showed relatively little ability to distinguish old and new items at intermediate confidence levels. This may be because he was only able to judge whether scenes were old and new on the basis of a single "memory strength" parameter, consistent with previous proposals that he has impaired recollection but intact familiarity-based memory processes. In contrast, on the faces test, he performed no differently from the controls at any confidence level. This indicates that the cognitive resources necessary for normal performance on this task were no different between Jon and the healthy adults.

# 8 Chapter 8: General Discussion

The aim of this thesis was to explore certain issues concerning how we are able to perceive and remember aspects of the environment around us, and what neural systems are necessary to do this. It is perhaps inevitable that no series of investigations can resolve the controversies that abound in these areas. However, it is necessary to evaluate whether the specific hypotheses tested were supported by the data and to establish the implications for prevailing theories in the light of this. Where the data are inconsistent with either the predictions made on the basis of established theories, or the findings of previous studies, possible reasons for the discrepancies should be discussed. I have done this in the Discussion sections of Chapters 2 and 4-7. In some instances I have attempted to re-evaluate the data from previous studies in the light of my results. This has highlighted potential new avenues for research. In this chapter I shall summarize the key findings from experimental chapters and place them in the wider context of research into visual and spatial cognition and memory.

### *8.1.1 Focal deficits and disconnection syndromes*

Chapter 2 investigated visual neglect following posterior cerebral artery stroke. The main finding of interest was not only that several of these patients manifested neglect, but also that the critical lesion appeared to be in the white matter of the occipital lobe. Through careful comparison of the critical lesion associated with neglect with tractography data in healthy humans, it was proposed that disruption of the white matter connecting the medial temporal lobe with the posterior parietal lobe may be important for causing neglect.

When two or more brain regions are both necessary for performing cognitive operations, it is obviously important to establish how distant areas "communicate" with each other. The rationale behind investigating disconnection syndromes and predicting patterns of cognitive deficits following damage to individual components of the system has had a long history in the literature and has recently been clearly articulated by Catani and Ffytch (2005). Nevertheless, our technique of combining detailed lesion analysis with DTI tractography data has rarely, if ever been used before. As the interconnections of regions in the human brain become better characterised, similar studies will be possible.

### 8.1.2 Perception and the medial temporal lobes

Studies of animals have implicated areas of the medial temporal lobe in high level visual perception (see Buckley & Gaffan, 2006). This is particularly the case when visual stimuli can only be distinguished by a unique combination of features and not on the basis of elemental features alone. Accordingly, researchers have attempted to replicate these findings in humans. The results have so far been contradictory. When impairments have been noted, they have generally been rather small in magnitude, particularly when taking into account concomitant impairments in other cognitive domains such as memory, which have been marked. In such cases, selection of the appropriate control group is critical, and differences in the overall ability and variability of the control sample may well account for the lack of consistency across studies. With respect to the hippocampal involvement in scene perception, our data were equivocal. The most compelling evidence was VC's perfectly normal performance on the task, despite his massive memory impairment. On the basis of this, it appears that memory and perception are not subserved by identical structures. Nevertheless, the retention of allocentric spatial information over even very short delays was dramatically affected by hippocampal damage. In the real world, forming an allocentric representation of the environment requires integrating the locations of landmarks across successive changes in viewpoint, and this ability may well be impaired by hippocampal damage (Gaffan & Hornak, 1997a).

### 8.1.3 Short-term retention of spatial information and the medial temporal lobes

One of the most important contributions that neuropsychology has made to our understanding of cognitive function is that short-term memory and long-term memory can be doubly dissociated (Shallice, 1988; Baddeley & Warrington, 1970). However, recent evidence has questioned whether this finding is necessarily the case for all types of memoranda (Olson et al., 2006). The data presented in Chapter 4 reveal a critical role for the hippocampus in retention of flexible representations of the spatial information contained in visual scenes. The delays used suggest that the hippocampus would be necessary for the online updating of representations of spatial information during navigation. This role of the hippocampus is consistent with cognitive map (O'Keefe & Nadel, 1978) and flexible-relational (Eichenbaum & Cohen, 2001) theories of hippocampal function. The finding that the hippocampus was not necessary to support representations of non-spatial but still configural aspects of visual scenes, is perhaps more compatible with the former theory.

### *8.1.4 Dissociations between face and scene recognition memory*

Chapters 6 and 7 demonstrated that the nature of the to-be-remembered stimuli has a profound effect on memory performance. We documented robust differences in scene and face recognition memory in the context of hippocampal lesions (see also Carlesimo et al., 2001; Lee et al., 2006). Although item recognition tests have little obvious relationship to behaviours that are important in our everyday lives, these tests appeared to tax meaningful cognitive modules, which are in some way separable. It is worth considering why this might be the case from a theoretical standpoint. Accurate recognition of people whom one has previously encountered is a useful skill for normal functioning in the world. Face recognition represents an interesting challenge, because we meet people in all manner of different contexts (places, times of the day, social situations, etc.). In fact, the formation of relatively context-free memories of faces might actually be useful in our daily life. It is plausible therefore, that perceptual and mnemonic circuits may have become specialized for face recognition. This proposal is supported by neuropsychological, neuroimaging and electrophysiological data from both humans and monkeys (Bodamer, 1947; Grill-Spector & Malach, 2004; Kanwisher et al., 1997; Kreiman, Koch, & Fried, 2000; Moscovitch, Winocur, & Behrmann, 1997; Tohgi et al., 1994; Tsao, Freiwald, Tootell, & Livingstone, 2006). In contrast to faces, places do not move (although we move relative to them). Therefore, any place that we encounter in our lives can at least theoretically be located in a spatial framework that could be used to aid subsequent recognition. Consistent with this, a network of areas involved with place perception and memory have been identified using neuroimaging and neuropsychological techniques (Burgess et al., 2002; Kreiman et al., 2000; Grill-Spector & Malach, 2004; Takahashi & Kawamura, 2002). One might posit that these circuits may be intimately linked with regions supporting the formation of spatial and/or associative memories; i.e. the hippocampus.

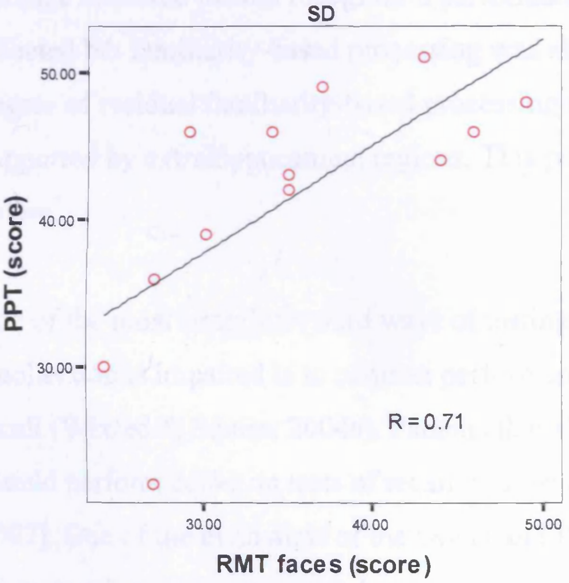
### *8.1.5 Which areas underpin face recognition?*

The data in this thesis have implicated the right hippocampus in the retention of flexible allocentric representations of scenes as well as item recognition of scenes, at least when many scenes have to be remembered. However, the hippocampus did not appear to be critical for item recognition of unfamiliar faces. In this section I will briefly speculate as to which areas may subserve this ability. There has been one reported case of selective impairment in face recognition memory in the context of an adult acquired brain lesion (Tippett et al., 2000). Specifically, this patient was unable to learn to recognize new faces. The authors speculated that the patient's lesion had disconnected areas involved in face perception and areas involved in memory formation, although the damage in this patient was too widespread to postulate how this disconnection occurred.

A wide body of research has implicated the right occipitotemporal lobe in face processing. Thus, prosopagnosia, a deficit of face recognition can occur after an isolated lesion to this area in the right hemisphere (Barton, Press, Keenan, & O'Connor, 2002; Takahashi, Kawamura, Hirayama, Shiota, & Isono, 1995; Tohgi et al., 1994). Neuroimaging studies have particularly implicated the fusiform gyrus in face processing (e.g. Kanwisher et al., 1997). These same areas have also been shown to be involved in face repetition priming and recognition memory (Henson et al., 2003; Kim et al., 1999; Maguire, Frith, & Cipolotti, 2001). Although not commonly identified through neuroimaging techniques, deficits in face recognition memory have also been documented in the context of anterior temporal lobe lesions (Barton et al., 2002; Damasio, Tranel, & Damasio, 1990; Evans, Heggs, Antoun, & Hodges, 1995; Lee et al., 2006; Simons et al., 2002). Overall, these results and our data suggest that posterior regions may be necessary for accurate face perception and their interaction with extrahippocampal anterior temporal areas may be critical for unfamiliar face recognition memory.

Patient JC, who was impaired on face recognition tests, also showed semantic memory deficits – at least in picture naming. Face recognition memory deficits have been documented in the context of semantic dementia. This suggests that areas involved in at least some aspects of semantic memory are anatomically close to, or even overlapping with, those involved in face recognition memory (Lee et al., 2006; Maguire & Cipolotti, 1998; Simons et al., 2002). This possibility was investigated by analysing the correlation between scores on a picture-picture matching test of semantic memory (the Pyramids and Palm Trees: PPT, Howard & Patterson, 1992) and the face recognition subtest of the RMT (data from Simons et al., 2002).

**Figure 8-1: Scores on the Pyramids & Palm Trees Test and the Faces RMT in 13 semantic dementia patients.**



**Legend**: Correlation between scores on a test of semantic memory (PPT) involving picture-picture matching and scores on the faces subtest of the RMT. Data kindly supplied by J. Simons (reported in Simons et al., 2002).

There are some important points to be made about the correlation shown in Figure 8-1. First, it is stronger than the correlation between the PPT and the verbal subtest of the RMT. Thus, the correlation is not directly related to LTM. This is particularly interesting, as some might consider words to be more clearly "semantic" than faces. Another important point is that the RMT for faces was not correlated with MMSE scores, and therefore the correlation does not simply reflect general cognitive resources. Therefore, there are at least two possibilities for the correlation. It is possible that areas underpinning face recognition memory are anatomically close to those underpinning (visual) semantic memory (anterior temporal lobe areas). Another possibility is that encoding and/or retrieval of unfamiliar faces uses the same cognitive systems involved in semantic memory, which may reflect an implicit or explicit strategy. Clearly much further research is needed in this area.

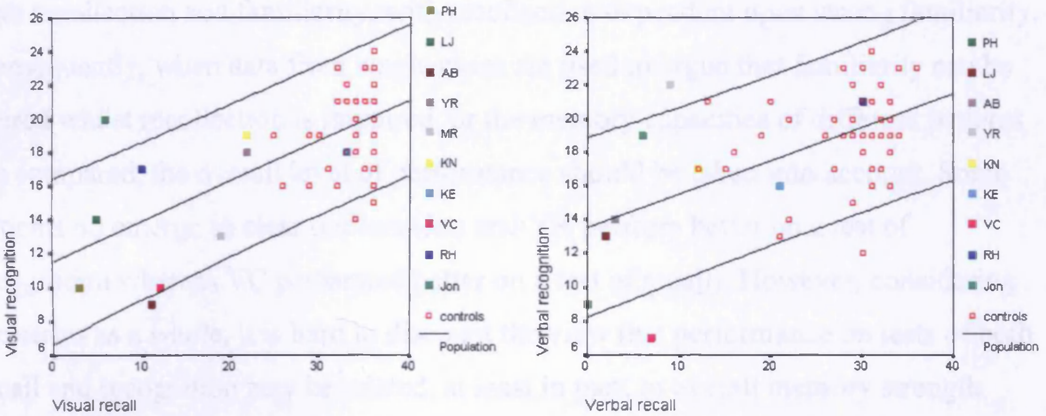
### *8.1.6 Recall and recognition in hippocampal amnesia*

The debate concerning the role of the hippocampus in recollection and familiarity is extensively summarised in Chapter 6. In Chapters 6 and 7 it was suggested that the most parsimonious interpretation of our data, and those from other single case studies of hippocampal amnesia is one of redundancy. In particular, when hippocampal damage impaired overall recognition performance, recollection was dramatically affected but familiarity-based processing was also compromised. Nevertheless, some degree of residual familiarity-based processing appeared to be capable of being supported by extrahippocampal regions. This position is explored in more detail below.

One of the most straightforward ways of testing whether familiarity is intact whilst recollection is impaired is to contrast performance on tests of recognition with tests of recall (Wixted & Squire, 2004a). Patients that show a relative sparing of familiarity should perform better on tests of recall in most circumstances (see Mayes et al., 2002). One of the main aims of the Doors and People Test (DPT) was that it would allow recall and recognition to be assessed on tasks that were approximately matched for difficulty (Baddeley et al., 1994). The fact that several patients with relatively selective hippocampal lesions have been administered the DPT allows us to analyse the performance of a relatively large group of such patients. In Figure 8-2 I have shown the raw scores for healthy adults and hippocampal patients on all four subtests of the DPT, comparing recall and recognition for visual and verbal stimuli separately. Since the aim is to compare the performance of the patients with themselves as well as to healthy adults, it is appropriate to use raw scores rather than scaled scores or z-scores. In order to plot these data on the same axes, it is necessary to assume that raw scores on the recall and recognition subtests of the DPT are linearly related and that this relationship is the same in healthy adults, and adults with hippocampal damage.

The best fitting linear relationship between all data points and 90% confidence intervals were calculated using SPSS (Figure 8-2).

**Figure 8-2: Performance of patients with hippocampal lesions and healthy controls on the Doors & People Test**



**Legend**: Performance of patients with selective hippocampal damage on the Doors and People Test. Control is from a group of 48 adults aged between 21 and 81 years (mean = 47.8, SD = 16.0). These unpublished data was kindly supplied by Dr M. Turner. Original source data for the patients is as follows: PH, LJ, AB, Manns & Squire, 2001; YR; Holdstock et al., 2000; MR, Bastin et al., 2004; KN, Aggleton et al., 2005; KE, VC, RH, Jon, Chapter 3, this thesis). Central straight line shows the linear regression of recall against recognition. Curved lines show the 90% confidence intervals. See text for more details.

The first point to be made is that there is considerable variability in the healthy adults, with there being a few clear examples of poor recognition in the context of normal recall and vice versa. It is also worth mentioning that there was a very large amount of variability in the shapes of the controls' ROCs who took part in the studies reported in Chapters 6 & 7. Whilst this is likely to be in part due to noise in the data as well as different strategies used by different individuals there is another possible explanation. It is conceivable that some individuals routinely rely more on "familiarity-like" memory processes than other individuals when performing item recognition tests. Some individuals might experience greater "familiarity" for previously encountered items, just as studies of visual imagery have demonstrated that some individuals have "good" visual imagery whilst others have "poor" visual imagery (e.g. Mast & Kosslyn, 2002).

If one follows the line of best fit through these data, it is apparent that performance on the recall subtests “falls off” more quickly than performance on the recognition subtests. This is not necessarily consistent with an independent processes account of recollection and familiarity (since all hippocampal patients should have unimpaired recognition), but is compatible with the view that similar brain regions play a role in both recollection and familiarity, with recollection dependent upon strong familiarity. Consequently, when data from single cases are used to argue that familiarity can be spared whilst recollection is impaired, or the memory capacities of different patients are compared, the overall level of performance should be taken into account. Some patients do emerge as clear outliers (Jon and YR perform better on a test of recognition whereas VC performed better on a test of recall). However, considering the series as a whole, it is hard to discount the view that performance on tests of both recall and recognition may be related, at least in part, to overall memory strength (when damage is limited to the hippocampus).

It has recently been argued on the basis of ROC data from recognition tests similar to those used in Chapters 6 and 7, that patients with hippocampal lesions show a similar pattern of responses as healthy adults, once the overall level of performance is equated between the groups, although the patients are impaired when performance on the same tests is compared (Wais et al., 2006). The performance of the patients (when tested with a large list length after no delay) and the healthy adults (when tested using the same list length after 7 days) was underpinned by familiarity, whilst recollection had dropped to around floor. Whether or not these residual familiarity-based processes are subserved by areas outside of the hippocampus is unclear. In the experimental psychology literature, several researchers have proposed on the basis of ROC analyses of recognition data from healthy adults that memory can be conceptualised as relying on both recollection and familiarity, but these processes are not independent of each other (Donaldson, 1996; Dunn, 2004; Heathcote, 2003; Glanzer et al., 1999; Wixted & Stretch, 2004). It is therefore plausible at least, that any type of brain damage that affects recollection might also have some impact upon familiarity.

### 8.1.7 Overview of memory processing

Some researchers have conceptualised familiarity and recollection as being independent processes, which may be supported by anatomically distinct brain systems (Yonelinas et al., 2002; Aggleton & Brown, 1999). This proposal does not appear to be well supported by the neuropsychological literature. Dual-process models seem to be based on the proposal that "remembering" and "knowing" that something has been encountered before are phenomenologically different (Yonelinas, 2002). However, it is unclear whether this is really the case. Episodes do not appear to be necessarily represented holistically (Trinkler, King, Spiers, & Burgess, 2006). Thus, "recollected" items are likely to be retrieved with varying degrees of additional information. During a recognition memory test, an item may be confidently recognised with the retrieval of no additional pieces of information, one additional piece of information or three additional pieces of information (and so on). Does the former example then reflect one process – familiarity; whilst the latter two examples reflect an independent process – recollection? At the other end of the spectrum, it is not clear whether weak familiarity is functionally different from perceptual priming (Kinder & Shanks, 2003).

Most patients with selective hippocampal damage appear to be relatively more impaired on tests using topographical than faces memoranda. Thus, the specific materials used when evaluating memory in patients needs to be considered before strong conclusions are made. Of course, I have not presented any data using other classes of non-verbal stimuli. It therefore remains an open question whether impairment of recognition memory for topographical materials such as scenes is associated with hippocampal damage over and above memory impairments for other materials such as objects and abstract patterns/shapes. Given the well-established role of the hippocampus in spatial memory, this might well be the case.

A suggested characterisation of the ventral visual system and medial temporal lobe involvement in the memory for faces and scenes is shown in Table 8-1. This takes into account the data presented in this thesis as well as from previous published cases of amnesia. The rational for this characterisation is discussed below.

**Table 8-1: Types of processing supported by different temporal lobe regions within memory for faces and scenes**

| | **Faces** | **Scenes** |
|---|---|---|
| **Hippocampus** | | |
| Representations | Cross modal | Cross modal<br>Flexible allocentric<br>Large number of single viewpoints |
| Memory supported | Contextual recall | Contextual recall<br>Highly confident item recognition |
| **Extrahippocampal MTL** | | |
| Representations | Face – face associations?<br>Large number of single viewpoints | Small number of single viewpoints |
| Memory supported | Highly confident item recognition | Weakly confident item recognition<br>Perceptual fluency (priming) |
| **Ventral visual stream** | | |
| Representations | Small number of single viewpoints | Constituent parts only (e.g. landmarks) |
| Memory supported | Weakly confident item recognition<br>Perceptual fluency (priming) | Perceptual fluency for parts (priming) |
| | | |

Different classes of visual stimuli may be processed in parallel regions of the ventral visual stream (Grill-Spector & Malach, 2004). When the same visual information is presented, these areas show repetition priming effects, which suggest that they support a degree of retention of the information (Henson, 2003). It has been shown that perceptual fluency, which is thought to underpin repetition priming, can give rise to feelings of recognition (Graf & Mandler, 1984; Jacoby & Dallas, 1981; Johnston, Dark, & Jacoby, 1985; Mandler, 1980). It is therefore possible that perceptual fluency is making some contribution to familiarity based memory processes. It may be that in more anterior regions of the ventral visual stream (e.g. perirhinal cortex, parahippocampal gyrus), perceptual fluency effects are sufficiently strong to support recognition judgements about the prior occurrence of these stimuli. According to this proposal perceptual fluency and what has been termed "familiarity" are not qualitatively different processes; they merely differ in the degree that they are available to consciousness (see also Kinder & Shanks, 2003).

The above suggestion was rejected by Knowlton (1998) on the basis that amnesic patients, who showed intact perceptual priming, were nevertheless impaired in their ability to make both "remember" and, critically, "know" responses (Knowlton & Squire, 1995). However, the interaction between group (control vs. amnesic) and response type ("remember" vs. "know") was significant, suggesting a partial preservation of "know" responses, which may be underpinned by perceptual fluency. Perhaps more importantly, it is often the case that amnesic patients have difficulty understanding the remember/know paradigm (Baddeley et al., 2001; Mayes et al., 2004). Therefore, the contribution of perceptual fluency to recognition performance, especially in the context of amnesia, when overall memory processes are weak and a degree of compensation might have taken place, deserves consideration.

According to this conceptualization, "familiarity" may arise due to persistent memory representations in different cortical areas in much the same way that "attention" may reflect enhanced processing of sensory information in different areas. In the case of faces, these areas may be able to subserve completely normal performance on item recognition tasks. Whether or not they are also able to support recognition memory for other materials depends on a number of different factors. These include the specific test format, and the degree to which a particular individual is able to use these regions to make recognition judgements. The hippocampus is necessary to subserve recollection. It is also my belief that for at least some types of memoranda (such as pictures of complex visual scenes that contain similar items), the hippocampus is necessary to subserve the ability to make highly confident recognition judgements. Note that items that are recognized with high levels of confidence will still vary in terms of the additional information that is retrieved with that item. Crucially therefore, I propose that the hippocampus is necessary to "know" that a scene has been presented before, even if no other associated information is retrieved. Whether or not the hippocampus is necessary for the confident recognition of other types of memoranda (such as words) is unclear.

### *8.1.8 Differences in the memory profiles between patients*

Even if taking into account the different materials used to test memory functions, there are clear differences between the memory profiles of different patients. I have already discussed some possible reasons for this. The analysis of the DPT data in Figure 8-2 demonstrates that there may be quite large individual differences in the general population with regards to performance on recall and recognition tests. It also highlighted the fact that overall level of performance needs to be taken into account, since recall performance is likely to be impaired before recognition.

It should be noted that neuropsychological assessment can only ever offer a snapshot of what is a dynamic process – the patient's attempts to compensate for their cognitive impairment. Some studies have reported patients who have shown considerable recovery of function across testing sessions (patient DF, Henke et al., 1999; patient KN, Aggleton et al., 2005; McKenna & Gerhand, 2002; patient BE, Holdstock et al., 2005). Interestingly, the recovery in these patients has been differential with regard to performance on different tests. Thus, performance on item recognition appears to recover before the ability to perform tests of recall, which may remain permanently impaired. It has been suggested that patient YR may have shown a similar initial pattern of improvement, since YR was first tested several years after her initial brain injury (Mayes et al., 2004). This is interesting with respect to VC, whose face recognition may have been impaired for several years following brain injury, but is now in the normal range. It should also be noted that 6 months after the investigation reported in Chapter 7, Patient JC was able to perform above average on the recognition subtests of the DPT, but scored much poorer on the recall subtests. His performance on tests of executive function remained inefficient (L Cipolotti, personal communication).

The framework outlined in Table 8-1 is consistent with these results. A patient with selective hippocampal damage will nevertheless be left with brain areas which are capable of subserving some degree of residual memory function. Some of the differences between patients may well reflect how well they are able to utilise these residual memory capacities. As discussed, there may be a premorbid bias as to how much the individual normally uses each area to make memory judgements. In addition, the integrity of remaining tissue in both the hippocampus and other medial temporal and cortical and subcortical areas will be critical. Obviously, the time since brain injury would be hypothesised to influence the degree of residual memory functioning. In addition, the age that brain injury occurred and the postmorbid level of general cognitive ability might be important.

## 8.2 Conclusions

The work contained in this thesis has contributed to our understanding of how we are able to perceive and remember objects and places in the environment. The critical role of the hippocampus in representing spatial information over both short and long time periods has been emphasised. Although significant differences exist between patients with hippocampal damage, with respect to the pattern of their impairments, correspondences have also been highlighted. A tentative framework for understanding the role of the hippocampus and related areas in the long term retention of faces and scenes has been proposed. Further research is necessary to test this framework and extend it to other types of memoranda.

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