

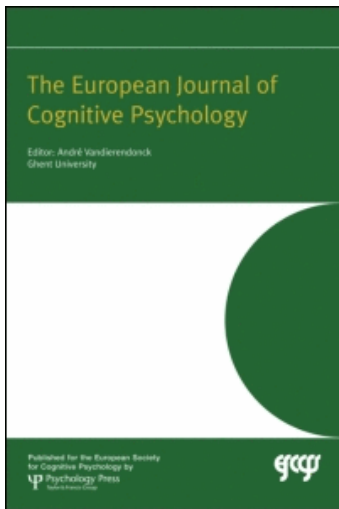
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Invited Address at the Occasion of the Bertelson Award 2005 Impairments in visual discrimination in amnesia: Implications for theories of the role of medial temporal lobe regions in human memory

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Invited Address at the Occasion of the Bertelson Award 2005

Impairments in visual discrimination in amnesia: Implications for theories of the role of medial temporal lobe regions in human memory

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A prominent and long-standing view of human long-term memory is that structures within the medial temporal lobe (MTL) work together to support the acquisition of memory for facts and events. In contrast to this view, recent studies in rats and non-human primates suggest dissociations in function between regions comprising the MTL. Evidence in support of such specialisation in humans, however, has been inconclusive, leading some researchers to propose that human MTL functions as a

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It was a great honour to be awarded the European Society for Cognitive Psychology Bertelson Prize in 2005, an accolade that would not have been possible without the valued contributions of my colleagues, collaborators, and students over the years. In keeping with this sentiment, two of my current research colleagues are authors on this paper; the work cited within emerged out of many discussions with them, and is a truly collaborative effort. I would also like to thank the participants in our experiments for their time and patience, as well as my many collaborators on much of this work—Mark Buckley, Tim Bussey, David Gaffan, Rik Henson, Betsy Murray, and Lisa Saksida. The Medical Research Council (UK) and the Alzheimer's Research Trust (UK) funded this research.

unitary system uniquely specialised for the acquisition and storage of long-term memory. This paper reviews some of the key studies from the animal and human literature that support an account of functional differentiation and discusses the different theoretical positions that have emerged from their findings. A series of recent experiments in humans designed to determine whether there is functional homogeneity in MTL regions across species are also reviewed and an alternative account of human memory—in which long-term memory is dependent upon representations distributed throughout the human brain rather than one specialised system—is proposed.

HUMAN AMNESIA

In 1954, Scoville (1954) reported severe amnesia as a complication of surgical removal of the medial temporal lobe (MTL) bilaterally. The resection, intended to resolve intractable epilepsy, extended posteriorly 8 cm along the medial surface of the temporal lobes and was reported to have destroyed much of the hippocampus and hippocampal gyrus, as well as the uncus and amygdala. Following on from this paper, Scoville and Milner (1957) investigated memory functioning in 10 individuals who had undergone similar temporal lobe resections and found that when the surgery involved a significant portion of the hippocampus bilaterally, profound loss of memory typically resulted. By contrast, if the surgery was restricted to one hemisphere or spared the hippocampus, there was no evidence of memory deficit (although see Milner & Penfield, 1955). Scoville and Milner drew two important conclusions from this study, both of which are still widely believed today: (a) that the hippocampus was important for normal memory functioning and (b) that the amount of damage inflicted to the hippocampus correlated positively with degree of memory impairment.

Scoville and Milner's (1957) seminal publication laid the foundation for more systematic investigations of the role of the hippocampus in human amnesia. Questions that were addressed by these experiments included: (a) whether the acquisition of all types of memory would be impaired after hippocampal damage (Cave & Squire, 1992; Cermak & O'Connor, 1983; Corkin, 1968; Haist, Musen, & Squire, 1991; Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995; Starr & Phillips, 1970; Walker, 1957; Woodruff-Pak, 1993); (b) the status of remote memories prior to the onset of injury (Beatty, Salmon, Bernstein, & Butters, 1987; Marslen-Wilson & Teuber, 1975; Salmon, Lasker, Butters, & Beatty, 1988; Victor, Angevine, Mancall, & Fisher, 1961; Zola-Morgan, Squire, & Amaral, 1986); and (c) the nature of the role played by the hippocampus in memory, including the persistence of any memory loss (Cave & Squire, 1991; Cummings, Tomiyasu, Read, & Benson, 1984; Drachman & Arbit, 1966; Milner, 1966; Milner, Corkin, & Teuber, 1968; Wickelgren, 1968; Woods, Schoene, & Kneisley, 1982).

A series of studies carried out in the single patient, HM, originally reported by Scoville and Milner (1957), provides a clear illustration of the overall conclusions that were drawn from these investigations. HM's memory loss seemed selective to the acquisition of memory for new facts and events (so-called declarative memory) and did not affect nondeclarative or procedural memory, including motor-skill learning (Corkin, 1968), visuoperceptual repetition priming (Keane et al., 1995), short-term memory (Cave & Squire, 1992; Wickelgren, 1968), and eye-blink conditional responses (Woodruff-Pak, 1993). HM, therefore, did not suffer from a global memory deficit, but rather a severe but selective impairment to the conscious recall of newly experienced facts and events, with preservation of skill or habit-based nonconscious memories (procedural memory).

On the basis of findings from cases such as HM, it was proposed, or assumed, that the hippocampus was key to this type of long-term memory, although some researchers did consider the role played by structures adjacent to the hippocampus (e.g., DeJong, 1973; Scoville & Milner, 1957). For example, Scoville and Milner (1957) wrote: "the importance of the amygdaloid and periamygdaloid region for memory mechanisms is open to question, considering the total lack of memory in the bilateral unectomy case (IS) [in whom there was no hippocampal damage]. But not enough is known of the effects of lesions restricted to the hippocampal area itself to permit assessment of the relative contributions of these two regions. This is a question on which selective ablation studies in animals could well shed important light, but unfortunately the crucial experiments have yet to be done" (p. 20). Parallel investigations in animals, therefore, became a powerful convergent tool in understanding the neural substrates of the amnesic deficits seen in humans.

ANIMAL STUDIES OF AMNESIA

Surprisingly, early attempts to model the severe and selective memory deficits seen in patients such as HM were largely unsuccessful, with medial temporal lobe lesions failing to produce similar memory deficits to those seen in human amnesia. For example, tests of discrimination learning, in which pairs of equally familiar stimuli are repeated over many trials until the subject learns which stimulus out of the pair is associated with reward, were easily solved by monkeys with hippocampal lesions (Correll & Scoville, 1965a; Orbach, Milner, & Rasmussen, 1960), despite impairment in humans (Hood, Postle, & Corkin, 1999). Similarly, performance on tests of recognition memory, in which a subject is shown a sample stimulus and after varying intervals is asked to either remember the identity of a previously seen stimulus amongst one or more foils (delayed matching-to-sample, DMS) or

indicate which item from an array has not been seen before (delayed nonmatching-to-sample, DNMS) was also normal (Correll & Scoville, 1965b). By contrast, humans with amnesia were impaired on these tasks (Bayley, Frascino, & Squire, 2005; Oscar-Berman & Zola-Morgan, 1980; Sidman, Stoddard, & Mohr, 1968), a result implying that there may be a substantial difference in the functional role of the hippocampus in memory in monkeys and humans, a conclusion still articulated today (Squire, Stark, & Clark, 2004; Stark & Squire, 2000).

In 1978, however, Mishkin resolved some of these discrepancies by modifying the DNMS paradigm to test memory using similar methods to those typically adopted in studies of human amnesia. Longer delays (e.g., up to 120 s) were adopted and the number of stimuli increased (up to 10 objects). Bilateral removal of either the hippocampus or amygdala alone had little effect on DNMS performance, but a combined amygdalohippocampal ablation significantly impaired memory, with impairments particularly evident in conditions stressing long delays with larger number of items. It was concluded that combined damage to the amygdala and hippocampus was necessary to cause the severe impairment in memory seen in individuals like HM. Consistent with this account, other studies in monkeys that used a similar surgical technique to Mishkin confirmed not only extensive difficulties with recognition memory (Murray & Mishkin, 1983), but also the classic pattern of concurrent preservation of procedural memories (e.g., motor learning; Zola-Morgan & Squire, 1984).

A key division that emerged from investigations around this time, therefore, was between declarative (or explicit) and nondeclarative (or implicit) forms of long-term memory, with the former thought to be dependent upon the amygdala and hippocampus (Cohen & Squire, 1980). While this was a plausible explanation for the profile of memory deficit elicited after lesions to the hippocampus in humans and monkeys, further research subsequently highlighted key functions for other MTL structures whose role in memory had been previously underestimated. Murray and Mishkin (1986) found that damage to amygdala and rhinal cortex (e.g., entorhinal and perirhinal cortex) resulted in a more severe memory deficit than that seen after combined hippocampal-amygdala lesions (see also Meunier, Bachevalier, Mishkin, & Murray, 1993; Suzuki, Zola-Morgan, Squire, & Amaral, 1993). Consistent with Murray and Mishkin's findings, HM's damage—more clearly identified by MRI scanning undertaken 40 years after his surgery (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997)—included the entorhinal and ventral perirhinal cortex, as well as the hippocampal complex and medial temporal polar cortex. Consequently, it was proposed that the different structures within the MTL (specifically, the hippocampal formation, entorhinal cortex, perirhinal cortex, and parahippocampal cortex) work as a single system supporting declarative

memory (Squire, 1982; Squire & Alvarez, 1995; Squire & Zola-Morgan, 1991).

The role played by these regions in memory retrieval is presumed to be only temporary, however, thereby explaining why some amnesic patients show better recall of memories from the remote compared to the recent past (Bayley, Hopkins, & Squire, 2003; although see Moscovitch et al., 2005). Under this view, a memory is initially formed via dynamic interplay between the MTL and distributed cortical sites located in other parts of the brain, with the MTL acting as an indexer for the location of the activated cortical regions. Repeated reinstatement of these experiences, during active retrieval and possibly sleep, results in the formation of more permanent links between the cortical elements comprising the new memory. Once these connections are fully formed, retrieval of the memory becomes independent of the MTL, and less vulnerable to damage occurring within this area (Alvarez & Squire, 1994; Marr, 1970, 1971; McClelland, McNaughton, & O'Reilly, 1995; Teyler & DiScenna, 1986). A critical prediction of this view is that there is no functional specialisation within the MTL, or at least, as proposed by Manns and colleagues (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Squire et al., 2004), none of our current psychological fractionations of memory (e.g., episodic vs. semantic, recall vs. recognition memory, recollection vs. familiarity, and so on) adequately map onto a neurobiological model of MTL function.

DO REGIONS WITHIN THE MTL PLAY DIFFERENT ROLES IN MEMORY?

Other researchers, however, disagree with this view and argue instead that different MTL areas subservise distinct mnemonic processes. For example, in a seminal publication, Aggleton and Brown (1999) extensively reviewed the literature on lesion, electrophysiological, and early gene imaging studies in animals, alongside investigations of human amnesia, and proposed two independent anatomical networks supporting memory. The hippocampal-diencephalic system, including the hippocampus, fornix, mamillary bodies, and anterior thalamus, is critical to the encoding and recall of previously experienced information, including spatial and temporal context, but is not necessary for recognition memory (Aggleton, Hunt, & Rawlins, 1986; Aggleton & Shaw, 1996; Mumby, Mana, Pinel, David, & Banks, 1995; Murray, 1996). By contrast, recognition memory is dependent upon nonhippocampal MTL regions, including the perirhinal cortex and medial dorsal thalamic nuclei. These structures are important for judgements of prior occurrence that may support a feeling of familiarity that an item was seen previously (Brown & Aggleton, 2001; Gardiner, 1988; Holdstock,

Shaw, & Aggleton, 1995; McMackin, Cockburn, Anslow, & Gaffan, 1995; Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997).

Supporting this latter proposal, primate electrophysiological studies have identified perirhinal neurons that decrease their firing in response to subsequent presentations of unfamiliar objects (Brown, Wilson, & Riches, 1987; Li, Miller, & Desimone, 1993; Sobotka & Ringo, 1993), a mechanism that may constitute the neural basis of recognition memory (for review see Brown & Xiang, 1998; see also, for complementary evidence from functional neuroimaging in humans, Henson, Cansino, Herron, Robb, & Rugg, 2003). Early gene-imaging studies are also consistent with these investigations (Aggleton & Brown, 2005). Measurements of the protein product (Fos) of the immediate early gene *c-fos*, which is expressed throughout the temporal lobe and has been associated with learning (Guzowski, Setlow, Wagner, & McGaugh, 2001), were increased in perirhinal cortex for the presentation of novel compared to familiar individual visual stimuli (Zhu, Brown, McCabe, & Aggleton, 1995). By contrast, there was no evidence of a Fos increase in the hippocampus, although this region does show increased expression of *c-fos* following exposure to a novel location (Vann, Brown, Erichsen, & Aggleton, 2000a,b). Thus, the perirhinal cortex seems to provide a mnemonic signal about prior familiarity of individual objects. In addition, it may also contain neurons that possess stimulus specificity but do not exhibit decremental response patterns (Xiang & Brown, 1998). In contrast, the hippocampus is involved during spatial location changes.

In the first double dissociation within a single experiment, Winters, Forwood, Cowell, Saksida, and Bussey (2004) showed that rats with hippocampal lesions were impaired on a test of spatial memory (radial maze), but performed normally on a test of object recognition using an apparatus designed to minimise putative spatial-contextual and locomotor confounds. The opposite pattern was observed in rats with lesions to perirhinal cortex. Using the same apparatus, Forwood, Winters, and Bussey (2005) found that rats with hippocampal lesions were no different from controls in their ability to remember objects after delays as long as 48 hours, a pattern consistent with the view that the hippocampus is only important when spatial-contextual factors are relevant to task performance. A dissociation has also been reported between the hippocampus and the perirhinal cortex in monkeys using a transverse patterning task (Saksida, Bussey, Buckmaster, & Murray, 2007). While animals with perirhinal lesions were impaired on acquisition of these configural discrimination problems, animals with hippocampal lesions showed better performance than control monkeys. There is accruing evidence, therefore, for a possible double dissociation in the functionality of the hippocampus and perirhinal cortex along the lines of spatial and object memory (also see Aggleton et al., 1986; Eacott & Gaffan, 2005; Ennaceur & Aggleton, 1997; Ennaceur, Neave, &

Aggleton, 1996; Gaffan, 1994; Zhu et al., 1995; Zhu, McCabe, Aggleton, & Brown, 1996, 1997).

While there has been little investigation of dissociations according to object versus spatial memory in humans with MTL damage (although see later), dissociations between recollective and familiarity-based processes have been reported in human amnesia but are nonetheless highly controversial. While some amnesic patients show preservation of recognition memory after hippocampal damage (Aggleton & Shaw, 1996; Baddeley, Vargha-Khadem, & Mishkin, 2001; Bird, Shallice, & Cipolotti, 2007; Cipolotti et al., 2006; Giovanello & Verfaellie, 2001; Holdstock et al., 2002; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Taylor, Henson, & Graham, 2007; Yonelinas et al., 2002), other individuals with hippocampal lesions demonstrate impairments in recognition memory across a number of different paradigms (Gold, Hopkins, & Squire, 2006; Hamann & Squire, 1997; Hirst et al., 1986; Hirst, Johnson, Phelps, & Volpe, 1988; Manns et al., 2003; Reed & Squire, 1997; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003; Wais, Wixted, Hopkins, & Squire, 2006). Evidence using functional magnetic resonance imaging (fMRI) is equally contentious. Some experiments provide evidence in support of a division of labour between familiarity- and recollective-based processes within the MTL (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004), demonstrating encoding activity in the hippocampus and posterior parahippocampal cortex predictive of subsequent source recollection, but uncorrelated with item recognition. In contrast, encoding activation in perirhinal cortex was found to be associated with later item/familiarity-based recognition, but not subsequent source recollection (Davachi et al., 2003). Other studies have failed to replicate these findings, reporting activations during item memory in many MTL regions, including the hippocampus (Gold et al., 2006; Kirshhoff, Wagner, Maril, & Stern, 2000; Otten, Henson, & Rugg, 2001; Stark & Okado, 2003).

Two alternative accounts of hippocampal function, with significant support from animal studies, also provide an explanation for human amnesia: the relational memory account (Eichenbaum, 2004; Eichenbaum, Otto, & Cohen, 1994) and cognitive map theory (O'Keefe & Nadel, 1978). In the former, the hippocampus is thought to be involved in rapid learning of associations between individual items and their associated context or event, thereby allowing episodic experiences to form relational networks that support both episodic retrieval and the generalisation of similarities (semantic memory) across experiences (Davachi & Wagner, 2002; Eichenbaum, 2000b; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Eichenbaum et al., 1994; Fortin, Agster, & Eichenbaum, 2002). By contrast, structures in parahippocampal cortex, particularly perirhinal cortex, are thought to encode the individual features that comprise objects (Cohen,

Poldrack, & Eichenbaum, 1997; Cohen et al., 1999; Eichenbaum & Cohen, 2001; Eichenbaum et al., 1994; Ryan, Althoff, Whitlow, & Cohen, 2000). Consistent with this view, Giovanello, Verfaellie, and Keane (2003) found that amnesic individuals showed poor memory for associations, in comparison to memory for items, when item recognition performance was equated to that of controls (Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; although see Stark et al. (2002). In a subsequent functional neuroimaging study, hippocampal activation was affected by the requirement for relational or associative processing at retrieval (Giovanello, Schnyer, & Verfaellie, 2004). Similarly, Davachi and Wagner (2002); see also Mitchell, Johnson, Raye, & D'Esposito, 2000) showed that the hippocampus was involved to a greater extent in relational processing (i.e., reordering a triplet of words on the basis of their desirability) than it was in item-based processing (i.e., repeating the words in the order they were presented). Entorhinal and parahippocampal gyri, however, were differentially engaged during item-based processing.

Another study also addressed the role of the hippocampus in relational processing. Kumaran and Maguire (2005) contrasted the activation patterns elicited during relational processing when participants navigated in a spatial environment compared to their own social network. Both these two conditions are considered to be dependent upon the associations and sequences of events that form relational networks, and consequently require normal functioning of the hippocampus (Eichenbaum, 2000b). By contrast, other theories, such as cognitive map theory (see later), predict a particular role for the hippocampus in spatial processing, particularly during navigation around large-scale environments. Kumaran and Maguire found that the hippocampus was recruited only when participants were required to navigate between places, and not when social relational processing was stressed or more general spatial processing, such as how many friends lived in a particular category of building. The authors interpret this pattern as providing "additional support for the notion that the hippocampus forms the cornerstone of a distributed network that supports spatial navigation in humans through its adeptness at processing the complex relationships between locations in our environment" (p. 7258).

Much of the evidence in support of a major role for the hippocampus in spatial memory, in particular representation of the location of an individual within wide-scale space (a so-called cognitive map; Burgess, Maguire, & O'Keefe, 2002; O'Keefe, 1991, 1999; O'Keefe & Nadel, 1978) comes from electrophysiological studies. These studies have shown that the hippocampus contains place cells that fire when a rat is in a particular location within an environment (O'Keefe, 1999; O'Keefe & Burgess, 1996; O'Keefe & Dostrovsky, 1971), even months after initial learning and when there are no spatial cues within the environment (O'Keefe & Speakman, 1987; Quirk,

Muller, & Kubie, 1990). The role of these place cells may not be restricted to spatial processing, consistent with a broader role for the hippocampus in declarative memory. For example, Huxter, Burgess, and O'Keefe (2003) demonstrated that hippocampal pyramidal cells can independently code the animal's location and speed of movement within an environment, thereby providing both a temporal and spatial signal.

Place cells have also been identified in humans: Ekstrom et al. (2003) found neurons in the hippocampus that responded to specific spatial locations within a virtual reality town and also cells in the parahippocampal cortex that fired more strongly to views of landmarks. These findings led the authors to propose that the parahippocampal region uses allocentric spatial information to form a coarse representation of space, whereas the hippocampus computes the flexible map-like representations of space that underlie navigation. Consistent with this view, there is a wealth of evidence that patients with hippocampal and/or parahippocampal damage are significantly impaired in spatial memory and navigation (Bohbot, Iaria, & Petrides, 2004; Bohbot et al., 1998; Burgess et al., 2002; Feigenbaum & Morris, 2004; Holdstock, Mayes, et al., 2000b; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Furthermore, in fMRI studies scenes are particularly effective in eliciting activation within the MTL, especially the hippocampus (Burgess et al., 2002; Burgess, Maguire, Spiers, & O'Keefe, 2001; Cansino, Maquet, Dolan, & Rugg, 2002; Duzel et al., 2003; Hartley, Maguire, Spiers, & Burgess, 2003; Henson, 2005; Henson, Hornberger, & Rugg, 2005; Maguire, Frackowiak, & Frith, 1997).

Notably, however, researchers, such as Eichenbaum, Cohen, and colleagues (Cohen & Eichenbaum, 1991; Eichenbaum et al., 1999), have rejected the idea that the hippocampus is specialised for spatial processing, citing work in which hippocampal cells are clearly active during the occurrence of nonspatial stimuli and behaviours when these events occur regularly (Eichenbaum et al., 1999; Eichenbaum, Kuperstein, Fagan, & Nagode, 1987; Fried, MacDonald, & Wilson, 1997; McEchron & Disterhoft, 1997; Wood, Dudchenko, & Eichenbaum, 1999). For example, hippocampal neurons have been shown to fire according to the learned significance of stimuli and responses in classical conditioning tasks (McEchron & Disterhoft, 1997), and Fried et al. (1997) reported hippocampal neurons that responded to visual stimuli in a recognition task, including cells distinguishing between faces and objects, facial gender and expression, or new versus familiar faces and objects (see Eichenbaum et al., 1999) for further examples). Eichenbaum et al. (1999) note that while in many of these tasks the items appear at particular locations this, by itself, was not obviously driving hippocampal firing. In Wiener, Paul, and Eichenbaum

(1989), the firing of hippocampal cells was seen only when the animal sampled a stimulus at a particular location, and ceased when the animal stopped tasting. Moreover, in an elegant study by Wood et al. (1999), in which odours were systematically moved within an environment, hippocampal firing for most cells corresponded with nonspatial factors, such as specific odours, approach to any odour and match/nonmatch status.

Given these findings, therefore, Eichenbaum and colleagues (Eichenbaum, 2000a; Eichenbaum & Cohen, 2001; Moses & Ryan, 2006) propose that the hippocampus is specialised for declarative memory, with hippocampal neurons providing a means to rapidly encode sequences of events comprising ongoing behaviour (including spatial and nonspatial cues, as well as actions). More specifically, the hippocampus is considered to be a memory system, uniquely specialised for forming long-term associations and relations amongst individual items, including in time and space, in order to provide flexible representations necessary for declarative memory.

A PERCEPTUAL ACCOUNT OF MTL FUNCTION

Some researchers have more forcibly challenged the view that there is a memory system or systems in the brain (Gaffan, 2002; Horel, 1978; Vanderwolf & Cain, 1994). In a review of this controversial proposal, Gaffan (2002; see also Gaffan, 2001) discussed a number of arguments inconsistent with a memory system account, including that, (a) temporal cortical regions are not specialised for memory, but also involved in perception and control of locomotion (Buckley, Booth, Rolls, & Gaffan, 2001; Buckley & Gaffan, 1997; Buckley, Gaffan, & Murray, 1997; Bussey, Saksida, & Murray, 2002; Eacott, Gaffan, & Murray, 1994; Lee, Barense, & Graham, 2005a; Meunier et al., 1993; Murray & Bussey, 1999), and (b) that amnesia is not caused by removal of specific cortical sites, but is instead due to widespread disconnection of temporal cortex basal forebrain and midbrain connections (Easton & Gaffan, 2000, 2001; Easton, Parker, & Gaffan, 2001; Gaffan, Parker, & Easton, 2001; Maclean, Gaffan, Baker, & Ridley, 2001). A key conclusion of this account is that “memory traces are stored in widespread cortical areas rather than in a specialised memory system restricted to the temporal lobe. Among these areas, the prefrontal cortex has an important role in learning and memory, but is best understood as an area with no specialisation of function” (p. 1111). Specifically, memory can be considered the outcome of a dynamic interplay between hierarchically organised perceptual representations distributed throughout the brain (see also Bussey & Saksida, 2005; Bussey, Saksida, & Murray, 2005; Murray & Bussey, 1999) and prefrontal cortex, which is nonhierarchically organised in order to undertake flexible and adaptive processing necessary for

supporting unpredictable task demands (Duncan, 2001; Gaffan, 1994; Parker & Gaffan, 1998; Wise, Murray, & Gerfen, 1996). Simple object features, such as colour, are represented in modality-specific visual cortex lateral and posterior to the perirhinal cortex (such as V4 and area TE/TEO). The perirhinal cortex, in turn, analyses the conjunction of these features, supporting representation of the unique configuration of features that define an individual object (see Murray & Bussey, 1999, for a more detailed description of this ventral “what” visual processing stream; see Baker, Behrmann, & Olson, 2002, for electrophysiological evidence). The hippocampus plays a key role in analysing spatial information, but not necessarily in the allocentric manner highlighted by cognitive map theory (Gaffan, 2001).

The majority of evidence for this view has come from experiments examining the role of perirhinal cortex in object perception (see, for reviews, Buckley, 2005; Bussey et al., 2005; Eacott & Gaffan, 2005; Lee, Barense, & Graham, 2005a). Bussey, Saksida, and Murray (2002, 2003) showed that monkeys with lesions to perirhinal cortex demonstrated severe object concurrent discrimination deficits when stimuli possessed overlapping ambiguous features (see later section on Visual Discrimination Learning for more details of this experiment). Furthermore, these deficits could be extended to single-pair discriminations, so long as there was significant feature overlap between stimuli. By contrast, performance on difficult colour and size discriminations was normal (see Bussey & Saksida, 2005, for review). Similarly, in a series of studies, Buckley and colleagues demonstrated clear visual discrimination deficits in monkeys with lesions to perirhinal cortex, including impairments in object recognition memory (Buckley et al., 1997; see also Eacott et al., 1994), concurrent discrimination [when the number of distracting stimuli or problems is increased (Buckley & Gaffan, 1997), and when objects are presented in different views (Buckley & Gaffan 1998b)], and configural learning (Buckley & Gaffan, 1998a). Furthermore, impairments have also been elicited by simple oddity judgement tasks in which monkeys were asked to indicate which stimulus out of an array of six was the odd-one out (Buckley et al., 2001). Colour, size, and shape discrimination was normal after perirhinal lesions, but performance on object and face oddity was impaired (particularly when different views were presented, see later section on Oddity Judgement for further details of this experiment). These different task adaptations stress feature ambiguity, a property of visual discrimination problems that emerge when discriminating between complex objects with a large number of visual features in common. The presence of feature ambiguity between objects forces the participant to make use of multiple object features to successfully discriminate between items, a process thought to be dependent upon perceptual representations within the perirhinal cortex.

Compared to the perirhinal cortex, there is much less evidence in support of a role for the hippocampus in spatial perception, with most researchers in the field focusing on how this structure supports spatial memory (see earlier section on *Do Regions within the MTL Play Different Roles in Memory?*). To address this issue, Buckley and colleagues developed a spatial version of their concurrent object discrimination task in which monkeys with fornix lesions were required to learn to discriminate “tadpoles”. Discriminations had to be made on the basis of a conjunction of spatial features, such as the tadpole’s position on the computer screen, tail length, and tail angle (Buckley, Charles, Browning, & Gaffan, 2004). Although this paradigm required learning, deficits were particularly evident when the numbers of foils was high and there was greater spatial ambiguity between features, a finding consistent with the possibility that the hippocampus is processing spatial conjunctions. Notably, despite these impairments on tasks that result in the need to process multiple spatial features, monkeys with hippocampal lesions do not show the poor performance on feature ambiguous object discriminations, contrary to the pattern seen after perirhinal damage (Saksida, Bussey, Buckmaster, & Murray, 2006). A key outstanding question, however, is whether these findings—thus far only described in animal studies—can be extended to human amnesic patients, in whom perception is typically reported to be normal.

Do these findings extend to patients with MTL lesions?

Until relatively recently, only a few experiments had attempted to investigate perceptual processing in humans (Buffalo, Reber, & Squire, 1998; Holdstock, Gutnikov, Gaffan, & Mayes, 2000a; Stark & Squire, 2000). These studies found little evidence to suggest that the patterns seen in animals were also true of humans with MTL damage, and typically demonstrated the classic delay dependent memory deficit on simultaneous and delayed matching to sample tasks (Holdstock et al., 2000a). This led some researchers to conclude, quite reasonably, that the function of these structures must differ across species, and that, consistent with most models, the human MTL functions exclusively in support of declarative memory (Stark & Squire, 2000). This conclusion, however, could partially reflect the fact that there has been little systematic investigation of perceptual processing in amnesia. Most experiments have employed only standard measures of visuospatial and perceptual ability on which amnesic individuals typically perform normally (see Lee, Barense, & Graham, 2005a, for a review). Thus, few studies have investigated the performance of amnesic participants on perceptual tests using items with a large number of overlapping features, a factor which has proved to be critical in eliciting

perceptual impairments in animal studies (Buckley et al., 2001; Buckley et al., 2004; Bussey et al., 2002; Eacott et al., 1994; see also the earlier section, A Perceptual Account of MTL Function).

To address this issue, a series of novel tasks were designed based on paradigms used previously in nonhuman primates. These were given to amnesic individuals with lesions to different structures within the MTL, and were administered during functional magnetic resonance imaging with healthy participants. As will be discussed later, these paradigms elicited significant deficits in perceptual processing in humans with MTL damage, thus providing evidence of homogeneity in MTL function across nonhuman primates and humans. Furthermore, the experiments extended findings from nonhuman primates by demonstrating, for the first time, a key role for the hippocampus in spatial processing, even when there was little or no demand for declarative memory. By contrast, the perirhinal cortex was critically involved in object processing, but only when conjunctions of object features (e.g., a representation of the object as a whole) were required. Two functional neuroimaging studies using similar tasks in healthy participants confirmed activation of MTL regions during discrimination of feature ambiguous stimuli (Lee, Scahill, & Graham, 2007b) and revealed two separate networks involved in spatial and object perception, respectively.

Visual discrimination learning

In the first study to directly investigate the role of feature ambiguity in object discrimination, Bussey et al. (2002) assessed the performance of monkeys with perirhinal cortex lesions on a series of concurrent discriminations in which the degree of feature ambiguity of the object stimuli was systematically varied. Monkeys were presented with pairs of stimuli, and over a series of repeated trials, they learned to discriminate between the rewarded and nonrewarded object. In a minimum feature ambiguity condition there was no overlap between the features that comprised the rewarded and nonrewarded stimulus, whereas in a maximum feature ambiguity condition all features were present in both the rewarded and nonrewarded stimulus. Solving the maximum ambiguity task, therefore, required learning the conjunction of the two object features. In an intermediate condition, one feature was similar across the rewarded and nonrewarded items. Strikingly, the authors found that the monkeys performed normally on the minimum feature ambiguity condition, but were impaired at both the intermediate and maximum conditions. This pattern indicates that feature ambiguity, not memory demand, was the critical factor influencing performance.

In a recent study by Barense et al. (2005), participants with focal lesions to the MTL were tested on modifications of this paradigm. Four new

conditions were developed—barcodes, blobs, bugs, and beasts—in which feature ambiguity was systematically manipulated (see Figure 1a for an example of the blobs stimuli). Two patient groups were contrasted: individuals with selective involvement of the hippocampus and participants with broader MTL lesions affecting the hippocampus and nonhippocampal structures, such as the perirhinal cortex (see Figure 1b). Strikingly, patients

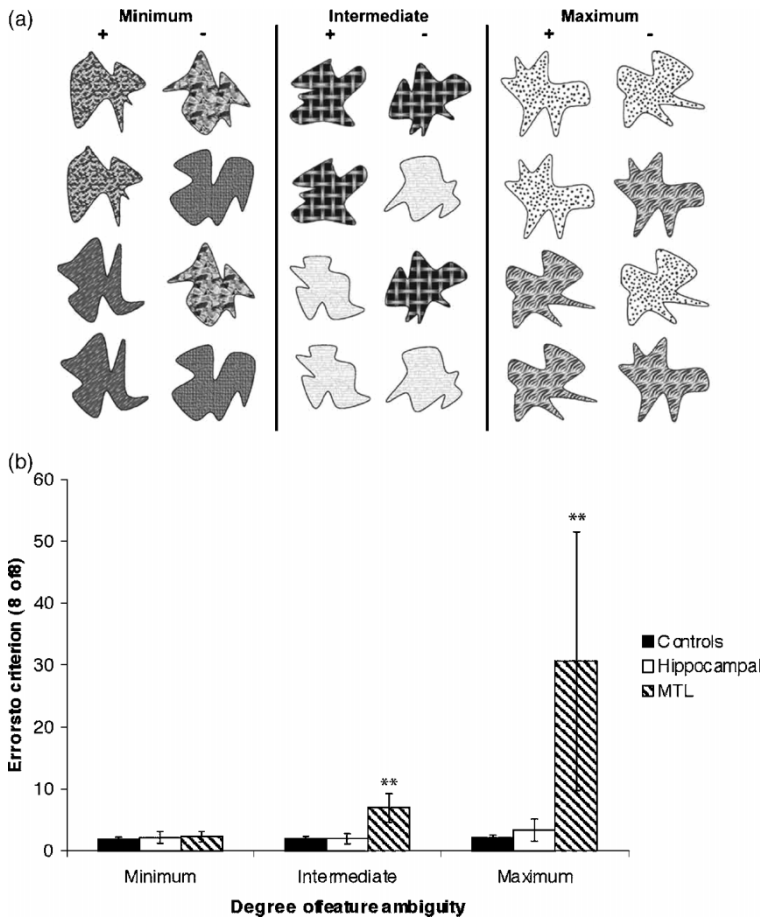


Figure 1. (a) Example of the blob stimuli used to investigate the impact of feature ambiguity on visual discrimination performance (see Barense et al., 2005, for more details); and (b) profiles of performance on minimum, intermediate, and maximum ambiguity stimuli, as measured by mean errors to criterion (eight consecutive correct responses), in three groups of participants (controls, individuals with selective hippocampal involvement, and subjects with more extensive MTL damage involving the hippocampus and other MTL structures, such as perirhinal cortex). One patient with MTL damage was unable to achieve the criterion of eight consecutive correct for the maximum ambiguity condition. ** $p < .01$ (MTL group vs. control).

with selective hippocampal damage showed no impairment in any of the four conditions, even at the highest level of feature ambiguity (maximum condition) or on especially difficult discriminations, a finding that has now been replicated in monkeys with selective hippocampal damage using the original monkey stimuli (see Saksida et al., 2006). By contrast, patients with broader lesions including perirhinal cortex were impaired, but only when feature ambiguity was stressed (e.g., in the intermediate and maximum ambiguity conditions). Performance was virtually normal on all four conditions of minimum ambiguity.

Another investigation using visual discrimination allows us to extend the conclusions drawn from Barense et al. (2005). In this experiment, participants were asked to indicate which of two items presented on the screen was the most similar to a target stimulus presented above the pair (Lee, Bussey, et al., 2005c). Critically, the pairs to be discriminated were created by blending two prototype images (one of which was the target stimulus) to create 50 new trial unique pairs 0–9%, 10–19%, 20–29%, 30–39%, and 40–49% of shared features. Different types of stimuli were tested, thus allowing the authors to assess the role of different MTL structures in processing feature ambiguous stimuli from different categories. As in Barense et al., two groups of patients were contrasted: individuals with selective hippocampal damage, and cases with more extensive lesions, including hippocampus and perirhinal cortex.

In support of the idea that the human hippocampus and perirhinal cortex may be critical to scene and object perception respectively, the two patient groups were impaired in the discrimination of spatial scenes, while the MTL group patients demonstrated an additional impairment in discriminating faces. Notably, object discrimination deficits in the MTL participants were much less robust on this task (see also Levy, Shrager, & Squire, 2005; Shrager, Gold, Hopkins, & Squire, 2006), although there was a small impairment in a version of the experiment in which the target was not presented above the pairs. Importantly, neither patient group had any difficulties discriminating between blended colour patches, indicating that the patients had a selective difficulty in discriminating between conjunctions of features, and were normal at single feature discriminations. Furthermore, analyses of task performance across trial blocks in each condition revealed no evidence of learning, as significant differences in performance between the patient groups and the controls were not restricted to the later blocks of trials on the scenes and faces conditions (Lee, Buckley, et al., 2005c).

One puzzle from this study was minimal impairment in object processing in the patients with broad MTL lesions, particularly in the context of clear problems with face discrimination. This pattern might lead one to conclude that structural damage more lateral and posterior in the temporal lobe was the underlying cause of the face perception difficulties seen in the MTL

group. As the same patients, however, showed striking impairments across four novel and familiar object intermediate and maximum ambiguity conditions in Barense et al. (2005), a more likely explanation is that to induce an object discrimination deficit, a more sensitive task that explicitly manipulates the degree of feature overlap is required.

These complementary studies of visual discrimination support a fractionation of MTL function along the lines of object and spatial processing, and furthermore highlight a critical—and previously little considered—influencing factor of feature ambiguity in human participants. As noted by Bussey and Saksida (2002), with particular reference to perirhinal cortex, the effects of lesions in this area, “are due not to the impairment of a particular type of learning or memory—for example, stimulus-reward or stimulus response, declarative or procedural—but to compromising the representations of visual stimuli” (p. 355). Although the spatial features of the environments shown in Lee, Buckley, et al.’s (2005b) study were not systematically manipulated, given the convergence of these findings with that obtained in monkeys using Buckley et al.’s (2004) spatial paradigms (i.e., concurrent discrimination learning of tadpoles that varied in terms of their spatial features), it seems reasonable to conclude that this region may be involved in processing conjunctive representations of spatial scenes. An interesting follow-on experiment that would bridge the gap between the animal and human work on spatial processing, would be to investigate whether patients with hippocampal lesions would show deficits for concurrent discrimination of tadpoles with spatially ambiguous features (i.e., the identical condition to that tested in monkeys), and whether this deficit could be attenuated by reducing the degree of spatial feature ambiguity.

Oddity judgement

A criticism of the work on visual discrimination is that the effects of perceptual load and feature ambiguity were observed in tasks that stressed learning and memory, and thus, drawing conclusions regarding perceptual ability may be limited. In a key publication from the animal literature, monkeys with perirhinal lesions were required to select the odd stimulus from an array of six images taken from a variety of stimulus categories (Buckley et al., 2001). While some of these discriminations could be made on the basis of single features (e.g., oddity judgement for shape, colour, and size), other discriminations placed a greater demand on perceiving conjunctions of features (e.g., oddity judgement for faces, and for objects masked with varying degrees of visual noise). Buckley and colleagues found that discrimination of simple single features was not dependent on the perirhinal cortex, whereas oddity judgements for objects and faces were impaired following selective perirhinal cortex lesions. An initial study in amnesic

individuals, however, using a similar version of the task developed by Buckley et al. (2001), failed to replicate these findings: Patients with perirhinal cortex damage performed within the normal range across all stimulus conditions, even on tasks that were sensitive to perirhinal cortex damage in monkeys. This difference in findings across species could not be attributed to a lack of difficulty—patients and controls performed around the 60% mark in the hardest oddity conditions (Stark & Squire, 2000).

Not all patients with MTL damage that includes perirhinal cortex, however, show normal performance on the oddity tasks developed by Buckley and colleagues (Buckley et al., 2001). Lee, Buckley, et al., (2005b) used the same tasks, and as adopted by Stark and Squire (2000), but introduced with one critical change: The number of stimuli presented was increased (sets of twenty items were used in comparison to ten in Stark and Squire (2000)). Large set sizes have been shown to be more sensitive in revealing deficits on visual concurrent discrimination following perirhinal cortex lesions (Buckley & Gaffan, 1997; Eacott et al., 1994; although see Hampton, 2005), presumably due to increasing feature ambiguity across trials. A substantial criticism that has been levelled at the original findings of Buckley et al. (2001) is that because stimuli were repeated, learning could have occurred. To address this, Lee, Buckley, et al. investigated performance on a set of novel oddity tasks in which trial-unique items were utilised, including face oddity as well as a spatial version of oddity judgement based on virtual reality rooms designed to be sensitive to the hippocampus. In the latter, a complete three-dimensional representation of the rooms within each trial was necessary to solve the oddity judgement (see Figure 2a for examples of stimuli).

In accord with their previous studies, Lee, Buckley, et al. (2005b) found that patients with selective hippocampal damage, but no obvious involvement of perirhinal cortex, were significantly impaired on oddity judgements for virtual reality rooms, but showed normal performance on oddity judgements involving faces, objects, and colour (see also findings from the categorisation task reported by Graham et al., 2006). Cases with broader MTL lesions, including the hippocampus and perirhinal cortex, were also impaired on oddity judgement for virtual reality rooms, but additionally demonstrated significant deficits when they were required to make oddity judgements for faces and objects (see Figure 2b).

In a follow-up investigation, Barense, Gaffan, and Graham (2007) systematically investigated object oddity by contrasting oddity judgement for low and high ambiguity stimuli. This study was the first to combine the crucial dimension of feature ambiguity within the context of trial-unique single discrimination problems with a minimal learning requirement. In one experiment, the patients were asked to indicate which of seven “fribbles” (stimuli made up of four features that were systematically manipulated to

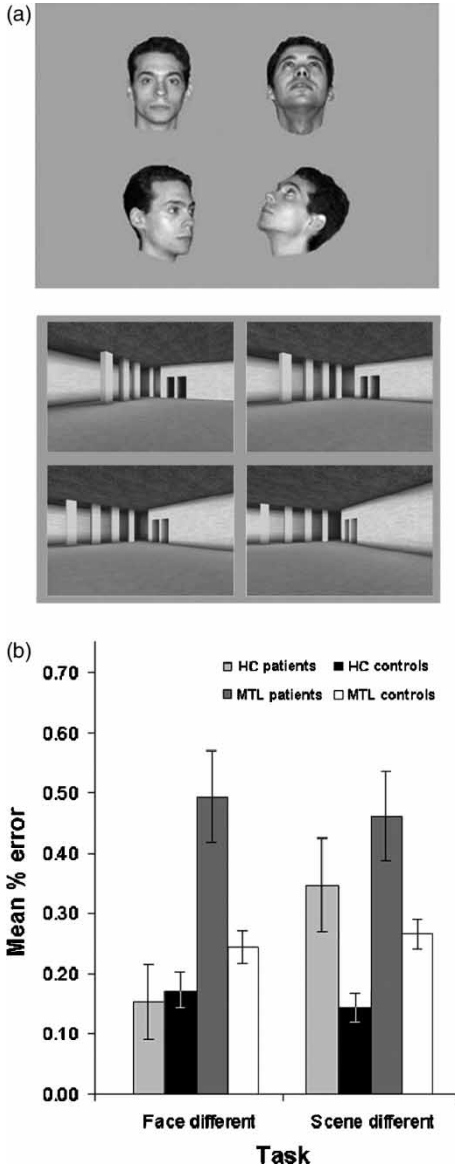


Figure 2. (See opposite page for figure caption)

create conditions of high and low ambiguity) did not have a pair (i.e., which fribble was the odd one out). In a second experiment, the original Buckley et al. (2001) oddity judgement paradigm was used but with two key differences: (a) the number of stimuli within an array was reduced to four, and (b) items

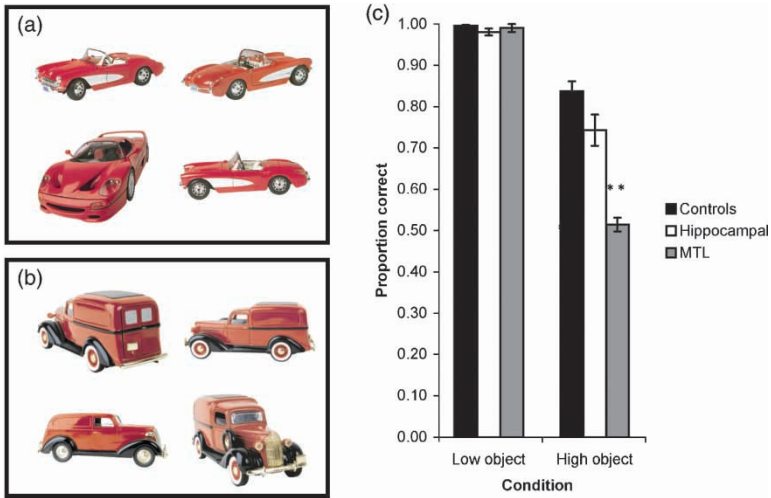


Figure 3. (a) Example trials from the familiar object oddity task (a—low ambiguity, and b—high ambiguity) developed by Barense et al. (2007), and (b) performance of two groups of patients, as measured by proportion correct, contrasted with a control group. While the group with selective hippocampal damage performed normally, individuals with broader MTL lesions, including perirhinal cortex, were found to perform significantly worse ($p < .01$) than the control group.

were separated into two conditions subjectively considered to have low and high ambiguity (see Figure 3a).

Consistent with the findings from studies on visual discrimination, but critically now in a task in which there was no overt requirement to remember stimuli across trials, Barense and colleagues (Barense et al., 2007) found severe deficits on both experiments in individuals with broad MTL lesions, as long as feature ambiguity was high. When there was no overlap of features, either in low ambiguity object conditions or when simple features were contrasted (colour and size), patients performed normally. This effect cannot be explained by task difficulty, as the two latter control conditions were as difficult as the high ambiguity oddity tasks. Consistent with Lee, Buckley, et al. (2005b), patients with hippocampal lesions showed no impairment on any condition (see Figure 3b). These findings are the first

Figure 2 (Opposite). (a) Example trials from the different view face and scene oddity tasks reported in Lee, Buckley, et al. (2005b). The participant was asked to select the odd stimulus from each four-item array. (b) Performance of two patient groups (HC—patients with selective hippocampal damage; and MTL—participants with extensive lesions to the medial temporal lobe), shown as mean percentage error, on the two oddity judgement conditions. Notably, patients with hippocampal damage were impaired on different view scenes, but not faces, even though these were equally difficult for a matched control group (HC controls). The patients with broader MTL lesions were impaired on both different view conditions compared to their matched control group (MTL controls).

to demonstrate robust deficits in object processing in patients with perirhinal involvement in a task in which there is no learning component. They are also important in that they counter recent investigations from Levy et al. (2005) and Shrager et al. (2006) in which patients with perirhinal damage performed normally, albeit numerically lower than controls (especially patient EP), on tasks similar to those reported by Lee, Bussey, et al. (2005c).

Are MTL regions recruited during these tasks in functional neuroimaging?

Patient studies play an important role in cognitive neuroscience by allowing researchers to investigate whether a brain region is critical to a particular cognitive process. A limitation of these studies, however, is the possibility that the patients under investigation may possess structural and/or functional deficits remote from their identified site of damage, and that it is these remote lesions that are responsible for the observed deficits. Functional neuroimaging can help address this problem by offering scientists the opportunity to identify brain areas recruited by a cognitive task, thus providing convergent evidence for the involvement of a particular brain region in healthy participants.

Visual discrimination tasks similar to those used by Lee and colleagues in amnesic individuals—in which participants have to indicate an object or spatial change or make a judgement about which item is the odd one out—have been adapted for using in functional neuroimaging in healthy control participants (Lee, Bandelow, Schwarzbauer, Henson, & Graham, 2006a; Lee, Scahill, et al., 2007b; Pihlajamaki et al., 2004). Lee, Bandelow, et al. (2006a), presented participants with two arrays of objects and asked subjects to indicate whether the arrays were identical (no change condition), differed with respect to the identity of one object (object change condition), or differed with respect to the spatial arrangement of the objects (arrangement change condition, see Figure 4a). Consistent with neuropsychological investigations reporting deficits in object processing after perirhinal damage, detection of an object identity change was associated with significant right perirhinal cortex activity (see Figure 4b; see also Pihlajamaki et al., 2004, albeit in the context of a memory paradigm). Greater hippocampal activity was not observed during the spatial arrangement condition, consistent with a recent study in which hippocampal amnesics did not show impaired memory for a single object location in a grid (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; although see Pihlajamaki et al., 2004). A plausible, although as yet untested, explanation for this lack of activation within the hippocampus is that the arrangement change condition was not

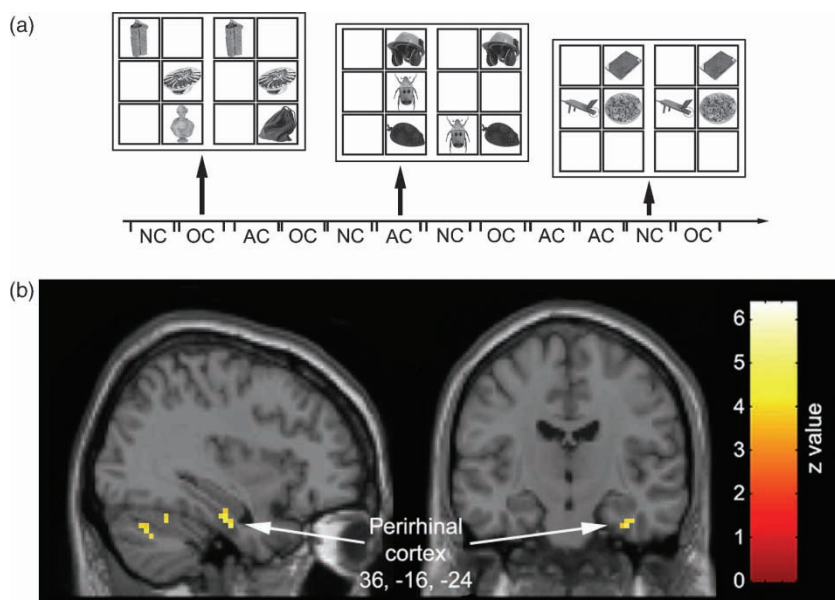


Figure 4. (a) Example trials from the Lee, Bandelow, et al. (2006a) functional neuroimaging study in which participants were asked to indicate object and arrangement changes across a pair of grids. OC = object change, AC = arrangement change, and NC = no change. (b) Greater activation was seen in the perirhinal cortex when object change trials were contrasted with no-change trials.

sufficiently spatially ambiguous or demanding to recruit this region (see Lee, Bandelow, et al., 2006a).

In a second experiment, Lee, Scahill, et al. (2007b) contrasted the brain regions recruited during scene, face and size oddity using the identical stimuli and tasks employed in previous studies (Lee, Buckley, et al., 2005b; see Figure 2a). Compared to face and size oddity conditions, oddity judgement for trial unique scenes was associated with increased activity in the posterior hippocampus and parahippocampal cortex (see Figure 5a). In contrast, perirhinal cortex and anterior hippocampus activity was observed during face oddity judgement (see Figure 5b), a very similar activation pattern to that reported in Lee, Bandelow, et al. (2006a) and Pihlajamaki et al. (2004). Further analyses revealed that while activity in the areas activated for the spatial oddity tasks declined over significantly repeated presentation of trials, this was not the case for the bold signal in perirhinal cortex during repetition of face oddity trials.

The authors interpreted the latter pattern—continued activation of perirhinal cortex as trials were repeated—as evidence against the possibility that the activation in perirhinal cortex reflected episodic memory encoding. Previous studies have shown decreasing levels of activity in MTL regions as

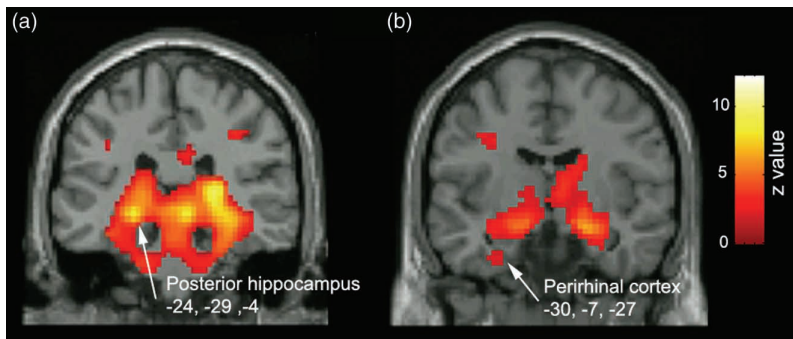


Figure 5. Diagram showing the MTL regions activated for (a) scene oddity and (b) face oddity when contrasted with size oddity (see Lee, Scahill, et al., 2007b, for further contrasts). As in Lee, Bandelow, et al. (2006a), the perirhinal cortex was activated during face oddity, while scene oddity resulted in activation in posterior hippocampus, as well as other regions (see text).

stimuli become increasingly familiar (Duzel et al., 2003; Kirchoff et al., 2000; Kohler, Dankert, Gati, & Menon, 2005; Strange, Hurlmann, Duggins, Heinze, & Dolan, 2005). It is not immediately clear, however, exactly how to interpret decreases in BOLD signal, or even increases typically associated with subsequent memory comparisons within MTL regions (see Henson, 2005). It seems plausible that a decrease in BOLD signal within MTL structures would be predicted by both a perceptual and mnemonic account. In the former, this would reflect a strengthening of novel perceptual representations resulting in faster and more efficient activation of these items (a form of perceptual learning and/or priming; Graham et al., 2006). In the latter, the decreases would reflect strengthening of an episodic trace that is storing information about the activation of a representation located elsewhere in the brain (e.g., fusiform face area or parahippocampal place area). It also seems likely that both these views would predict subsequent memory effects in these regions: The stronger the perceptual representation or episodic trace, the greater the likelihood of successful memory. Further studies, looking for possible interactions between stimuli type (scenes vs faces/objects), MTL region (hippocampus vs. perirhinal), and type of memory (item vs. source) would be useful additions to this literature.

An interesting, and puzzling, finding from Lee, Scahill, et al. (2007b) was the recruitment of hippocampal regions for both face and scene oddity judgement. For the face oddity judgement, there was a robust anterior hippocampal activation and in scene oddity posterior involvement of the hippocampus. This seems contradictory to our neuropsychological work in which hippocampal damage impaired scene oddity, leaving equally face oddity judgement intact (see also Graham et al., 2006). The simple explanation—that the anterior hippocampus is not damaged in the

hippocampal patients—is clearly incorrect, as detailed structural analyses carried out in these individuals highlighted damage to anterior hippocampal structures. This leads one to the less than satisfactory conclusion that anterior hippocampal regions must not be critical to the performance of a face discrimination task, but that in the normal brain perirhinal cortex and anterior hippocampus function in some complementary manner that is currently unclear. Functional neuroimaging using the types of tasks reported in this paper might help bridge the gap between the neuropsychological and neuroimaging findings, and provide a means to test this hypothesis.

That there may be functional dissociations between the role of anterior and posterior regions of the hippocampus, however, may not be without merit. Anterior hippocampal activity during memory and discrimination tasks involving objects has been previously documented (Bernard et al., 2004; Kohler et al., 2005; Pihlajamaki et al., 2004), whereas tasks involving spatial stimuli, such as navigation and memory for spatial locations, are more typically associated with activity in the more posterior extent of the hippocampus (Burgess et al., 2001; Maguire et al., 1997; Parslow et al., 2004; Pihlajamaki et al., 2004). For example, Pihlajamaki et al. (2004) found anterior hippocampal activity when subjects noticed a different object between two groups of images presented across successive trials. In contrast, activity in more posterior hippocampal regions was observed when a change in the spatial arrangement of the objects was detected. Anatomically, studies in animals have shown that different regions of the hippocampus receive unique afferents from the entorhinal cortex (Dolorfo & Amaral, 1998; Witter, van Hoesen, & Amaral, 1989) and electrophysiological investigations have found a greater number of neurons active in posterior hippocampal regions (compared to anterior) during tasks of spatial memory (Colombo, Fernandez, Nakamura, & Gross, 1998). It remains to be determined, however, exactly what roles these different hippocampal regions are playing in perception versus memory and it is currently unknown which regions within the broad networks activated during object and scene tasks play a role in mnemonic processing.

As mentioned earlier in this paper, the perirhinal cortex, while notoriously difficult to image due to sensitivity artefacts and difficult to identify consistently across studies, has been implicated in recognition memory. This structure typically demonstrates a deactivation when hits are contrasted with correct rejections (i.e., an activation for old items; Henson et al., 2003; Herron, Henson, & Rugg, 2004; Jessen et al., 2001; Rugg, Henson, & Robb, 2003; see Henson, 2005, for a review). Perirhinal cortex has also been shown to be more active during semantic tasks, although in a manner which has been interpreted in the context of a role for the perirhinal cortex in object identification (see Bright, Moss,

Stamatakis, & Tyler, 2005, for a review of these findings). Greater activation has been reported for basic level naming of visually presented objects (i.e., naming the picture itself, for example “cat” or “dog”) compared to naming at a domain level (i.e., classifying an object as living or nonliving), a pattern thought to reflect the greater demand of basic naming, compared to domain level naming, on fine-grained differentiation among objects (Tyler et al., 2004). Similarly, patients with damage to perirhinal cortex as a consequence of encephalitis performed significantly worse on basic-level naming relative to domain-level naming. In a second experiment, these findings were extended to show that activation in the anteromedial temporal region considered to include perirhinal cortex was also modulated by semantic category, with greater activation for categories in which items had greater perceptual overlap (e.g., animals, fruits, and vegetables; Moss, Rodd, Stamatakis, Bright, & Tyler, 2005).

More recently, a role for perirhinal cortex in crossmodal integration of object features has been documented in human subjects (Taylor, Moss, Stamatakis, & Tyler, 2006). Monkey studies have suggested that the perirhinal cortex may be important for crossmodal associations, with lesions to this region impairing tactual-visual memory (Goulet & Murray, 2001). Similarly, Taylor et al. (2006) found perirhinal cortex activity in healthy participants during crossmodal integration of auditory and visual features of real objects in fMRI. Consistent with this pattern, individuals with damage to perirhinal cortex were more impaired on the same crossmodal task compared to a unimodal auditory or visual integration condition. While other regions in the temporal lobe were also activated by crossmodal integration, notably posterior superior temporal sulcus, activity in perirhinal cortex only was modulated by semantic variables, such as semantic congruency (i.e., whether the crossmodal stimuli were meaningfully related or not) or semantic category (e.g., living vs. nonliving). The patients with perirhinal damage were also influenced by these semantic variables, and showed disproportionate deficits on living items compared to nonliving. Consistent with Murray and Bussey, (1999), therefore, who argued that the perirhinal cortex “is the core of a system specialised for storing knowledge about objects, analogous to a semantic memory system in humans” (p. 146), Taylor et al. conclude that “perirhinal cortex integrates perceptual feature information into higher-level semantic memories of meaningful objects” (p. 8243). Functional neuroimaging studies, therefore, have provided some convergent evidence that there are functional differences in the contributions made by the hippocampus and perirhinal cortex in memory. While it cannot be proven beyond doubt that activations within these regions are perceptual, as it is possible they reflect memory encoding into long-term memory (see later for more discussion), it is reassuring that the same tasks that are impaired

in patients also recruit the same MTL regions—differentially—in healthy participants.

INTERPRETING THESE FINDINGS IN TERMS OF CURRENT VIEWS OF HUMAN MEMORY

The series of experiments reported above clearly demonstrate the limitations of a model of memory in which MTL structures play an exclusive role in declarative memory (Squire et al., 2004). Although there is no doubt that damage to this region results in memory impairments, the underlying cause of these deficits and the role of distinct MTL structures in different kinds of memory is hotly debated. Critically, in our studies, and in similar animal investigations (for review see Buckley & Gaffan, 2006; Bussey & Saksida, 2005), normal performance on both mnemonic and perceptual tests in patients with amnesia was not influenced by memory load (number of features to be remembered; Barense et al., 2005; Bussey et al., 2002), or memory task (explicit vs. implicit; Graham et al., 2006). Instead, patients showed similar profiles of performance to normal controls when simple nonconjunctive stimuli were used, but were impaired at perceiving, learning, and remembering complex objects and scenes with ambiguous features. Similar impairment across all stimulus types—a direct prediction of a unitary memory account of MTL function—was not seen. While patients with broad MTL lesions demonstrated poor performance on scenes, objects, and faces, individuals with selective lesions to the hippocampus were impaired only on scene processing. Consistent with these neuropsychological dissociations in behaviour, functional imaging studies have provided convergent evidence that MTL regions were recruited even when there was no obvious declarative memory demand, and that the patterns of activation obtained for different stimulus types were distinct. Broad anatomical networks were recruited for object and spatial processing. For faces and objects, we observed a swath of activation in the temporal lobe that included fusiform cortex and perirhinal cortex, culminating in anterior hippocampus, whereas scenes were associated with a more posterior spatial network involving posterior hippocampus, parahippocampal cortex and the posterior cingulate.

The patterns obtained in our series of experiments support the view that there is no benefit to considering the MTL a memory system (Gaffan, 2002). Like nonhuman primates, humans with MTL damage show deficits that are not restricted to memory, and consequently the role of the MTL cannot be uniquely mnemonic. Instead, a parsimonious explanation of our results is that memory is dependent upon a hierarchically organised network of modality-specific perceptual representations distributed throughout the

brain. Anatomically, although not necessarily cognitively (see Milner, Dijkerman, & Carey, 1999), structures in the MTL, in particular the hippocampus and perirhinal cortex, form the apex of the “what” and “where” processing streams, respectively. These structures, therefore, should be considered not as bystanders that store an episodic trace of activations provided by these streams, but as active players that represent complex conjunctive representations necessary for combining information about objects and places. These representations are critical to performance on both mnemonic and perceptual tasks, and thus, damage to MTL regions impairs performance on both.

The spatial aspect of this account of hippocampal function clearly has some similarities with cognitive map theory, which holds that the firing of hippocampal pyramidal cells provides information about an individual's location within an environment (Ekstrom et al., 2003; Hori et al., 2003; O'Keefe, 1976; O'Keefe & Burgess, 1996; O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; Ono, Nakamura, Fukuda, & Tamura, 1991; Ono, Nakamura, Nishijo, & Eifuku, 1993; Wilson & McNaughton, 1993). As mentioned earlier in this paper, cognitive map theory gains support from studies demonstrating deficits in spatial memory following hippocampal damage, particularly for allocentric, but not egocentric, spatial scenes (Bohbot et al., 1998, 2004; Burgess et al., 2002; Feigenbaum & Morris, 2004; King et al., 2002, 2004; Spiers et al., 2001). Consistent with this theory, our findings extend the deficits after hippocampal damage to the perception of scenes (Lee, Barense, & Graham, 2005a), but also imply a possible role for the hippocampus beyond allocentric processing (Lee, Buckley, et al., 2005b). This latter result is consistent with the findings that lesions to the fornix impaired the concurrent discrimination of pairs of tadpoles when they had maximum overlap in their spatial features (Buckley et al., 2004).

A reasonable criticism that can be made of both the cognitive map theory and our more broadly based representational account is the following: How can simple deficits in spatial or object processing fully account for the phenomenology of the amnesic syndrome? For example, how can a view which holds that the hippocampus is specialised for spatial processing explain deficits that are not overtly spatial, such as difficulties with story recall in an amnesic patient (see the cases reported by Lee, Buckley, et al., 2005b), or the firing of hippocampal cells in circumstances that do not immediately appear spatial, such as approaching a goal or sniffing at a food well (Eichenbaum et al., 1987)? In terms of cognitive map theory, plausible answers to this question are described throughout the papers published by its proponents (see O'Keefe, 1991, 1999, for reviews). In brief, the argument put forward in these articles is that findings, such as the firing of hippocampal cells in nonspatial situations may be due to the misinterpretation of the spatial output from the cells or can be considered a secondary

characteristic of the cells, such as arousal or movement (O'Keefe, 1999; O'Keefe & Burgess, 2005). Furthermore, Huxter et al. (2003) found that hippocampal place cells are capable of coding two independent variables: the animal's location and their speed of movement through the environment. Together, these two variables may allow simultaneous coding of location and content (see also O'Keefe & Burgess, 2005).

To the same question, Gaffan (2002); see also Horel, 1978) notes that it is highly likely that deficits in spatial processing will impair performance on some nonspatial tasks, particularly when successful retrieval requires some spatial differentiation of one event from another. He also argues that, consistent with a spatial account, hippocampal or fornix lesions often leave nonspatial forms of memory intact (Aggleton et al., 2000; Baxter & Murray, 2001; Gaffan et al., 1984; Murray & Mishkin, 1998). Perhaps most importantly, Gaffan points out that the question of how to map the spatial role of the hippocampus onto episodic memory is not sufficient evidence to reject the premise that the hippocampus functions as a memory system. That said, there are clearly some remaining issues with this account (see Buckley, 2005, for a longer discussion of this issue): A recent study reported that monkeys with fornix transection showed long-lasting deficits in learning nonspatial associations, such as tapping, briefly touching, and contacting for a longer period of time a complex visual stimulus (Brasted, Bussey, Murray, & Wise, 2003). These findings were interpreted as evidence of involvement of the hippocampus in associative learning outside of the spatial domain, consistent with views of the hippocampus that stress its role in relational processing (Cohen et al., 1999; Eichenbaum & Cohen, 2001; Fortin et al., 2002; Wallenstein, Eichenbaum, & Hasselmo, 1998) or rapid associative learning (McClelland et al., 1995; O'Reilly & Rudy, 2000).

Relational memory theory proposes that the hippocampus is involved in memory for relationships among perceptually distinct items (Cohen et al., 1999; Eichenbaum & Cohen, 2001; Eichenbaum et al., 1994; Ryan et al., 2000), whereas parahippocampal structures (the entorhinal, perirhinal, and parahippocampal cortices) house conjunctive representations of stimulus elements, thereby supporting memory for single objects. Consistent with this, our studies suggest that the hippocampus mediates the association of relations among elements of scenes, while perirhinal cortex is necessary for the binding of features of individual objects (Barens et al., 2005, 2007; Lee, Buckley, et al., 2005b).

Contradictory to relational accounts, however, in which MTL structures in relational memory is considered restricted to declarative memory (Cohen & Eichenbaum, 1993; Cohen et al., 1999; Eichenbaum, 2000a, 2000b; Eichenbaum & Cohen, 2001), our studies find impairments in scene and object processing in conditions in which there is no overt demand for long-term memory (simultaneous discrimination; Barens et al., 2005, 2007;

Graham et al., 2006; Lee, Buckley, et al., 2006b; Lee, Buckley, et al., 2005b; Lee, Bussey et al., 2005c; Lee, Levi, Davies, Hodges, & Graham, 2007a). To account for findings that reveal deficits in amnesia beyond long-term memory, some researchers have proposed that these impairments reflect a failure to benefit from newly formed (or forming) long-term memories that may contribute to online object processing (Ryan & Cohen, 2004). Others have proposed that these deficits may be due to a deficit in very short-term memory, in particular an inability to hold information online across the saccades required to compare the stimuli presented simultaneously on the screen (Ranganath & Blumenfeld, 2005; Ranganath & D'Esposito, 2005).

Three very recent investigations have directly addressed the status of working memory in amnesia (Hannula, Tranel, & Cohen, 2006; Olson, Moore, Stark, & Chatterjee, 2006; Olson, Page, et al., 2006). Consistent with our account, they find evidence that working memory is deficient—particularly when conjunctions of stimuli (object-place; Olson, Page, et al., 2006), and relations amongst objects within a scene (faces-scenes; Hannula et al., 2006) are tested. For example, in Hannula et al. (2006), participants with amnesia secondary to an anoxic episode were tested on recognition memory for relations among items embedded within scenes and for face-scene pairs. The authors hypothesised that while both conditions tested relational memory, the first was specific to the spatial domain while the second tested more general relational memory, thereby providing a means of testing between the relational and cognitive map theories (Eichenbaum & Cohen, 2001; Kumaran & Maguire, 2005). Consistent with our account in which memory will be impaired following hippocampal damage whenever scenes are a critical component of learning, the patients showed poor memory in both conditions, even at the shortest lag when the studied item immediately preceded the test probe. Similarly, in Olson, Page, et al. (2006), item memory for individual objects and locations was preserved, but memory for object-place conjunctions was impaired.

Contrary to our view, however, the deficits evident in these patients did not seem to be due to difficulties in perceptual processing. For example, in Hannula et al. (2006) patients showed intact item memory for the scenes presented in the spatial condition. It should be noted, however, that controls performed close to ceiling on this test, and in a recent study from our laboratory individuals with hippocampal damage showed impaired recognition for scenes at a long (over 10 min) delay (Taylor et al., 2007; see also Bird et al., 2007; Cipolotti et al., 2006). Also problematic for our account are other recent studies showing normal perceptual processing of scenes (Hartley et al., 2007; Shrager et al., 2006) and objects (Levy et al., 2005; Shrager et al., 2006) in amnesic individuals with MTL involvement. In Hartley et al. (2007), five patients, four of whom had selective hippocampal damage, were tested on match-to-sample and delayed-match-to-sample

(2 s delay) tests requiring the participants to match a sample scene to a target (same place from a different view) when presented alongside three foil scenes with similar topography. While all four patients showed clear deficits on the topographical memory condition, only two of the four participants were impaired (as measured by z -scores) on the topographical perception condition. Similarly, Shrager et al. (2006) used a visual discrimination paradigm similar to that originally developed by Lee, Bussey, et al. (2005c), and reported normal performance in two patients with MTL damage including the perirhinal cortex. Although there was some evidence of poorer performance in one of the MTL cases, EP (see also Levy et al., 2005), the authors suggest that this can be explained by difficulties with remembering information about target stimuli over trials (consistent with the object impairments seen in Lee, Bussey, et al., 2005c). It remains to be seen, therefore, whether other research groups can find evidence of the perceptual deficits we have consistently found in our patients.

Two further sets of evidence can be considered as support for the nonperceptual account of MTL function: (a) that years of research in amnesic individuals have failed to find evidence of perceptual deficits, and (b) that most clinicians would concur that patients with amnesia do not present to the clinic with complaints of perceptual problems, instead individuals cite memory difficulties as the primary referring symptom. Just because patients fail to complain of perceptual problems, however, does not necessarily mean that memory is the only cognitive domain affected. In a recent e-mail exchange, we asked one of our patients with selective hippocampal damage exactly how she thought her memory affected her everyday life. She wrote, "The areas of my life that I find most challenging are when I am given a series of directions, remembering my way around somewhere (familiar or unfamiliar), how I got into a building and how I can get out of it again, driving somewhere not only for the first time, but many times, remembering where I left my car and how I got into the car park in the first place, which way to turn out of a car park to get home. . . . Whichever angle I look, everything looks the same. . . . I would prefer not to call my experiences '*memory problems*', they are not. This is a total misrepresentation of the damage I have. What I experience are '*orientational problems*'. This leads me onto how I manage my orientation. I check my position at regular intervals. I literally take mental photos by stopping, turning round and taking a visual snapshot. When it is time to find my way back, I rely on my mental snapshots. I think my visual memory is good and it compensates for the reduced spatial memory I have. I guess the mental snapshot strategy is a bit like trawling through the photos on a digital camera." Thus, in our case, when we took the time to ask the patient to describe their cognitive difficulties, we find a description highlighting perceptual problems that

seems to argue strongly against an interpretation of their deficits as mnemonic in nature.

That said, how does one resolve this discrepancy in this literature? We believe that part of the problem across studies is the frequent use of stimuli that are not sufficiently complex to stress feature ambiguity. While one reasonable criticism of our account might be that we have been ambiguous about what we mean by feature ambiguity (although see Bussey, Saksida, & Murray, 2002), this is a topic for further research. This progress, however, is dependent upon memory researchers taking seriously the possibility of a nonmnemonic account of MTL function. In the context of discussing the working memory deficits seen in Buffalo et al. (1998) and Ryan and Cohen (2004), Olson, Page, et al. (2006) state eloquently:

When hippocampally based WM [working memory] deficits have been observed in the past, the data collide with the paradigmatic view of memory and the hippocampus: that it is only important for LTM [long-term memory]. ... These results [the authors are referring to Buffalo et al., 1998, and Ryan & Cohen, 2004] were interpreted as being attributable to the influence of impaired long-term memory in amnesia. Unfortunately, the circular logic of this interpretation (e.g., if amnesia is defined as an impairment in long-term memory then any memory impairment, regardless of delay, must be an impairment in long-term memory) renders it impotent. This problem can be skirted by defining the theoretical construct of working memory as the activated contents of long-term memory (Cowan, 1995; Ericsson & Kintsch, 1995) and the functionality of working memory as maintaining information from long-term memory in a readily accessible state (Ryan & Cohen, 2004). However, a strong version of this definition renders working memory tantamount to consciousness (R.C. O'Reilly, Braver, & Cohen, 1999) or attention, and fails to account for the ability to retain novel information in WM. (p. 4599; our explanations in square brackets).

We completely agree with this statement. It is important, however, to point out that while we are heartened by the move to consider long-term memory no longer a specialised function of the MTL, that swapping one type of memory function (long-term memory) with another (working memory) can lead to similar circularity in the interpretation of our own findings. For example, that the perceptual deficits observed on our tasks must reflect either difficulties with forming long-term memories (if the researcher believes the MTL is important for long-term memory) or impairment in very short-term memory necessary for making saccades across stimuli (if the individual is a proponent of a working memory account of MTL function). Paraphrasing Olson, Page, et al. (2006), when perceptual deficits have been observed in amnesia, the data collide with which ever paradigmatic view of memory and the hippocampus the individual believes, and the impairment must therefore be a consequence of this failure of

memory. It need not be so; instead perception and memory may be intrinsically interlinked throughout the brain, and memory may be best considered a dynamic interplay between distributed perceptual representations, task demands, and motivational goals.

In summary, this review cites new data that challenges outstanding accounts of the MTL as a memory system, and proposes instead that memory is dependent upon a hierarchically organised network of modality-specific perceptual representations distributed throughout the brain, with structures in the MTL acting as the apex of two anatomically separate streams for processing information about objects and scenes.

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